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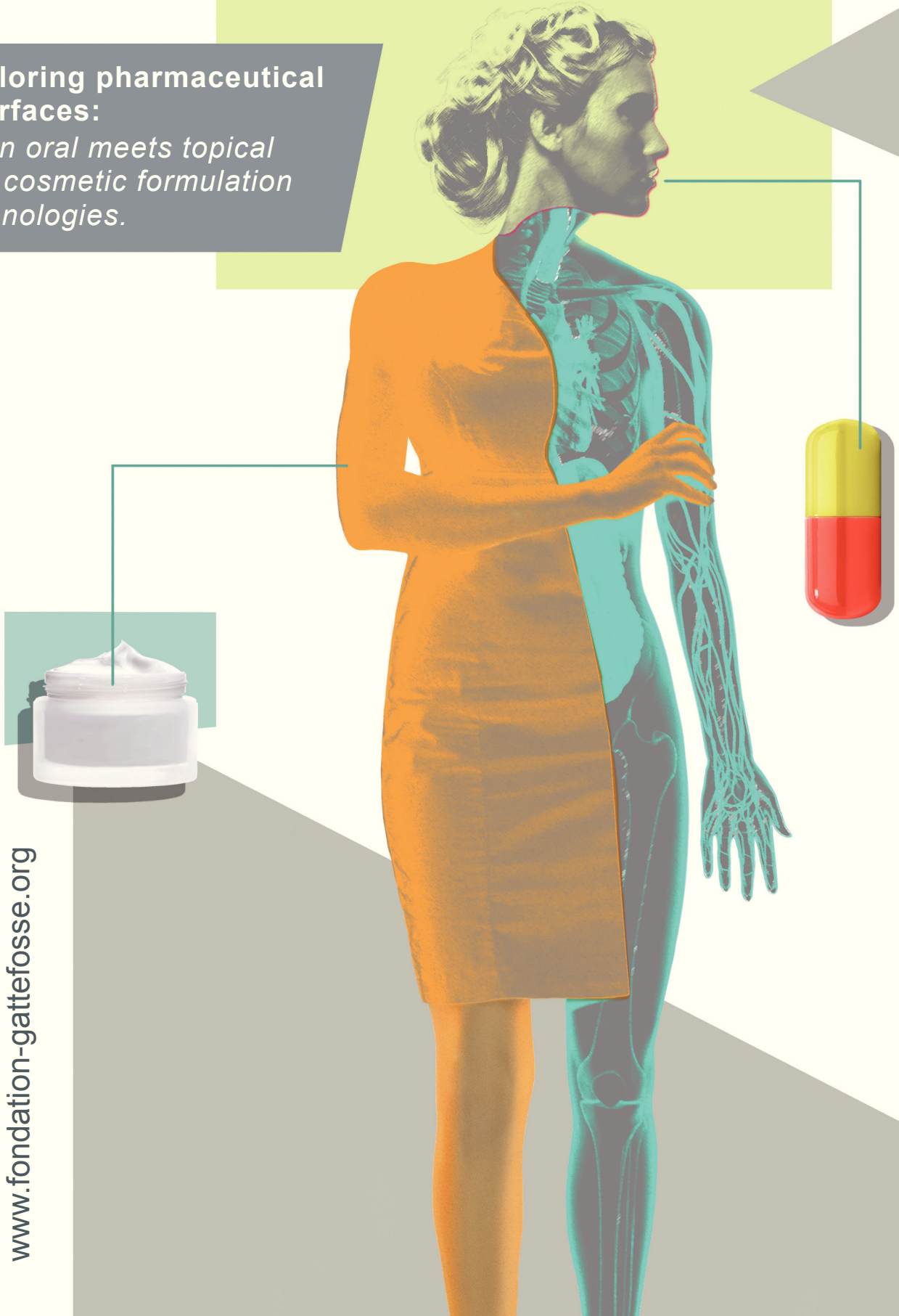
Exploring pharmaceutical interfaces:
when oral meets topical and cosmetic formulation technologies.



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  Amit Kumar Jain
  National Institute of Pharmaceutical Education and Research, Punjab, India. For the poster presented at AAPS "Antioxidant containing solid self nano-emulsifying drug delivery system (s-SNEDDS) of tamoxifen: Implication on oral bioavailability, antitumor efficacy and hepatotoxicity".

  Mitan R. Gokulgandhi
  University of Missouri, Kansas City, MI, USA for the poster presented at AAPS "Novel Conjugates of Cidofovir: Transporter affinity, bioreversion, antiviral activity and sustain release formulation".

- Graduate Student Travelship Awards:
  Mohammed Maroof Alvi
  St John's University, NY, USA. Poster presented at AAPS "An Evaluation of Nonionic Formulation Excipients for Enhancing Absorption of Hydrophilic Drugs through Paracellular Pathway".

  Pramod Sambhaji Jagtap
  Bharati Vidyapeeth's College of Pharmacy, Shrirampur, India. Poster presented at AAPS "Formulation and Ex Vivo Evaluation of Solid Lipid Nanoparticles (SLNs) Based Hydrogel for Intranasal Drug Delivery".

We also thank all the researchers who submitted their papers for the awards.

These awards are presented at the American Association of Pharmaceutical Scientists annual congress.

For further information please refer to the AAPS website:
http://www.aaps.org/About_AAPS/Annual_Meeting___Exposition_Awards/

GATTEFOSSÉ

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THE GATTEFOSSÉ FOUNDATION

The Gattefossé Foundation was established in 2008 to provide a conduit for the company's staff and family share holders to express their corporate, intellectual and philanthropic values and those of the company's founders.

The Foundation's actions are focused on three key missions; support of research and development; dissemination of scientific knowledge and involvement in community and social initiatives. To find out more please visit our website: http://www.gattefosse.com/en/gattefosse-foundation

The annual Journées Galéniques, held in St. Rémy de Provence, France began in the 60's. The ethos of the meeting was (and still is) the open sharing of data, eclectic discussion and acute listening on the part of the participants; these being drug development researchers (both academic and corporate) from around the world. The ultimate aim of the meeting, that remains the same today, is to catalyze advancements in medicines and healthcare.

The 47th Journées Galéniques was a wonderfully interactive and inter-disciplinary scientific meeting. The programme was developed by Prof. Bill Charman (Monash University, Australia) in concert with Prof. Richard Guy (University of Bath,UK). An impressive group of invited experts adressed the subjects or oral and topical delivery with insight and passion.

The aim of the meeting and the task of the speakers and participants was to explore the interfaces between drug delivery and formulation technologies for the oral and topical routes of administration. The outcome was an intriguing examination of the overlap and differentiation between these fields and the insight obtained when viewing these subjects from distinctly different angles.

As President of the Gattefossé Foundation, I am delighted to share with you the content of this meeting, and I extend my sincere gratitude to the Chairmen and to all the authors for their contribution.

Lastly, whether you are a corporate, academic, or student researcher, I hope you find these articles of use, interest and possibly inspiration for your research projects.

Sophie Gattefossé - Moyrand
President of the Gattefossé Foundation

FOREWORD

EXPLORING PHARMACEUTICAL INTERFACES: WHEN ORAL MEETS TOPICAL AND COSMETIC FORMULATION TECHNOLOGIES.

In this edition of the Gattefossé Foundation Bulletin Technique the authors provoke reflection on opportunities for scientific creativity which can drive improvement of healthcare products, both pharmaceutical and cosmetic. The Chairmen of this unique scientific gathering and subsequent Bulletin Technique sum up the objective of the meeting:

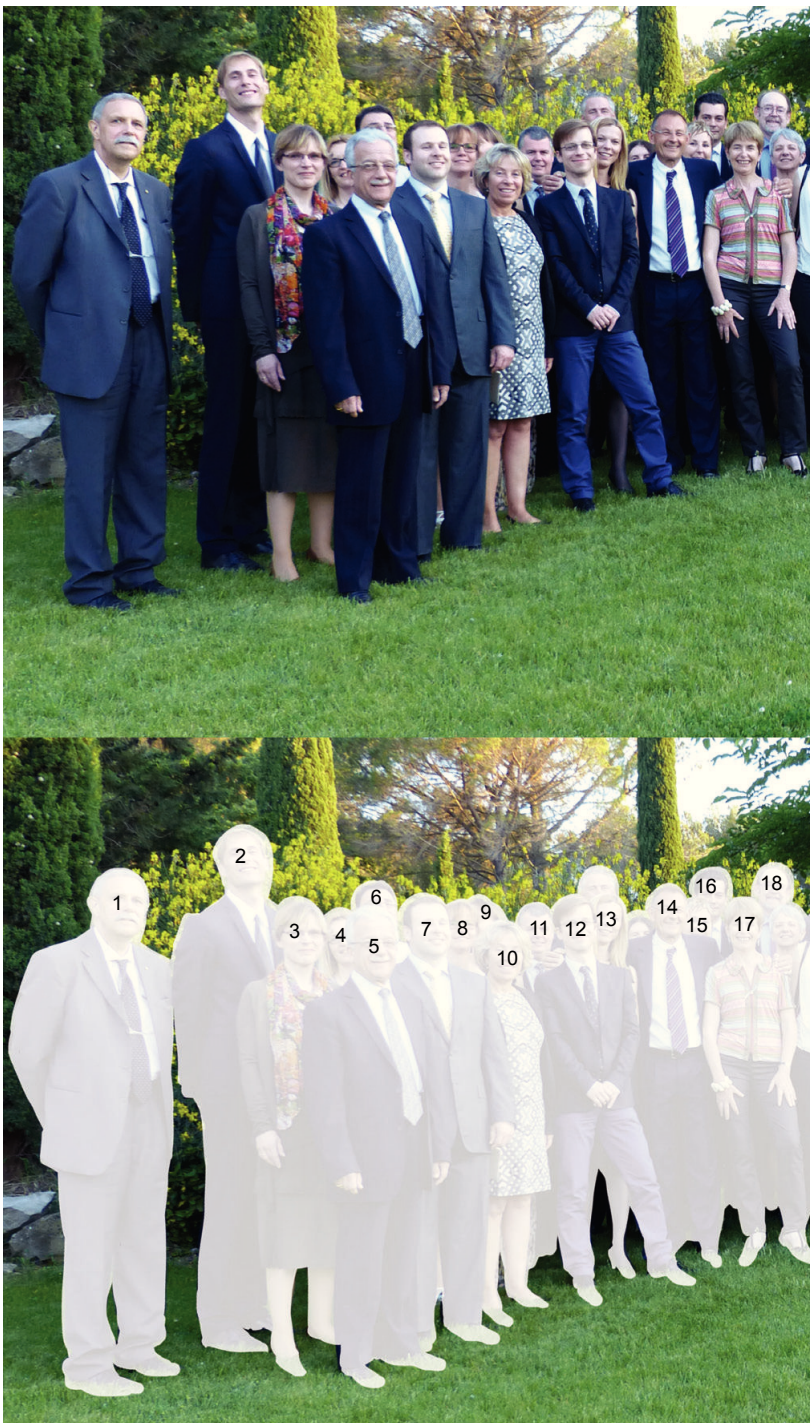
Prof Bill Charman

We need to constantly challenge being siloed and ring-fenced within our particular fields of scientific endeavour. Often, these fields are narrowing in scope and the science being undertaken is becoming less risky and more incremental. So, what to do? Well, one option is to seek to learn and understand the "interfacial science" opportunities that arise when working at the scientific intersection of disciplines. Applying this thinking to the design of next generation pharmaceutical formulations, the programme of the Journées Galéniques conference aimed to explore, probe and extend what we believe are untapped scientific learnings and insights that exist at some common interfaces of 3 major fields of formulation technology ie. oral, topical and cosmetic.

Prof Richard Guy

This meeting aimed to involve participants in an in-depth appreciation of the demands that must be met to develop successful oral and topical products containing specific active ingredients. The contrasts and parallels between these distinct routes of administration are identified and illustrated, and the state-of-the-art described and critically evaluated. Specifically: [1] the overlap between the physicochemical and biological factors that impact on the ultimate bioavailability of an active moiety delivered either orally or topically will have been elucidated; and [2] the events taking place at the interface between the delivery system and the membrane, through which absorption occurs, will have been examined in detail. A particular 'take-home' message from these proceedings is how the underpinning science is translated into practical application; many key principles discussed are applicable to the challenges of formulation optimisation and enhanced bioavailability across diverse biological barriers.

We hope you enjoy the Bulletin Technique and find it useful and feel free to share it with colleagues and associates.



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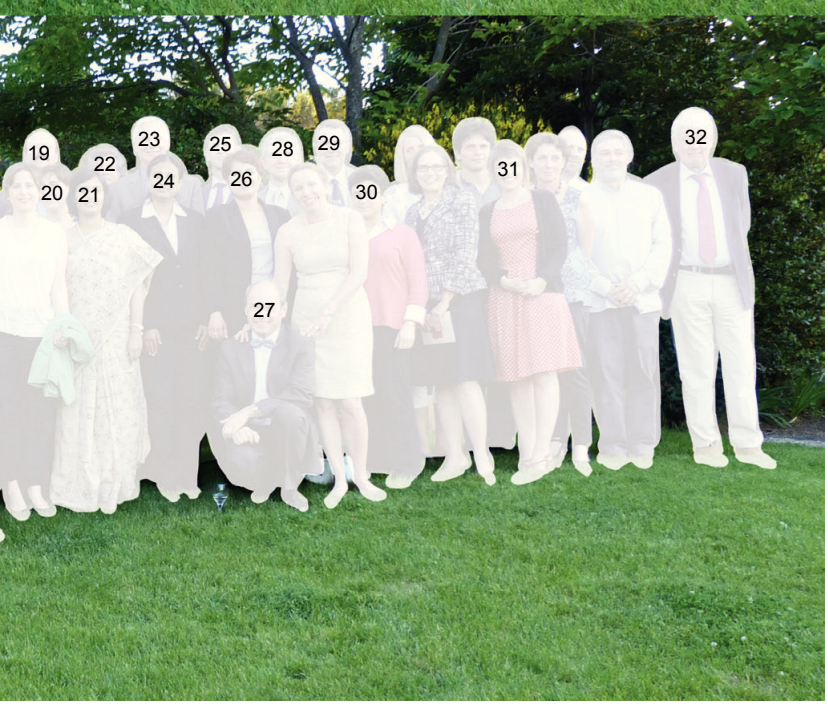

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SOLUBILIZATION FOR ORAL DRUG DELIVERY: PRINCIPLES AND APPROACHES

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Abstract

Advances in understanding the drug absorption process and principles underlying formulation approaches to enhance oral bioavailability have led to a renaissance in the last two decades. Computational models of drug absorption have advanced beyond static considerations of drug solubility and permeability by including GI tract heterogeneity and dynamic considerations coupled to the local micro-environment (e.g. gradients in pH, drug, enzymes, excipients, etc.) that may affect drug absorption and formulation performance. While the properties of the drug itself may impose limitations on the maximum oral bioavailability attainable, much can be done via formulation design to optimize the driving force for absorption. Approaches that may be considered to maximize solubility and the driving force for absorption include selection of the proper form of the API (e.g., salts, co-crystals, amorphous dispersions, prodrugs, etc.; and appropriate formulation matrix/excipients (e.g. lipids, polymer excipients, complexing agents, etc.). At present, mechanism-based models are needed that allow one to both understand and predict equilibrium solubility and design strategies to stabilize non-equilibrium states (e.g., high energy dispersions, supersaturation). Recent studies in our laboratory relating to these goals include molecular dynamics computer simulations of drug solubilization and experimental investigations of crystal growth and its inhibition.

Keywords

Amorphous dispersions, lipid-based drug delivery systems, molecular dynamics, oral bioavailability, salts, solubilization, solubility prediction, supersaturation.

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1. Solubility and oral bioavailability

Consider a possible scenario unfolding at any number of small and large pharmaceutical companies on any given day. A promising lead candidate is being considered for further development as an oral product but questions have arisen regarding the likelihood that it can be delivered orally due to bioavailability concerns. Perhaps the compound is known to exhibit poor solubility and the discussion therefore focuses on whether or not the lead optimization program should continue with the aim of identifying analogues with improved “druggability”. Alternatively, the development team may decide to rely on their formulation scientists to develop a suitable delivery system to ensure good oral bioavailability despite the unsatisfactory solubility characteristics of the API itself. In evaluating whether or not to continue the synthetic program to identify more “druggable” candidates, time delays associated with further syntheses and the necessary continuation of potency and toxicity assays must be considered. Certainly, this avenue would be more attractive if useful guidelines were available to assist the synthetic chemists in the design of more soluble candidates without sacrificing other desirable properties. On the other hand, for the formulation route, knowledge of the options available and their prospects for success would also be desirable. These are the themes that underly this presentation.

While the discussion thus far has implied that any potential shortcoming in oral bioavailability is due to the drug candidate’s solubility, it is important to first consider why compounds might not exhibit 100% bioavailability. As noted by Benet *et al* [1], the fraction of an orally administered drug that ultimately reaches the systemic circulation can be attributed to three separable contributions depicted in Equation 1:

$$F_{oral} = F_{abs}F_{int}F_{hep} \qquad \text{Equation 1}$$

where F_{hep} is the fraction not metabolized by the liver during the first pass, F_{int} is the fraction not metabolized by the intestinal wall, and F_{abs} is the fraction of an oral dose that is actually absorbed from the gastrointestinal tract. F_{abs} may vary with the dose, the membrane permeabilities of the various drug species, and the lumenal solubility of the drug. As it is generally understood that the drug must be in solution to be absorbed, the solubility can play an important role in oral bioavailability. Solubility also governs the drug dissolution rate from solid dosage forms. Together, the solubility, dissolution rate, and membrane permeability are all governed in part by states of ionization of the drug as determined by the drug’s pKa values and the microenvironment pH. The latter quantity varies with position in the gastroinestinal tract (GIT). Moreover, drug binding to mixed bile salt-lecithin micelles, lipid vesicles, and other lipid particles present in the intestine during digestion also influence F_{abs} both by enhancing drug solubility while at the same time reducing the driving force for free drug transport across the intestinal wall [2].

Amidon and others developed the biopharmaceutical classification system for drug candidates in an attempt to more clearly define the relative contributions of drug permeability, solubility, and dose to the overall fraction of drug that can be absorbed [3]. Figure 1A illustrates the combined influences of the drug permeability coefficient and solubility (at pH 7) on the overall % absorption assuming a basic drug having a pKa of 8 and a single oral dose of 100 mg [4]. BCS class 2 compounds are highly permeable but poorly soluble such that solubility limits their % absorption while BCS class 3 compounds are sufficiently soluble but their % absorption is limited by their permeability. The absorption of BCS class 1 compounds is not limited by either their membrane permeability or solubility.

Figure 1A is useful conceptually, but it masks the complex interplay of factors underlying drug absorption. One of those factors that can be very important is the dose of the compound, a quantity that may not be known in early stages of drug development. To incorporate dose considerations as well as permeability and solubility into the model for absorption Oh *et al*. [5] defined three dimensionless ratios, the absorption number (**An**), the dose number (**Do**), and the dissolution number (**Dn**), to classify drug absorption characteristics of compounds. **An** is the ratio of the radial absorption rate based on the effective permeability to the axial convection rate through the intestine, **Dn** is the ratio of the residence time to the dissolution time, and **Do** is the ratio of the dose to the drug solubility in an aqueous volume of 250 mL. Figure 1B illustrates the importance of **Do** and **Dn** in determining the fraction absorbed. Drug absorption is maximized by rapid dissolution and a low dose.

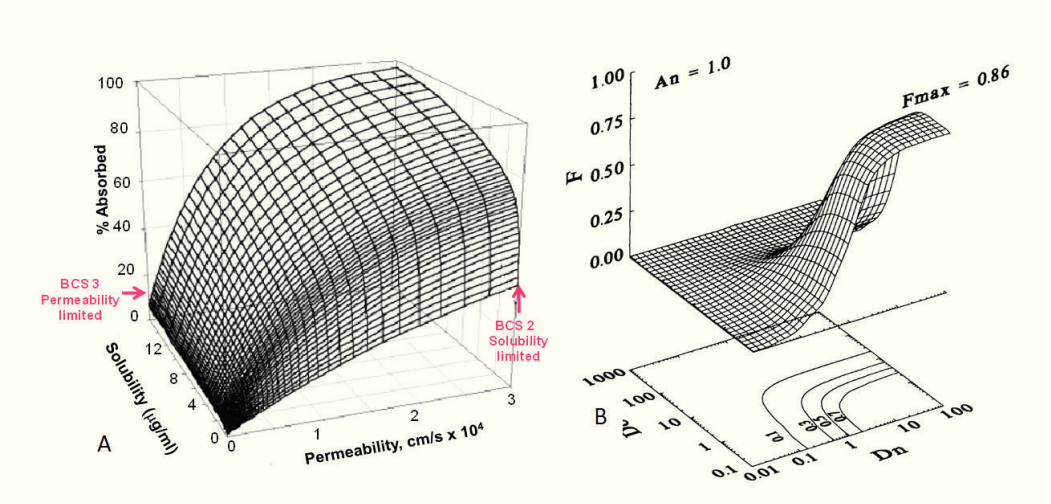


Figure 1. (A) % of drug absorbed orally as a function of solubility and permeability (adapted with permission pending from reference [4]). (B) Dependence of the fraction of a dose absorbed versus the dose number (Do) and the dissolution number (Dn) (Reprinted with permission from reference [5]).

Figures 1A-B indicate that even when first pass intestinal and liver metabolism can be ruled out as causes of low bioavailability, the culprit may not be low solubility but rather low permeability (Fig. 1A). If permeability can be eliminated as a rate limiting factor, increasing dissolution rate, say, by reducing particle size, may be an effective strategy but the benefit of this strategy may depend on the dose.

With increasing doses the bioavailability may become limited by the solubility in the lumen regardless of dissolution rate (Fig. 1B). It is important for the drug development scientist to understand the complexities of the absorption process before embarking on a particular solubilization strategy.

2. Solubilization approaches: Factors governing solubility in lipid-based delivery systems

Shown in Figure 2 is a diagram that classifies some of the approaches that might be considered in improving the oral absorption of poorly soluble drugs. Notice that the first level of classification distinguishes particle size reduction and prodrug formation from solubilization by formulation approaches. Particle size reduction has been shown to be an effective strategy for improving oral bioavailability in cases where dissolution was rate-limiting but it will not be addressed in the current presentation. Prodrug modification of poorly soluble parent compounds may also be effective in improving bioavailability. This strategy will not be considered in this discussion because it involves a covalent modification to produce a new compound, albeit perhaps reversibly. This is not intended to imply that prodrug formation might not be a worthwhile avenue to pursue, but it would necessitate additional syntheses and evaluation of new chemical entities. This could prolong the overall development timeline if not initiated at an early stage.

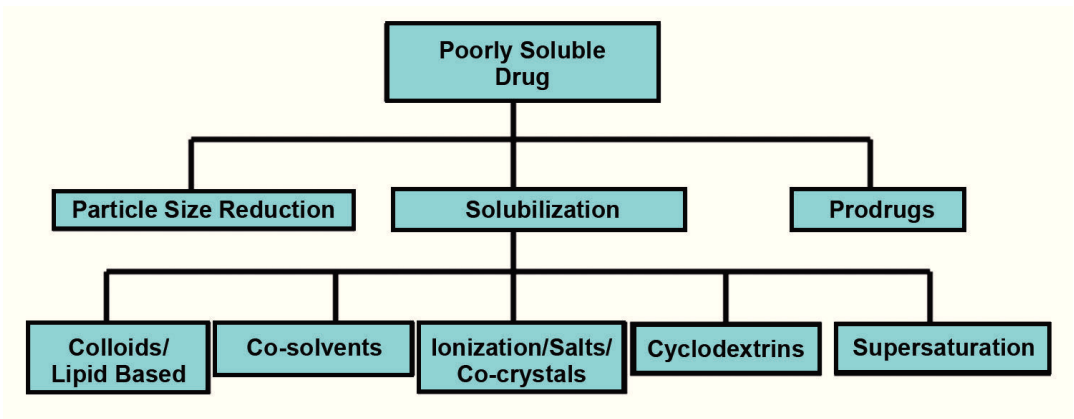


Figure 2. Some approaches to consider to improve oral absorption of a poorly soluble drug.

Primarily we are interested here in approaches that improve the solubility characteristics of a given parent drug without covalent modification. Of course, it would also be very helpful to have reliable predictive relationships that would enable one to predict the solubility of a given compound solely from its structure and the solvation properties of the vehicle/delivery system. A brief discussion of the factors that influence solubility and the "state of the science" with respect to solubility prediction would therefore be a useful starting point.

Drugs that are poorly soluble in water are often placed into one of two groups depending on the suspected cause of the poor solubility: 1) the compound may be very hydrophobic, which simply reflects the fact that it may be very poorly solvated by water due to the tendency of water to form strong hydrogen bonds to other water molecules rather than to the drug compound; or 2) the intermolecular interactions in

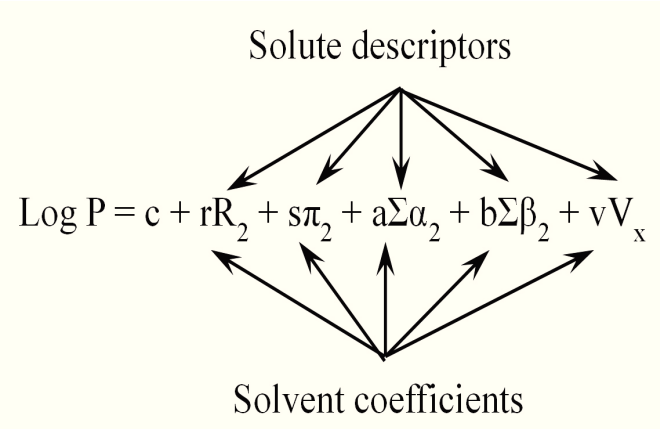
the crystalline state of the drug are so strong that the escaping tendency of the drug from its crystal is very low. Conceptually, these two types of contributions can be captured in the general solubility equation (GSE) for nonelectrolytes as developed by Yalkowsky and colleagues [6] over a number of decades. One form of this equation is shown below:

$$\log S = 0.5 - \log P_{o/w} - 0.01(T_m - 25) \qquad \text{Equation 2}$$

where S is the molar solubility at 25°C, $P_{o/w}$ is the octanol/water partition coefficient, and T_m is the melting point in °C. The term containing the melting point in the above equation was originally derived from the ideal solubility equation which assumes that the ideal solvent for a given compound would have solvent properties identical to the supercooled melt and that the solubility in that hypothetical supercooled melt would decrease as the temperature is reduced from the melting point. To obtain an estimate of aqueous solubility, one must then assume that the transfer of the solute from the supercooled melt to water can be quantitatively mimicked by the octanol/water partition coefficient ($P_{o/w}$). Of course, the supercooled melt of any give drug molecule would not precisely resemble the solvent nature of octanol, which would be a source of uncertainty in the GSE equation. Also, the melting point must be known, necessitating the synthesis of the compound and experimental determination of its melting point because this is not yet a property that can be predicted. Computational approaches directed towards the prediction of melting point are of considerable interest, however, and there have been recent advances [7], so perhaps this quantity will be predictable in the future.

While reliable methods to predict drug solubility solely from molecular structure are not currently available, computational approaches to estimate *relative* solubilities in a variety of solvents are more advanced. An area in which this capability would be valuable is in the selection of a suitable combination of lipid-based solvents to solubilize poorly soluble drugs in order to enhance oral bioavailability. Lipid-based formulations for oral delivery may be liquids, semi-solids, or solids and may consist of a variety of components including triglycerides, diglycerides, and monoglycerides having a range of alkyl chain lengths, as well as other surfactants and cosolvents. Ideally, lipid based systems should be dispersed in the g.i. tract, ultimately undergoing digestion and absorption while retaining the drug in solution and possibly producing a supersaturated concentration of the drug to facilitate absorption. These are complex processes that are beyond the scope of this discussion but they have been reviewed recently [8].

Empirically derived linear free energy relationships (LFERs) such as those developed by Abraham and colleagues [9] may be useful for predicting relative drug solubilities in a variety of solvents. The fundamental equation (Eq. 3) enables calculation of log P, the partition coefficient between the organic solvent of interest and water once various descriptors representing the solute and coefficients representing the solvent of interest are known [9]. We have recently explored the predictive capabilities of such LFERs for lipid-based delivery systems [10-12].



Equation 3

In the above equation, rR_2 reflects solute-solvent interactions through n- and π -electron pairs, $s\pi_2$ reflects dipolar/polarizability dependent interactions, $a\Sigma\alpha_2$ refers to H-bonding interactions with the solute as donor, $b\Sigma\beta_2$ refers to H-bonding with the solute as the H-bond acceptor, and vV_x reflects the solute volume dependent cavity formation in the solvent. Solute descriptors can be estimated from published tables for various fragment contributions to each descriptor but the solvent coefficients must generally be obtained experimentally for each solvent system of interest. Table 1 provides representative examples of the solvent coefficients (c, r, s, a, b, and v) that have been reported in the literature [9]. By combining these relationships, it is possible to estimate relative solubilities of a given solute molecule in different lipid solvents, providing that solvent coefficients are available for each solvent of interest. Unfortunately, given the number of potential lipid vehicle combinations that might be considered for a lipid-based delivery system, it is unlikely that the necessary solvent coefficients would be available in a published data base.

Our interest was in determining if systematic relationships between the solvent functional group composition and the values of key solvent coefficients could be identified. If this were possible, the need to generate a new data base for each lipid vehicle combination might be avoided. For triglyceride containing vehicles, for example, the key solvent coefficients differentiating one triglyceride or triglyceride mixture from another appear to be s and a, as suggested by the comparison of LFERs for olive oil/water versus alkane/water in Table 1.

Table 1. Linear free energy relationships for predicting relative solubility/partitioning- solvent coefficients [9]

$$\log P_{solvent/water} = c + rR_2 + s\pi_2 + a\Sigma\alpha_2 + b\Sigma\beta_2 + vV_x$$

Solvent	c	r	s	a	b	v
alkane (n=173)	0.28	0.65	-1.7	-3.5	-4.8	4.3
olive oil (n=111)	-0.09	0.58	-0.86	-1.4	-4.9	4.3
octanol (n=584)	0.08	0.59	-1.1	0.03	-3.4	3.8

$$\text{Log } P_{oil/alkane} = -0.37 - 0.07R_2 + 0.84\pi_2 + 2.1\Sigma\alpha_2 - .01\Sigma\beta_2$$

$$\text{Log } P_{oil/alkane} \sim -0.37 + 0.84\pi_2 + 2.1\Sigma\alpha_2$$

The emergence of significant differences in a and s coefficients between olive oil and alkane solvents indicates the importance of dipolar/polarizability dependent interactions and H-bonding interactions with the solute as donor, both of which increase in olive oil due to the presence of the carbonyl ester linkages. Our laboratory explored the effect of triglyceride ester concentration on these solvent descriptors in a paper published by Cao *et al* [10]. The vehicle/water partitioning of a series of model solutes with varying hydrogen bond donating/accepting abilities were determined in various squalane/tricaprylin solvent mixtures. General LFERs having the form shown in Table 1 were generated at each solvent composition. An examination of the solvent coefficients indicated that those representing the sensitivity of the solvent to the solute dipolarity/polarizability, s, and to the hydrogen bond acidity of the solute, a, varied systematically with the concentration of triglyceride ester moieties in the solvent mixture. Empirical equations were developed that could be used to predict triglyceride/water partition coefficients and in some cases, solubility in hydrated, fully-saturated triglyceride solvents for any small molecule for which Abraham solute descriptors were available.

We later extended this approach to explore both water uptake and the solubilities of twelve model solutes varying in hydrogen bond acidity, basicity, polarity, and molecular volume in various triglyceride-monoglyceride lipid mixtures [11]. Solubility profiles for a given solute in the various lipid mixtures were superimposable when plotted as a function of the molar monoglyceride concentration, producing a single master curve for each solute. Solutes possessing polar, hydrogen-donating groups such as benzamide or p-toluic acid exhibited substantial increases in lipid solubility with increasing monoglyceride content while solutes lacking hydrogen bond donor groups such as anthracene decreased in solubility with an increase in monoglyceride content. As illustrated in Figure 3 (left panel), the solvent coefficients s and a in the Abraham equation increased systematically with increases in monoglyceride concentration, indicating an increasing ability of the solvent to interact with dipolar/polarizable solutes and the hydrogen bond basicity of the mixture, respectively. The solvent coefficient related to the ease of cavity formation, v, decreased with increasing monoglyceride concentration. Thus, cavity formation becomes energetically less favorable in lipid mixtures containing increasing monoglyceride concentrations. This may be an indication that triglyceride/monoglyceride mixtures are more structured than the pure triglycerides.

Plots of log(S/So) versus the molar concentration of monocaprylin are shown in the right panel of Fig. 3 for various solutes, where S represents the solubility in a monocaprylin-containing mixture and So is the solubility of the same solute in tricaprylin. The solubility of hydrogen bond donating solutes such as benzamide (▲) increased significantly with an increase in monoglyceride concentration while the non-polar solute 9,10-bis(chloromethyl)anthracene (+) exhibited decreasing solubility with increasing monocaprylin concentration. Higher water content in these lipid mixtures (at 100% RH) enhanced the solubility of solutes possessing polar, hydrogen bonding groups and further decreased the solubility of solutes lacking such groups in comparison to relatively dry lipid mixtures (at 6% RH), indicative of further increases in organization of the solvent molecules in water saturated lipid mixtures.

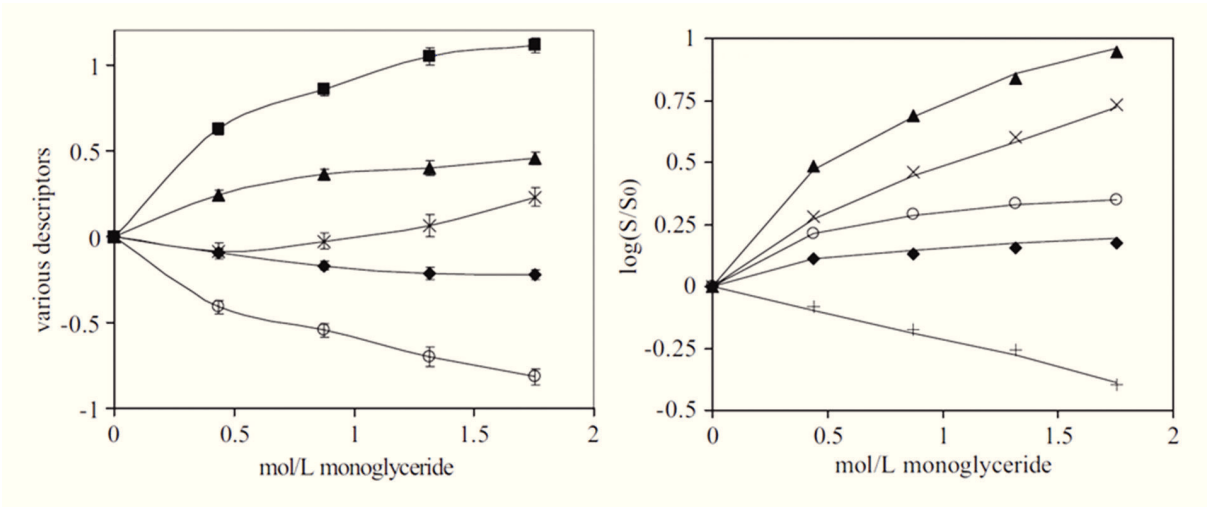


Figure 3. Left panel: changes in solvent coefficients for tricaprylin/1-monocaprylin lipid mixtures as a function of 1-monocaprylin concentration at 100% RH. Symbols: Δr, (♦); Δs, (■); Δa, (▲); Δb, (x); and Δv, (O). Right panel: Plots of experimental and fitted values of log (S/S0) in tricaprylin/1-monocaprylin lipid mixtures as a function of 1-monocaprylin concentration at 100% RH. Symbols: 9-Anthracene methanol (♦), benzamide(▲), p-xylylene glycol (x), 9,10-Bis(chloromethyl) anthracene (+), and 9-Anthracene carboxylic acid (O). Reprinted with permission from Rane et al, 2008 [11]

Molecular dynamics simulations were explored to extract molecular level insights into the organizational changes that may occur in these lipid mixtures with increasing water content [12-13]. Shown in Figure 4 (upper left panel) are plots of the experimental results for the solubility of benzamide in tricaprylin-monocaprylin (C8) or tricaprylin/monocaprin (C10) lipid mixtures as a function of the molar concentration of either monoglyceride at both 6% and 100% RH. In the lower left panel of Fig. 4 are shown the water contents in benzamide saturated tricaprylin-monocaprylin (C8) or tricaprylin/monocaprin (C10) lipid mixtures as a function of the molar concentration of either monoglyceride at 100% RH. On the right-hand side of Fig. 4 is a snapshot taken from a molecular dynamics simulation of the system containing 60% tricaprylin-40% monocaprylin (wt/wt) corresponding to the highest monoglyceride concentration shown in the left-hand plots. The water molecules and a single benzamide molecule are highlighted in the Figure. Clearly, the water molecules are not uniformly distributed throughout this lipid mixture but rather exhibit extensive clustering. Although it is not apparent in Fig. 4, water clustering was accompanied by an increase in lipid organization. The concentrations of polar lipid –OH and ester moieties were enriched at the surface of water clusters, reminiscent of inverse micelle formation. Interestingly, although occasionally a water molecule would migrate to a position in close proximity to the benzamide molecule and briefly form a hydrogen bond with benzamide before relocating into a water cluster, the increase in benzamide solubility at 100 % RH did not seem to be attributable to direct hydrogen-bond formation with water. The increased solubility of benzamide at higher water content may be an indirect result of changes in lipid organization.

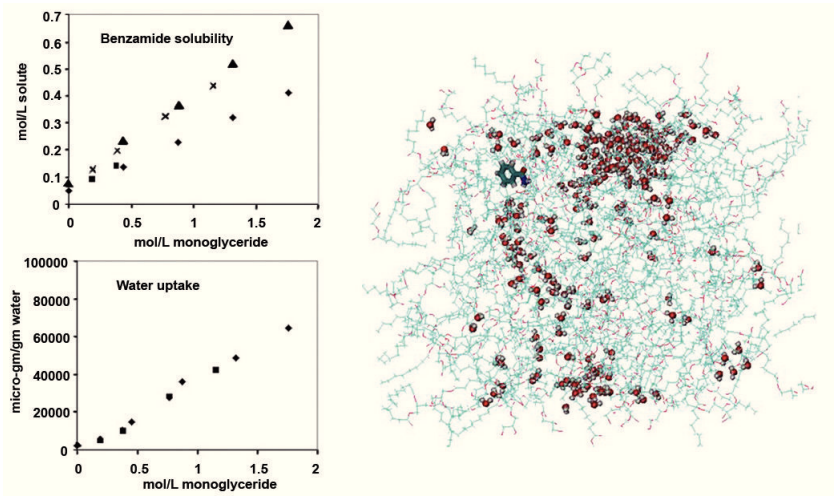


Figure 4. Upper left panel: Benzamide solubility at 37°C in tricaprylin/monocaprylin (C8) or tricaprylin/monocaprin (C10) mixtures under wet (100% RH) and dry (~6% RH) conditions. Symbols: C8-WET (▲); C8-DRY(♦); C10-WET (x); C10-DRY(■). Adapted with permission from reference [11]; Lower left panel: Water uptake at 37°C in the same mixtures saturated with benzamide as above under wet (100% RH) conditions. Symbols: C8(♦); BEN-C10(■). Adapted with permission from reference [11]. Right panel: Molecular dynamics simulation of a water-saturated 60% tricaprylin/40 /40% monocaprylin mixture. Water molecules are highlighted. Also shown is a single benzamide solute molecule.

3. Ionizable drug molecules: salt formation, co-crystals, and supersaturation

Thus far, the discussion has focused primarily on nonelectrolytes, but most drugs and drug candidates have at least one ionizable functional group or a functional group that may be derivatized reversibly, allowing the attachment of an ionizable moiety. A classical illustration of the pH-solubility behavior for terfenadine, a weakly basic compound that can undergo ionization is shown in Fig. 5 [14]. Terfenadine in its neutral form is poorly water soluble, but as shown in Fig. 5, protonation of its tertiary amine group as the solution pH is reduced from 7 to the pH range of 3-5 produces dramatic increases in water solubility, particularly for the lactate salt. The region between pH 3-5 where plateaus in solubility are observed in the diagram reflects the pH range in which the solid phase in equilibrium with the solution is the salt, while at higher pH the solid phase is terfenadine free base. Note that salt solubilities also vary with pH in the region where the salt is the solid phase, as evident by decreases in solubility that occur at pH values below 3. In the illustration shown, decreases in solubility with decreasing pH likely reflect the common ion effect, as the pH was reduced by adding increasing amounts of the salt-forming acid.

One might conclude from Fig. 5 that a lactate salt might be the best choice to enhance water solubility of poorly soluble amine-containing drugs to improve oral bioavailability. However, lactate salts have appeared only infrequently in commercial products and no lactate salts have been approved by the FDA for oral delivery [15]. Paulekuhn in 2007 [16] surveyed the anions employed in commercial products and found a large array of possible salt forming anions have been used and the diversity has been increasing. This reflects the complexity in finding a salt that not

only has the desired solubility but all of the other attributes that are required for a suitable oral salt product apart from its solubility behavior, such as the physical and chemical stability, manufacturing properties, etc. Nevertheless, salt formation is frequently considered when a drug's oral bioavailability is limited by solubility or dissolution, because of the wide range in solubilities that may result, depending on the counterion and API.

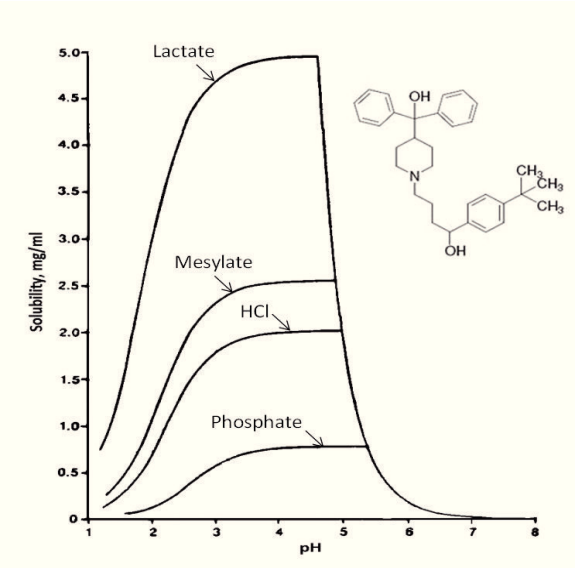
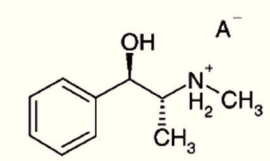


Figure 5. pH-solubility profiles for terfenadine salts. Modified with permission from reference [14].

Unfortunately, there are no reliable computational models or methods to predict salt properties, so salt selection remains a largely empirical, trial-and-error activity. As pointed out previously in the context of computational methods to estimate nonelectrolyte solubility, predicting the free energy or escaping tendency of drug salts from their crystalline solids is just one of the difficulties. A recent publication by Black *et al*. [17] reported that several attempted salts for the weak base ephedrine could not even be crystallized, as shown by the results in Table 2. The same article noted that as of the date of that publication "the ability to predict which salt forms will have desirable physical properties is essentially nonexistent".

Table 2. Ephedrine salt crystallization & properties from a 25 anion screen [17].



(1R, 2S)-(−)-ephedrine salt structure.

	Fraction Crystalline		ΔpKa (Acid-Base)	
Acid description	Water	Methanol	Water	Methanol
Strong Acids (pKa<2)	9/10	6/6	8-12	2-6
- inorganic & organic				
Weak Acids (pKa>3)	8/15	0/9	4-6	-2->1
- carboxylic*, dicarboxylic**, & hydroxy acids				
* 3 hydrates; **4 crystallized from an initial amorphous solid				

In some cases, particularly when the pKa difference between the drug and counterion is small (e.g., 0-3 units), an attempt to prepare a salt may instead lead to a co-crystal, as recently discussed by Childs *et al*. [18] Co-crystals may provide a wide range of pH-solubility behaviors for a given API [19] and some may be useful in improving oral bioavailability. One example is shown in Fig. 6. The compound AMG 517 is poorly soluble having multiple ionizable groups but no pKa values within the physiological range. Bak *et al*. [20] were able to improve both the apparent solubility of AMG 517 and its oral bioavailability in rats by administering a 1:1 sorbic acid:AMG 517 co-crystal, even though the co-crystal eventually reverted back to the free base hydrate.

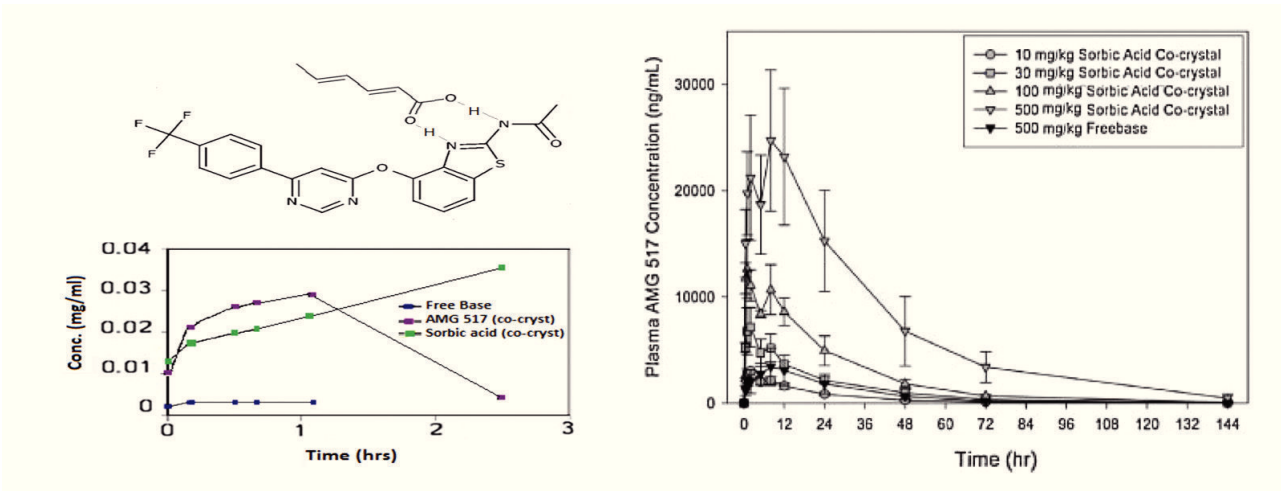


Figure 6. Left: Hydrogen bonds in the sorbic acid co-crystal and apparent solubility of AMG 517 free base and its sorbic acid co-crystal vs time in simulated intestinal fluid. Right panel: Plasma AMG 517 concentration vs. time profiles after oral administration of suspension formulations of AMG 517 sorbic acid cocrystal and free base to rats. Modified with permission from reference [20].

The dynamic nature of the GIT and especially the pH gradients that exist, with an acidic pH range of 1-3 in the stomach and higher pH values in the duodenum and small intestine, lead to the possibility that a given salt solution will be exposed to a pH at which the poorly soluble neutral form of the drug precipitates either as a free acid in the stomach or free base within the intestinal lumen prior to complete absorption. This process, referred to as disproportionation, can also occur in solution formulations containing drug salts that are themselves water soluble, depending on the formulation pH. For example, the tromethamine salt of flurbiprofen has as an aqueous solubility of nearly 0.1 M, but when an aqueous solution of the salt is prepared at this concentration a precipitate forms due to disproportionation [21]. This occurs because the dissolution of that concentration of salt produces a pH of approximately 6.2 (pH = ½(pKa_{acid} + pKa_{base}), where the pKa values of the API and tromethamine are 4.2 and 8.2, respectively) and the solubility of flurbiprofen free acid at this pH is <0.01 M. Disproportionation may also occur in solid matrices such as oral tablet formulations that contain acidic or basic tablet excipients. For example, Rohrs *et al.* found that tablets containing the mesylate salt of the non-nucleoside reverse transcriptase inhibitor delavirdine exhibited decreasing rates and extent of tablet dissolution with time after storage at 40°C and 75% relative

humidity [22]. The problem was ultimately traced to conversion of the salt to the free base (i.e., disproportionation) as a result of the presence of croscarmellose sodium in the tablet matrix.

The tendency of a given compound to either remain in a supersaturated state or rapidly crystallize under conditions that lead to supersaturation appears to be somewhat related to certain structural features of the compound. Box and Comer [23-24] observed during the titration of ionizable drug solutions that some compounds readily precipitated such that significant supersaturation did not occur while others resisted precipitation and tended to remain as supersaturated solutions. They referred to the latter category as “chasers” because they chase equilibrium. Chasers were typically high melting compounds with ≥ 3 hydrogen bond donors and acceptors while non-chasers were low melting and had little hydrogen bonding capacity.

In some cases, salt disproportionation of a salt may occur but the solid phase that forms is not the crystalline free acid or base, but an amorphous form that exhibits higher solubility. If the amorphous form is sufficiently stable such that a higher drug solubility (relative to the crystalline form) can be maintained for several hours, the oral bioavailability may not be compromised. An example was recently reported by Takano *et al.* [25] for the farnesyltransferase inhibitor FTI-2600. This compound exhibits solubility limited absorption and low bioavailability as the crystalline free base leading to the exploration of a water soluble HCl salt. *In vitro*, the HCl salt dissolved immediately in simulated intestinal fluid but rapidly precipitated as an amorphous free base having a 5-fold higher solubility than the crystalline form. *In vivo* studies in dogs demonstrated that administration of the HCl salt resulted in a 4-fold increase in oral bioavailability in comparison to the crystalline free base which correlated with the increase in intraluminal drug concentrations in the presence of the amorphous precipitate.

4. Amorphous dispersions and supersaturation

Amorphous drug formulations have been extensively studied recently because, as high energy forms, they can produce supersaturated solutions upon dissolution and thereby improve the oral bioavailability of poorly soluble drugs that exhibit solubility-limited absorption. The relative oral bioavailability of an amorphous form of a drug in comparison to its crystalline counterpart has been shown to be proportional to the degree of drug supersaturation produced. For this reason, the solubility advantage that may be possible for a given amorphous drug or for a dispersion of an amorphous drug in an amorphous polymer or other excipient matrix is of considerable interest. Murdande *et al.* [26] recently refined an approach initially developed by Hancock and Parks [27] to estimate the solubility advantage of an amorphous form of a drug relative to the crystalline form. The equation they developed for the solubility enhancement ratio, Rs, and the solubility enhancement obtained experimentally for indomethacin are shown in Figure 7. The equation shown takes into account the free energy difference between the amorphous and crystalline forms as estimated by modulated differential scanning calorimetry where ($\mu_2{}^{\bullet a}$ - $\mu_2{}^{\bullet x}$) is the difference in standard state chemical potential between the crystal and the dry amorphous

state, the amount of water that the amorphous solid can absorb and the effect of that absorbed water on the activity of the drug as represented by the term exp[I(a_2)], and the differences in the degree of ionization of the two forms upon dissolving as contained in the ratio,

$$\frac{(1-\overline{\alpha}^{x})}{(1-\overline{\alpha}^{a})}$$

given that the differences in intrinsic solubility may lead to differences in solution pH.

The predicted Rs for amorphous indomethacin was 7.0 and the experimentally observed value from Figure 7 was 4.9.

$$R_s \equiv \frac{\overline{c}_T^{a}}{\overline{c}_T^{x}} = \frac{(1-\overline{\alpha}^{x})}{(1-\overline{\alpha}^{a})} \exp[I(a_2)] \exp\left[\frac{(\mu_2^{\bullet a} - \mu_2^{\bullet x})}{RT}\right]$$

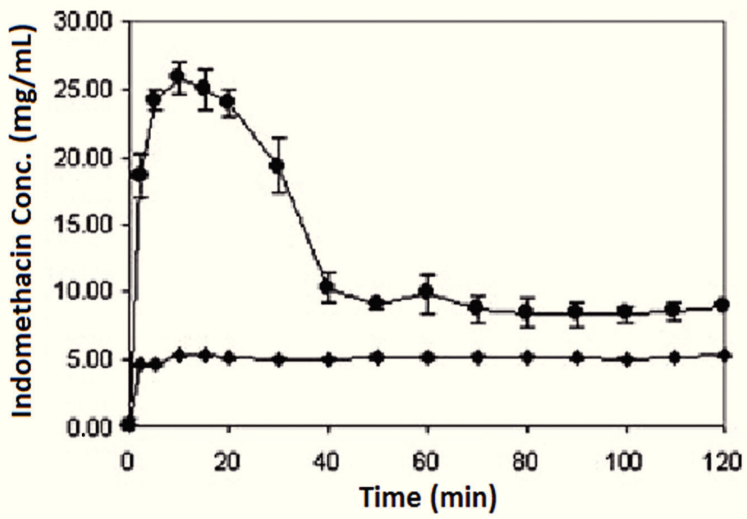


Figure 7. Experimental apparent solubilities of amorphous (•) and crystalline (♦) indomethacin versus time in deionized water at 25°C by Murdande et al [26]. The theoretical solubility enhancement ratio for the amorphous versus crystalline form, Rs (see equation), is 7.0, close to the experimental ratio of 4.9. Reproduced with permission from reference [26].

We recently conducted molecular dynamics simulations of amorphous indomethacin and amorphous indomethacin-PVP mixtures to explore the various intermolecular hydrogen bonding interactions occurring in these systems and their effects on both amorphous drug-excipient miscibility and the aqueous solubility enhancement to be expected as a function of drug/PVP ratio [28]. The Scheme shown in Fig. 8 illustrates the various thermodynamic states of interest and the relative chemical potentials (or free energy) of the drug in each state. The crystalline form of indomethacin is the lowest energy state. Differences in free energy (or free energies of transfer) can be used to infer, for example, the relative solubility advantages in water produced by the pure amorphous form or an amorphous indomethacin-PVP mixture in comparison to crystalline indomethacin.

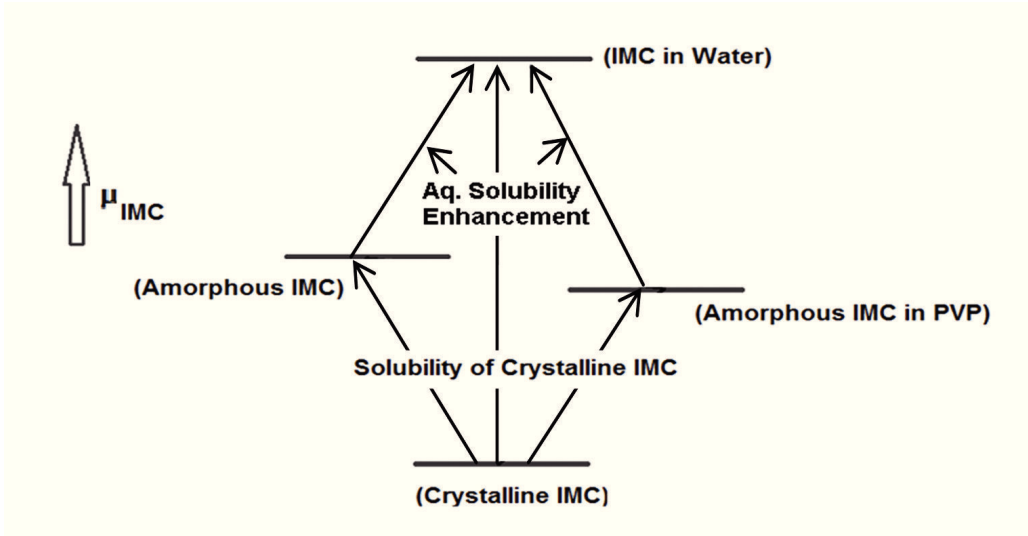


Figure 8. Thermodynamic states of interest in the design of amorphous formulations and the relative chemical potentials of the API (indomethacin) in each state. Reproduced with permission from reference [28].

Molecular dynamics simulations of amorphous indomethacin and indomethacin-PVP mixtures revealed that for pure indomethacin most of the carboxylic acid groups are involved in hydrogen bonding with other indomethacin molecules whereas with increasing PVP concentration these indomethacin-indomethacin hydrogen bonds are replaced with indomethacin-PVP hydrogen bonds (Fig. 9A). As a consequence, the calculated Flory-Huggins χ value of – 0.61 indicated that amorphous indomethacin and amorphous PVP are completely miscible, as others have verified experimentally. We then employed Murdande's value for the difference in free energy between amorphous and crystalline indomethacin [26] combined with our molecular dynamics simulations to estimate the relative solubility advantages of indomethacin/PVP mixtures as a function of the volume fraction of PVP, as shown in Fig. 9B. Note that the estimates in Fig. 9B have not included the effects of water sorption on the activity of the drug nor the effects of ionization upon dissolving. Water sorption into the amorphous solid would significantly reduce the solubility enhancements shown. With the inclusion of the effects of water sorption, this type of calculation could be very useful in the future for the design of amorphous formulations that can provide maximum aqueous solubility enhancement while avoiding phase separation in the solid matrix.

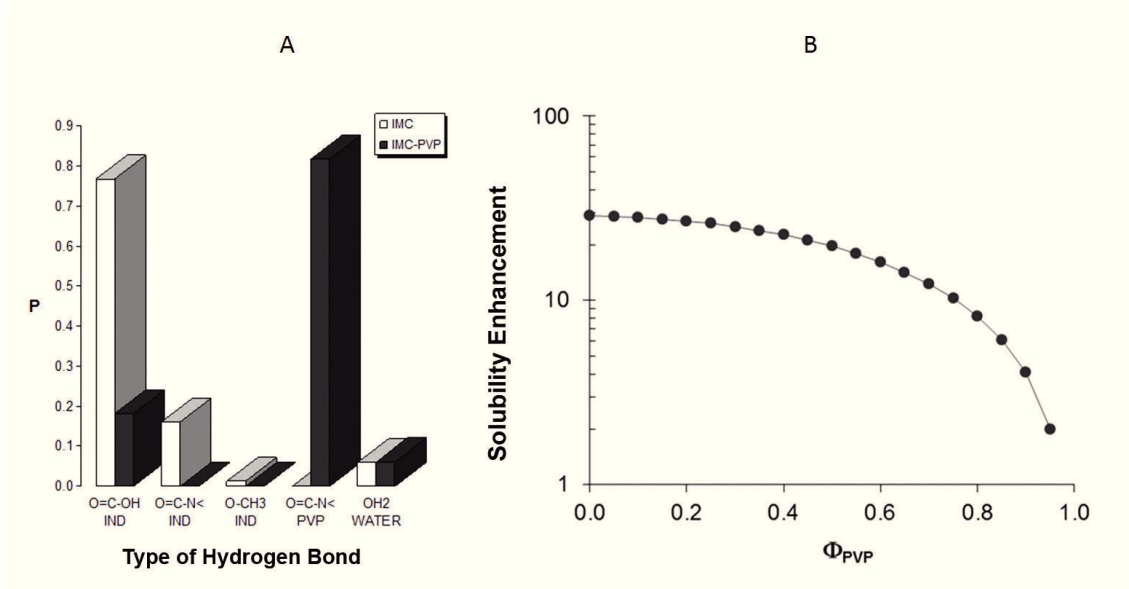


Figure 9. A) Probabilities for different hydrogen bond acceptor sites to form hydrogen bonds with the indomethacin -COOH in simulations of pure amorphous indomethacin (white bars) and in a 58%:41%, w/w indomethacin:PVP mixture (black bars) at 298 K. B) Predicted aqueous solubility enhancement for indomethacin from simulated indomethacin–PVP mixtures compared with $_{\gamma}$-crystalline indomethacin at 298 K. Reproduced with permission from reference [28].

While the theoretical equilibrium solubility enhancement produced by an amorphous form may account for the improved oral bioavailability for some amorphous pharmaceuticals, the stability of the supersaturated state resulting from the dissolution of an amorphous drug is also important in determining the oral bioavailability that is ultimately achieved. Ozaki *et al*. [29] recently demonstrated for five out of six amorphous compounds studied that the length of time that supersaturation could be maintained without crystal nucleation was the determining factor in the enhanced bioavailabilities observed. Thus, inhibiting nucleation or crystal growth may be very important for ensuring that amorphous formulations actually perform their intended function of enhancing oral bioavailability.

Inhibition of nucleation or crystal growth is often observed on dissolution of high energy dispersions in the presence of certain types of excipients, such as cyclodextrins or larger polymer excipients. We recently examined the crystal growth of indomethacin at both high and low degrees of supersaturation in the presence of known suspension concentrations of well-defined seed crystals [30-31] and the effects of three model excipients (hydroxypropyl-β-cyclodextrin (HPCD), polyvinylpyrollidone (PVP), and hydroxypropyl methylcellulose(HPMC E5)) on this process. The excipient effects were quite different from each other and very much dependent on the initial degree of supersaturation. The crystal growth inhibition results at high degrees of supersaturation (S>3) are illustrated in Fig. 10. In the presence of HPCD in solution at either 0.05% or 0.2% w/w the crystal growth of indomethacin was only slightly affected, leading to inhibition factors (R) for HPCD of slightly less than one (0.91 and 0.78, respectively). Both PVP and HPMC were highly effective at either concentration with inhibition factors well below 0.1. It is likely that surface adsorption will play a significant role on crystal growth

inhibition but quantitative models are lacking. However, there is a substantial ongoing effort in the pharmaceutical sciences community to elucidate the mechanisms and effectiveness of various crystal growth and nucleation inhibitors on maintaining supersaturation so one can look forward to significant progress in the future.

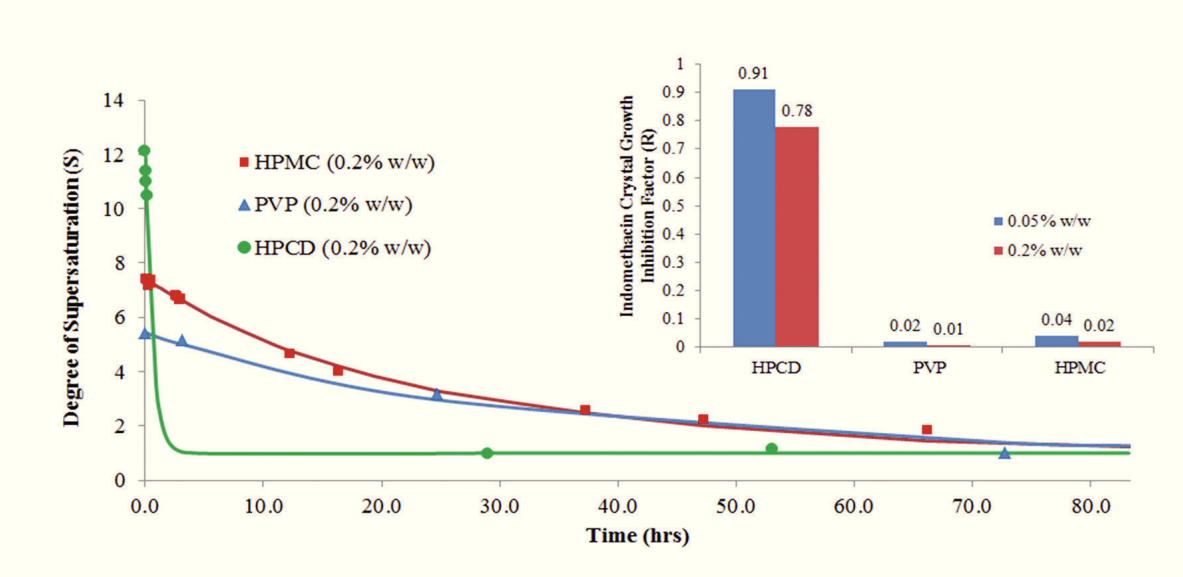


Figure 10. Effect of various excipients on indomethacin crystal growth measured by decreases in indomethacin concentration versus time from solutions at high degrees of supersaturation (S>3) in the presence of a controlled concentration of seed crystals. Inset: Crystal growth inhibition factors relative to suspensions containing no additive for HPCD, PVP and HPMC at 0.05% and 0.2% w/w concentrations.

5. Conclusions

The expanding number of drug candidates that exhibit poor solubility has led to significant advances in understanding of drug solubility and the development of new methods for solubilization for oral delivery. Along with these advancements has come an appreciation for the myriad of factors that determine drug solubility, particularly in those advanced drug delivery systems that may not be completely at equilibrium. Moreover, the dynamic environment oral delivery systems encounter in the GIT highlights the need to understand solubility not only as an equilibrium property but as a kinetic phenomenon whereby portions of the system of interest may be at equilibrium while others are not. The abilities to predict solubility and oral bioavailability solely from molecular structure of the drug and composition of the environment therefore remain attractive goals for future research.

6. References

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THERMODYNAMIC ACTIVITY OF DRUG AND FUNCTIONAL EXCIPIENTS IN TOPICAL DERMATOLOGICAL DESIGN

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Abstract

This paper describes an integrated process for the design of topical dermatological formulations. Firstly, the best drug in class is selected on the basis of skin penetration / potency, which ratio predicts its therapeutic potential. From an estimate of the skin penetration required for efficacy, a minimum therapeutic dose is predicted and this informs on solubility requirements for formulation solution systems. If enhancement of skin penetration is required above simple Level 1, saturated formulation design, Level 2 and Level 3 options exist. Level 3 systems, containing the drug at or near saturation and with functional excipients to increase drug solubility in, and diffusivity through the stratum corneum barrier, have the potential to enhance by a factor of 20-40 fold or more. This enhanced drug delivery leads to improved and robust efficacy, in cases where current treatments are marginally effective or there is variation between subjects due to pharmacogentic differences. In combination with low but rational drug doses, enhancement technologies may greatly reduce the potential for local and systemic adverse effects, essentially by retaining dose control within the formulation rather than within the skin.

Keywords

Absolute bioavailability, adverse effects potential, diffusion coefficient, dermal clearance, drug selection and design, enhancement strategy, enhancer dose, enhancer formulation, enhancers, formulation design, functional excipients, nonvolatile residual phase, partition coefficient, pharmacokinetic-pharmacodynamic, potency, rational dosing, saturation, selectivity, skin flux, skin penetration, skin target site, solubility, supersaturation, systemic clearance, topical dermatological therapy.

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1. Definitions

Historically, but with some few exceptions, topical dermatological formulation development has focused on Pharmaceutical Quality; the chemical stability of drug and key functional excipients and physical stability of the formulation. Throughout the 1980's and 1990's and later, it was common to conduct proof-of-principle clinical trials in which neither the clinical relevance of the drug class to the disease etiology nor the ability of the formulation to deliver an effective concentration of drug to the target site were known. Clinical failures propagated the use of irrationally high doses of applied drug, and with little understanding that dose applied and dose absorbed are very poorly correlated within the majority of topical dermatologicals. Finally, the aesthetics and tolerance of topical formulations were, and generally still are, barely considered, such that adherence to informed and prescribed dose regimens is poor. This flawed process has greatly impacted the clinical performance of current topical therapies. The Nobel Prize-winning HSV-1 antivirals, with outstanding specificity for infected human cells, are marginally effective when applied topically owing to their inability to achieve inhibitory drug concentrations during the early growth phase of the infection. Ironically, the first scientific publications of a rational topical dermatological pharmacokinetic-pharmacodynamic design process were described for topical antivirals. In other cases, notably the topical corticosteroids, topical therapy is very effective, but on highly permeable skin sites, such as the face and the anogenital region, absorption is increased by 10-40 fold such that there is potential for local adverse effects as dose absorbed increases to affect local fibroblast and keratinocyte cells. The response of the pharmaceutical industry has been to synthesise new molecules with greatly increased specificity [1], such that, although the skin site, rather than the formulation, still controls the dose absorbed, there is very much reduced potential for local adverse effects. However, rational drug and functional excipient dose selection and formulation design offer as much to improve the therapeutic potential of topical dermatologicals as does new drug discovery.

2. Dermatological product design

A Topical Dermatological Product is defined as one that is applied topically and designed to work within or just under the skin, as distinct from a Transdermal product, which is applied topically to work systemically. Figure 1 shows a cartoon of a Dermatological Product Design Map. From the bottom left to top right the design stages are described; drug design (or selection), formulation design and, finally, product design, in which the formulation and the packaging compete in an arena of consumer needs and competitive product claims and performance.

Here we will assume clinical relevance of the drug class and focus on the drug design components of drug potency and specificity, and local and systemic pharmacokinetics. Within formulation design we will focus on drug dose and drug delivery, and the selection and dose of functional excipients that affect these.

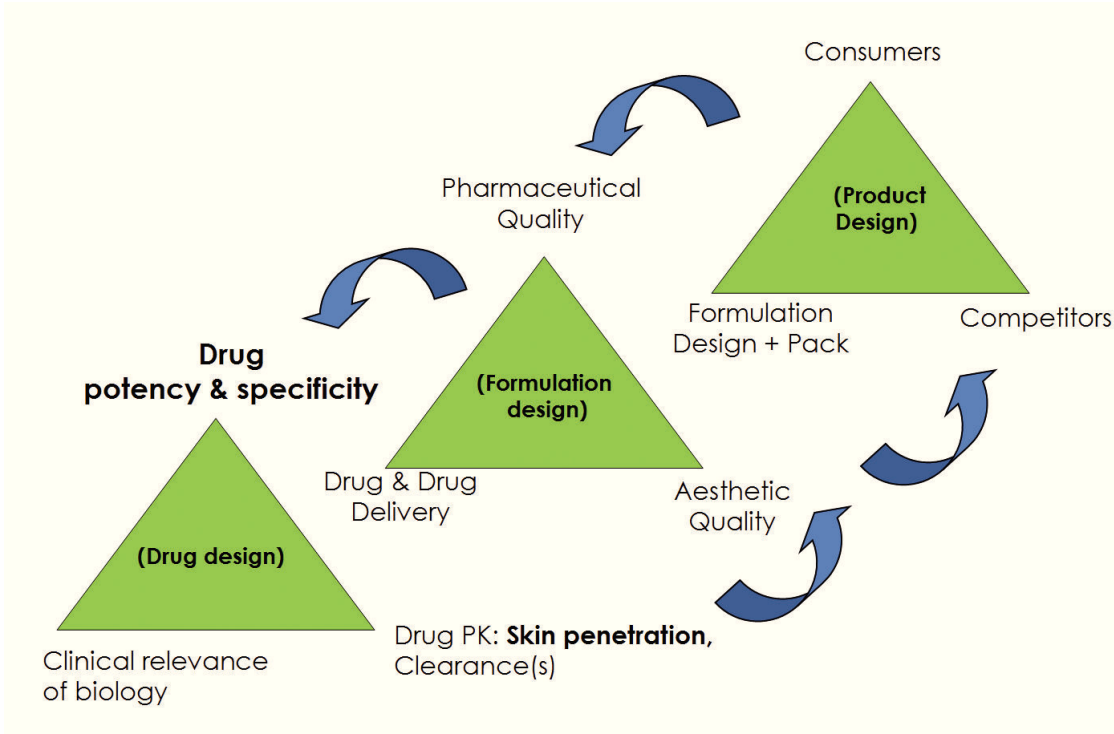

Figure 1. Dermatological Product Design map.

3. Dermatological drug design

In dermatological design, identification of the lead drug candidate, together with its potency and estimates of topical dose and intrinsic skin penetration are essential. Figure 2 shows a cartoon of the skin and target sites for various skin diseases. Whatever the disease and associated skin target site, all that is needed to ensure efficacy is *to achieve and sustain pharmacologically active drug concentrations at the target site in the skin*. Intuitively, the terms *drug concentration* and *pharmacologically active* lead to consideration of pharmacokinetic-pharmacodynamic (PK-PD) models.

A simple steady state PK-PD model has been widely used in the design of transdermal delivery systems. Considering drug plasma levels, constant at steady state, then drug input equals drug output and:

$$\text{Flux} * \text{Area} = C_{plasma} * Cl \qquad \text{Equation 1}$$

where flux is the rate of skin penetration in mass/cm^2/time, A is area of application in cm^2, C_{plasma} is in mass/cm^3 and Cl is systemic clearance in volume/time. An efficacy index is defined as C_{plasma} / $C_{plasma\ IC50}$ and when C_{plasma} = $C_{plasma\ IC50}$ the efficacy index =1.
Rearranging Equation 1 and substituting C_{plasma} for Efficacy Index * $C_{plasma\ IC50}$ we get:

$$\text{Flux} / C_{plasma\ IC50} = \text{Efficacy Index} * \{Cl/A) \qquad \text{Equation 2}$$

Thus, the ratio flux / $C_{plasma\ IC50}$ (a measure of potency) is proportional to Efficacy (Index) linked by the pharmacokinetic term Cl/A. Again this is intuitively correct. The higher the flux and the lower the potency term (expressed, for example, as an IC_{50} concentration) the higher is the ratio flux / $C_{plasma\ IC50}$ and the higher the probability of efficacy.

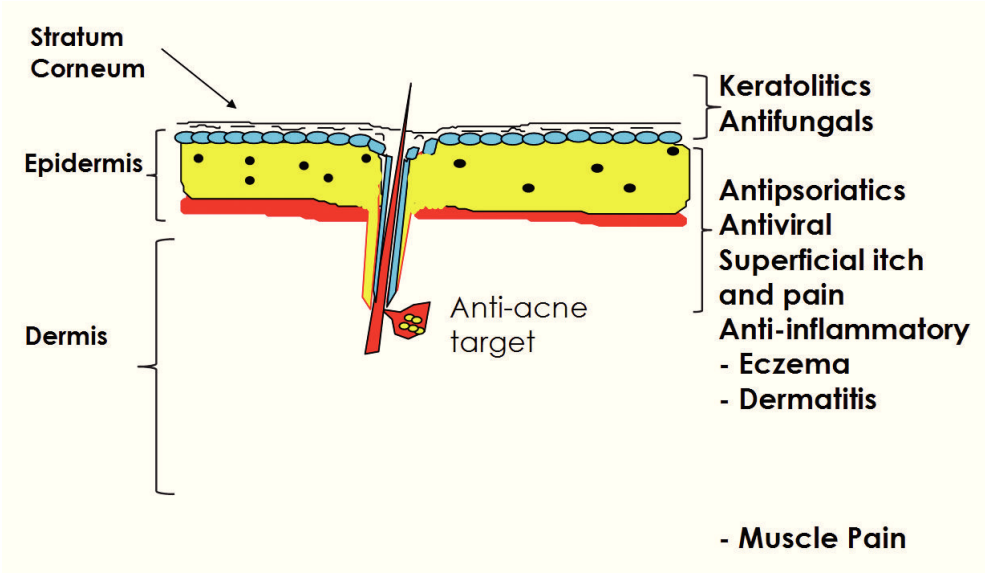

Figure 2. Target sites for various drug classes within the skin.

Several authors have used the ratio flux/potency to rank the therapeutic potential of compounds within the same drug class.[2,3]. For example, Freeman and Spruance [2] show a linear correlation between reduction in viral skin lesional area and log_{10} of an *in vitro* index, defined as J/ID_{50} where J is the *in vitro* skin flux and ID_{50} is the drug concentration that inhibits HSV-1 viral growth by 50% *in vitro*.

Table 1 below, is adapted from Mertin and Lippold [3] and shows the flux and potency of a series of nail antifungals. The far right column shows the efficacy coefficient, the ratio of flux / *in vitro* antifungal potency. There is a considerable difference in the efficacy coefficient, showing the importance of selecting the right compound from the class as a topical development candidate. Also, the efficacy coefficient values are only rankings (high to low in Table 1) such that all, none, or just the top few may exhibit meaningful clinical efficacy. However, Amorolfine and Ciclopirox are commercially available and have been shown to be efficacious in clinical studies. Thus, the simple ratio of flux to potency, especially used with a clinically effective benchmarked compound, can give valuable insight into efficacy potential.

Table 1. Flux and potency of MIC (potency) a of series of antimycotic antifungals.

Antifungal	Flux,J, mg/cm²/s (saturated)	Potency (MIC) mg/L	Efficacy ranking
Amorolfine	2.15 x 10^{-4}	0.01	2.15 x 10^{-2}
Naftifine	5.38 x 10^{-4}	0.55	9.78 x 10^{-4}
Econazole	4.74 x 10^{-5}	0.35	1.35 x 10^{-4}
Ciclopirox	1.98 x 10^{-4}	2.0	9.87 x 10^{-5}
Bifonazole	1.39 x 10^{-8}	0.1	1.39 x 10^{-7}
Clotrimazole	7.77 x 10^{-8}	2.3	3.38 x 10^{-8}
Ketokonazole	5.85 x 10^{-8}	2.23	2.62 x 10^{-8}
Griseofulvin	7.56 x 10^{-8}	3.1	2.44 x 10^{-8}
Tolnaftate	3.36 x 10^{-9}	0.55	6.11 x 10^{-9}
Nystatin	4.02 x 10^{-9}	4.5	8.93 x 10^{-10}

Those readers interested in the development of dermatological pharmacokinetic-pharmacodynamic models are referred to Amanidis *et al*.[4] and references therein. Cordero *et al*.[5] measured the *in vitro* human skin flux and *in vitro* COX-2 inhibitory activity of a series of nonsteroidal antiinflammatory (NSAID) compounds and derived equations 3 and 4 for the ITAA (Index of Topical Antiinflammatory Activity; also generally referred to as ITA, Index of Topical Activity)).

$$\text{Flux} / IC_{50} \text{ potency} = \text{ITAA(ITA)} * \{2D_d/h_d) \qquad \text{Equation 3}$$

Where D_d is the dermal diffusion coefficient and h_d is the thickness of the dermis. Rearranging:

$$\text{ITAA(ITA)} = \text{Flux} / IC_{50} * h_d / 2D_d \qquad \text{Equation 4}$$

From equation 4, ITAA has no units as $m*t^{-1}*cm^{-2}$ / $m*cm^{-3}$ * cm / cm^2*t^{-1} is dimensionless. Also, it is important that units are consistent, for example, flux is in ug/cm²/hr, IC_{50} is in ug/cm³, h_d is in cm and D_d is in cm²/hr. Cordero *et al*. use a value of 0.02 cm (200µm) for h_d, 0.036 cm²/hr ($1*10^{-5}$ cm²/second) for D_d and thus, for diclofenac where flux is 1.4 ug/cm²/hr and IC_{50} is ~0.009 ug/cm³ (~0.03 µM) then ITAA = 1.4 / 0.009 * 0.02 /2*0.036 which equals 43.8 as shown in Table 2, column 4. Table 2 uses a traffic light metaphor; in which those compounds with ITAA significantly greater than one, and thus candidates for development, are shown in green.

Thus, we have available two related methodologies for estimating the efficacy potential, for example, of a portfolio of drugs, to determine the lead candidate. The ratio of flux rate, determined *in vitro* from saturated non-enhanced solution systems, to *in vitro* potency, either alone compared with a clinical benchmark or using equation 4 of Cordero *et al*.[5] can be used to estimate efficacy potential. If the ITAA is somewhat less than 1.00, for example, in the range 0.1-1.0 or below, there is the option to use skin penetration enhancement technologies in formulation design.

Table 2. Flux and potency to calculate ITAA (or ITA).

NSAID	Flux, J ug/cm²/hr	IC_{50} (COX-2), uM	ITAA
Diclofenac	1.4	0.03	43.8
Ketorolac	13	0.38	37.2
Ketoprofen	16	0.74	23.6
ITAA when predicted free drug concentration in dermis is equal to drug IC_{50}			1.00
Tenoxicam	0.7	55.26	0.01
Piroxicam	0.08	34.9	0.002

4. Dermatological formulation design: Estimate of minimum dose

Firstly, it is desirable to design dermatological formulations as drug solution systems, thus to avoid any potential for slow drug release; for example, as a result of a dissolution process. From this, because drug solubility in the vehicle is an important determinant of partition of the drug into the skin, it is necessary to get an early estimate of the drug dose. Table 4 shows how equation 5 can be used to calculate a minimum topical dose. From equation 3 and where ITAA =1:

$$\text{Flux} / IC_{50} \text{ potency} = \{2D_d/h_d\}$$

Rearranging:

$$\text{Flux} = IC_{50} \text{ potency} * \{2D_d/h_d\} \qquad \text{Equation 5}$$

Table 4 column 1 shows the potency values for a series of compounds. Numbers are rounded for clarity of process. In column 2, the potency value is multiplied by an estimate of $2D_d/h_d$ of 2.0, to give an estimate of the flux required to achieve and sustain a free drug IC_{50} concentration. Then, assuming a 10-hour dose interval and minimum mass of drug per cm^2 of skin is calculated. Finally, assuming that the whole formulation (gel or cream) is dosed at 2mg of formulation/cm^2 of skin, the drug concentration in the whole formulation can be calculated. Using hydrocortisone as an example, 5ng/cm^3 potency times 2 gives a predicted flux required for efficacy of 10ng/cm^2/hour which, over 10 hours, is 100ng/cm^2. 100ng in 2mg is 100/2,000,000*100 = 0.005% w/w. Although this value seems at first to be incredibly low compared with concentration of hydrocortisone currently used in the range 0.5-1.0% (column 5, Table 3), it is very close to estimates of their absolute bioavailability. For example, 0.5% at 1% absolute bioavailability (“99% is lost” Maibach [6]) equates to 0.005% w/w. This, of course, is the very minimum dose associated with efficacy, but based on these dose estimates, for example, times 5-10 fold, might be used as first estimate for formulation design. It is also useful at this stage of formulation design, to estimate drug systemic exposure potential; for example, using equation 1. or as a worst case analysis based on (total) drug concentrations in the product

and knowing the area of skin application. Depending upon the indication and its severity, which define skin area, and drug systemic clearance, there may be a case to work with doses nearer to the minimum dose.

Table 3. Calculation of minimum dose based on equation 5.

Drug potency Ng/cm³	**Flux, J#, for efficacy in dermis: ng/cm²/hr**	**Dose/ cm²/10hr: ng**	**% in product @ 2mg/ cm² (A)**	**Drug %age in typical products (B)**	**Estimate of bio-availability %(A)/(B) x 100**	**Drug example with this potency**
Calculation	Potency *2Dd/hd (= ~2)	Flux *10	Dose/10hr/ 2,000,000* x 100			
0.05	0.1	1	0.00005 %	0.005-0.05 %	10.-0.1 %	Fluticasone propriate (Cutivate)
0.1	0.2	2	0.0001 %	0.025-0.1 %	0.4-0.1 %	Retinoic acid (Retin-A)
0.5	1.0	10	0.0005 %	0.03-0.1 %	1.67-0.5 %	Tacrolimus (Protopic)
5	10	100	0.005 %	0.5-1.0 %	1.01-0.5 %	Hydrocortisone (generic)
250	500	5,000	0.25 %	5 %	5 %	Ibuprofen (generic)

5. Dermatological formulation design: Enhancement strategies

Figure 3 shows a cartoon of the skin penetration diffusional process after Higuchi.[7] Considering only passive skin penetration enhancement technologies, Fick's First Law, equation 6, describes the diffusion process across the stratum corneum barrier, and thus the enhancement technology options.

F = **Cv * Pc * Dc** /h (Equ. 6) and as **Pc =** $\frac{\textbf{satsol Sc}}{\textbf{satsol V}}$ then F ~ = **Cv *** $\frac{\textbf{satsol Sc}}{\textbf{satsol V}}$ *** Dc** /h

and as $\frac{\textbf{Cv *}}{\textbf{satsol V}}$ **= DSv**, F~ **DSv * sat sol Sc *Dc** /h Equation 7

Thus, skin penetration of drug from a formulation is dependent upon its degree of saturation within the vehicle, **DSv**, its solubility in the stratum corneum **sat sol Sc** (which may be increased by inclusion of solvents such as propylene glycol) and its diffusion coefficient within the stratum corneum **Dc** (which may be increased by inclusion of, typically, C_{10}-C_{14} fatty acid derivatives).

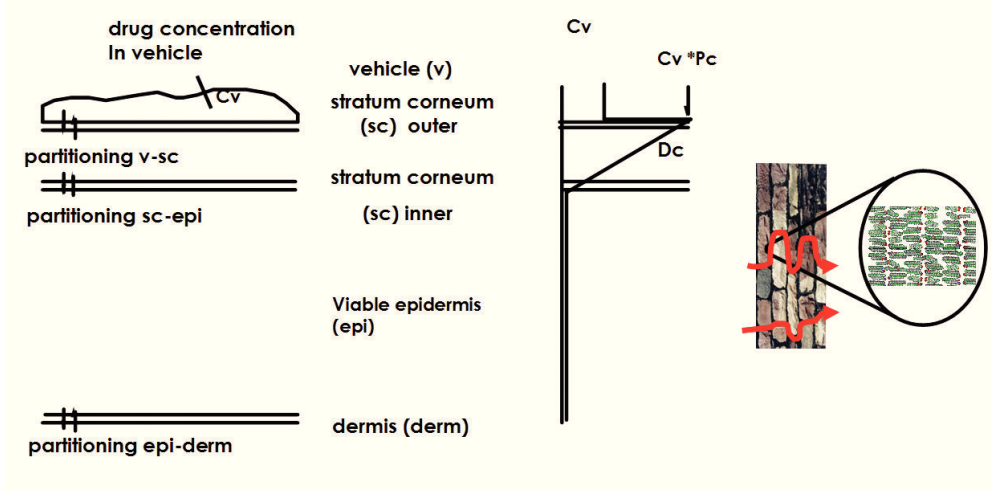

Figure 3. A cartoon of drug diffusion across the stratum corneum barrier, after Higuchi (1960).

There is one other important design consideration; that these technologies should be optimised within the residual non-volatile phase of the total formulation. Indeed, it is desirable to formulate topical dermatologicals as the residual phase and then to "disguise" these into gels or creams by addition of suitable volatile excipients. Figure 4 shows a cartoon of this process.

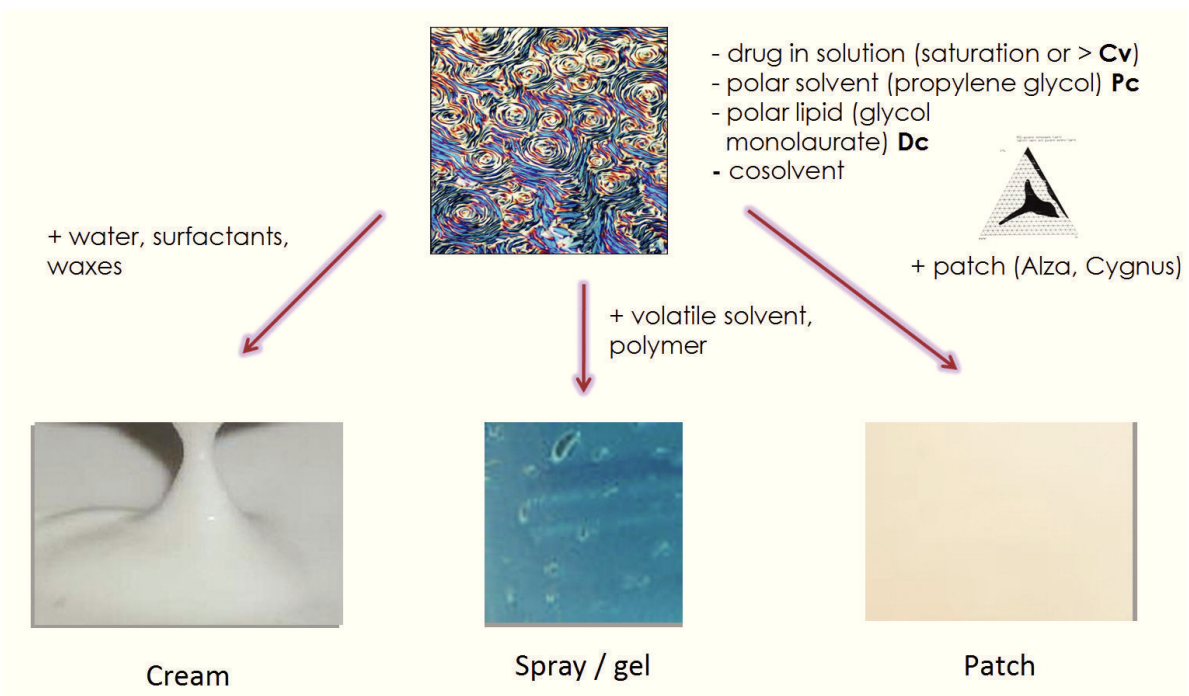

Figure 4. A cartoon of formulation design based on design of non-volatile residual phase and subsequent formulation formatting.

Historically, the three enhancement technology-strategies **DSv**, **sat sol Sc** and **Dc** have developed and been integrated with time. For example Level 1, Level 2 and Level 3 technologies, broadly associated with the 1950-70's, 1980-90's and 1990's to date, respectively, can be described:

- ***Level 1:*** *Drug at or near saturation or supersaturated in the residual phase (DSv technology)*
- ***Level 2:*** *Drug at or near saturation or > AND high level of polar solvent (DSv + sat sol Sc technology)*
- ***Level 3:*** *Drug at or near saturation or > AND high level of polar solvent AND a fatty acid derivative (DSv + sat sol Sc + Dc technology)*

Level 1: In the late 1960's Poulsen *et al*.[8,9] described the use of drug saturation and supersaturation to enhance the skin penetration of flucinolone acetonide and its acetate ester. More recently, as shown in Figure 5, Davis and Hadgraft [10] have shown that *in vitro* transport of hydrocortisone acetate is linearly proportional to degree of saturation over the range DSV 0.25-8.00.

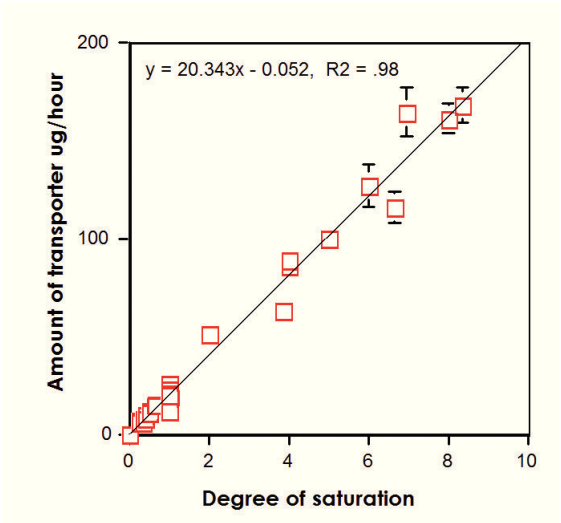

Figure 5. Linear transport of hydrocortisone over the range DSv 0.25-8.00: transport from saturated –supersaturated solutions, $Cv_{sat\text{-}ssat}$ L1 technology.

Various techniques are available for use in the formation of saturated and supersaturated states in topical dermatologicals [11].

Figure 6 shows the qualitative formulation of Dovonex lotion (0.005% calcipotriene). The second column shows the excipients, and it is difficult from this alone to understand that Dovonex lotion is a Level 1 technology. However, column 3 shows that the residual phase is essentially calcipotriene dissolved in propylene glycol. All the information that is needed to design this system is the solubility of calcipotriene in propylene glycol. Especially given the rational dose used of 0.005%, this a simple, but beautifully elegant example of topical formulation design.

Dovonex® (calcipotreine) 0.005%

Function	Whole vehicle	Residual phase
Oil phase	-	
Structuring system (gellant)	Hydroxypropyl cellulose	Hydroxypropyl cellulose
Aqueous solvent phase	Isopropanol Purified Water Propylene glycol Menthol	Propylene glycol (glycerol) = antinucleant polymer
Buffer system	Sodium citrate	-
Preservative	-	-

Lotion 0.005% L1

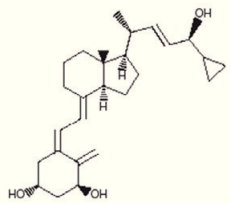

Figure 6. Design of Dovonex® lotion as a Level 1 residual phase technology Dovonex® is a registered trademark of Leo Laboratories Limited.

Level 2: A variety of solvents including propylene glycol [12], ethanol [13] and Transcutol® [14] have been shown to increase stratum corneum solubility and skin penetration of a range of drugs. These solvents were widely used in the 1980-90's to increase the skin penetration of antiviral, antifungal and nonsteroidal antiinflammatory drugs from topical formulations. Figure 7 shows a more recent example, in which increasing concentrations of propylene glycol were shown to increase the stratum corneum concentration of ibuprofen from saturated solutions.

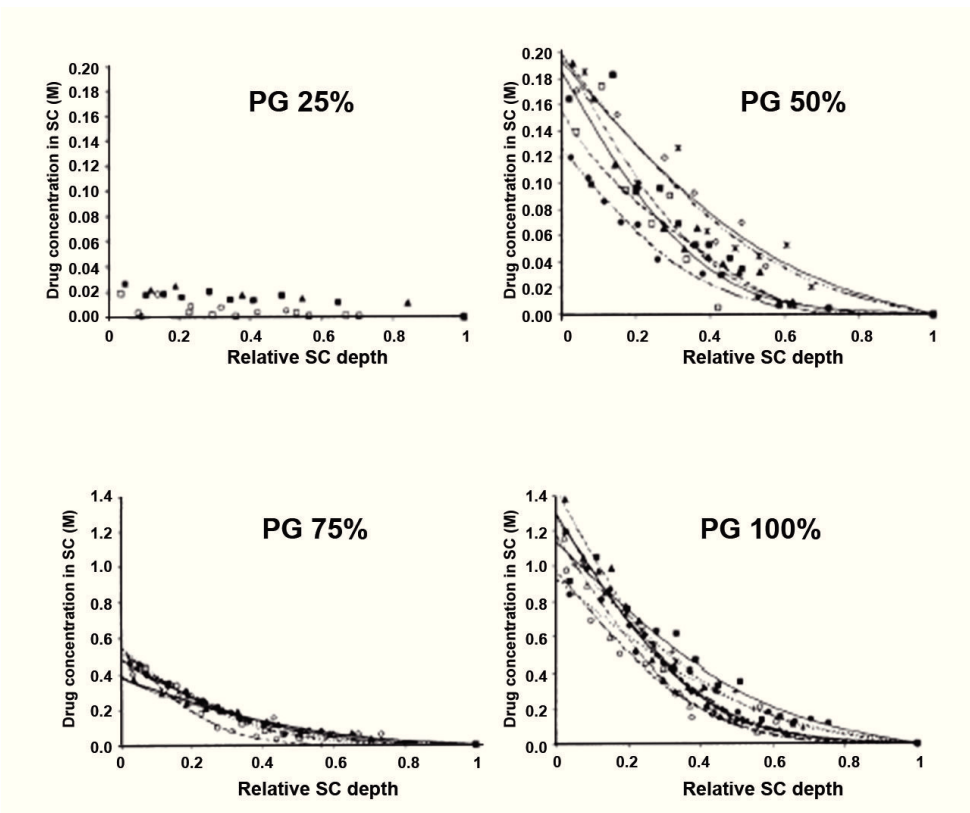

Figure 7. Increase in ibuprofen uptake into stratum corneum dependent upon propylene glycol concentration, DSv + sat sol sc L2 Technology, by Herkenne et al, [12].

Level 3: DSv + sat sol sc +Dc L3 technology was developed for use in Trandermal patches in the 1990's. Figure 8 shows that low concentrations of isopropyl myristate (C_{14} ester) are able to very significantly increase the skin penetration of diclofenac sodium compare with 40% propylene glycol alone (Cv + sat sol SC + Dc L3 technology) from Arellano A *et al*.[15].

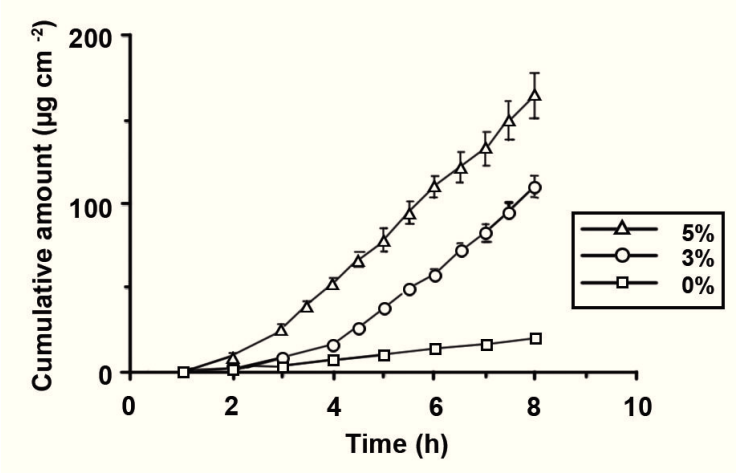

Figure 8. Isopropyl myristate increases the skin penetration of diclofenac sodium from 40% propylene glycol solutions, (Cv + sat sol SC + Dc L3 Technology) from Arellano A, et al. [15]

Combinations of fatty acid derivatives with propylene glycol were very extensively studied by Aungst *et al*. [16] in the early 1990's. In comparative studies on the efficacy and irritancy potential of fatty acid derivatives, Aungst used a fixed concentration of 10% fatty acid derivative in propylene glycol. Although these early studies gave great insight, in retrospect, they are flawed in that the solubility of fatty alcohols, fatty acids and fatty acid esters is very different in propylene glycol. This leads to two important design considerations. Firstly, it is important to consider the dose of the fatty acid derivative needed and this may be addressed by measurement of fatty acid derivative flux across the skin [17] Secondly, and in the same way that it is important to ensure drug saturation, it is important to ensure saturation of the fatty acid derivative within the formulation residual phase [18]

Level 3 systems, designed using these principles, are able to provide a 20-40-fold or more increase in skin penetration and thus deliver the therapeutic potential of lead candidate compounds whose skin penetration / potency ratio are somewhat less than optimum.

Table 4 shows the formulation of a simple gel system to exemplify these principles. Column 3 shows the residual phase. Consideration is given to the dose of propylene glycol [19] and also to the dose of the fatty acid derivative. The ratio of propylene glycol:cosolvent:fatty acid derivative (89:10:1) is such that the fatty acid derivative is just on the miscibility phase boundary. Also, the design ensures that the drug is at saturation or above in the residual phase. Thus, the ratios of water:ethanol ensure drug solubility in the whole gel, but on loss of the volatile solvent supersaturated solution may be formed, pseudo-stabilised with an antinucleant polymer.

Table 4. A simple gel using sat-supersat Level 3 formulation design principles.

Ingredients	0.1%*Gel 100gm	Residual phase	Function
Active	0.01	0.10 (0.31)	Active
Propylene glycol	26.70 (89)	26.70 (89)	PC enhancer
Cosolvent	3.00 (10)	3.00 (10)	Cosolvent
Fatty acid derivative	0.30 (1)	0.30 (1)	DC enhancer
Ethanol	40.00	-	Volatile solvent
Water	27.90	-	Volatile non-solvent
HPMC 613	0.25	0.25	Anti-nucleant
Carbopol Ultrez -10	1.00	1.00	Alcohol tolerant gelation system
Phenoxyethanol	0.50	0.50	Preservative
Triethanolamine to to pH 6.50 +/- 0.5	0.25	0.25	pH adjustment
Total (xl)	100		

6. Dermatological formulation design: Therapeutic benefits

Topical dermatological products, based on best-in-class drug selection and appropriate and optimised passive drug delivery technologies, have the potential to greatly improve topical therapy. Clearly, enhanced drug delivery may result in improved and robust efficacy, where current treatments are marginally effective or there is variation between subjects owing to pharmacogentic differences. Also, for example with topical corticosteroids, dose rationalisation in combination with optimised passive drug delivery technologies, may greatly reduce the potential for local and systemic adverse effects, essentially by retaining dose control within the formulation rather than within the skin. Low-dose formulations of absolute bioavailability of around 50%, both safe and effective applied at normal trunk and body skin sites, can do no more than double the dose delivered, even when applied to skin sites with grossly impaired barrier function.

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THE CRITICAL ISSUE OF COMPLIANCE - FORMULATING TOPICAL PRODUCTS FOR COSMETIC ACCEPTABILITY

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Abstract

AG Lafley, the CEO of the Procter & Gamble Company once said, "*People remember experiences, they don't remember attributes or benefits...*". This author agrees passionately and his assertion is that the question, "*What will make the use of my product a delightful experience…?*" is every bit as important as, *"What is the best technical benefit I can deliver…?*". Why so? First of all, from the pure viewpoint of driving the business. Marketing drives trial and purchase, but experiential delight drives retrial and loyalty. Secondly, because of technical efficacy. Efficacy can be defined as the product of activity, delivery and use. Let us assume that we in R&D have done our jobs properly and that we have superior activity in a topical form which can be delivered effectively. All of this, however, comes to nothing if there is zero use (or, in dermatological terms, there is "no compliance") as this equals zero efficacy. Likewise, lower use (or "lower compliance") equals lower efficacy.

To answer the question, "*What will make the use of my product a delightful experience…?*", we will consider briefly four main drivers which can be manipulated:

- Product application profile
- Acute skin appearance
- Fragrance
- Packaging and the "First Moment of Truth"

Keywords

Digital image, emollient, fragrance, packaging, polymer, sensory, topical, tribology.

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1. Product application profile

Any formulator will be familiar with a classic trade-off which exists between technical performance and consumer acceptance. Most will know the glycerine paradigm where superb hygroscopicity is countered by extremely challenging aesthetics. There are two main aesthetic product killers, summarised by the consumer terms “Greasiness" (one often also hears the terms “coated”, “heavy”, “slow absorbing”), and “Stickiness” (or “Tackiness”).

Greasiness is driven typically by emollient oils / waxes and Tackiness by humectants and polymers. Can these properties be measured objectively? To a certain extent, yes. Emollients can be classified by two basic properties, Spreadability and Lubricity. Spreadability may be indexed *in vitro* by measurement of contact angle on a suitable substrate, while Lubricity may be measured by a variety of methods (many derived from the oil industry!). This takes the R&D scientist automatically into the realm of Tribology, the study of interacting surfaces in relative motion. As such, understanding and befriending the Stribeck Curve (Figure 1) and the various forms of lubrication (Boundary, Mixed and Hydrodynamic) is advisable. In terms of the measurement of lubrication, this author remembers using a Soda Pendulum, although happily there now exist a number of superior modern instruments and the reader is directed to, e.g., the excellent PCS Instruments company in this respect.

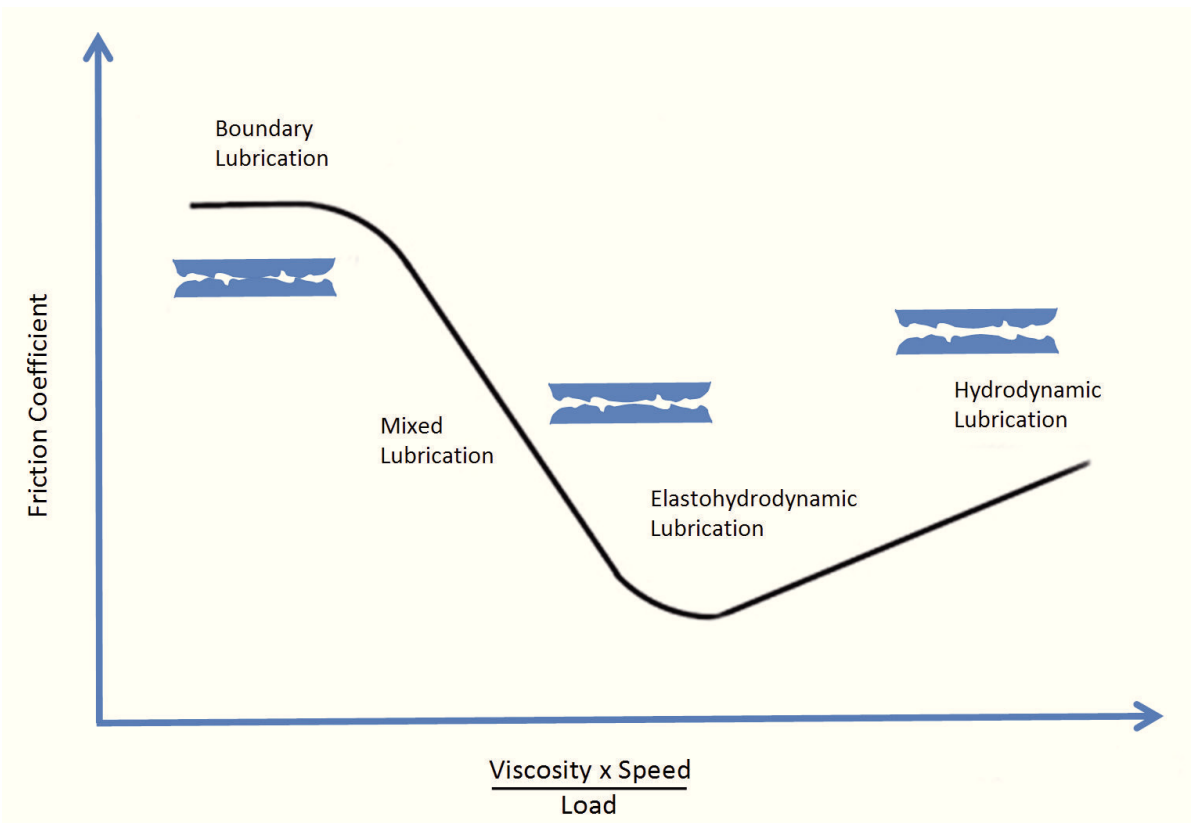

Figure 1. The Stribeck Curve.

Sticky materials have a relatively high tack potential, typically with a low elastic modulus relative to that for “critical energy release rate”, allowing intimate contact with the surface and the formation of bridging fibrils (i.e., they have some flow at high tensile stress) [1]. Low-tack systems seem to be characterised by efficient edge and internal crack propagation leading to rapid de-bonding of surfaces. High-tack systems, in contrast, seem to be characterised by bulk cavitation phenomena and the formation of bridging fibrils in the de-bonding process. Remarkably, consumers claim they are often able hear as well as feel tack, which may well be attributable to cavitation. Humectant-polymer interactions are often the chief suspects in high tack systems. During dry-down, the evaporation of water from the product chassis leads to an often dramatic increase in relative polymer / humectant concentrations. The humectant may, thus, become a preferential solvent for the polymer backbone, converting a low-tack microgel into a highly viscous network.

What options are available to the formulator to reduce stickiness / tackiness? Strategies include changing to polymers for which glycerin (or other agents) is not the ideal solvent, the use of highly cross-linked polymers not capable of swelling easily and the use of associatively-thickening polymers. Beyond manipulation of polymers, the use of particles can also transform the perception of tackiness / stickiness in topical products. These materials sit in and above the product film and act probably to promote internal crack propagation, more rapid de-bonding and a reduction in fibrillation.

How can one measure sticky / tacky skin feel? This author has experience of *in vitro* tribological instrumentation (PCS Instruments), and the *in vivo* use of Tribometers and a variety of different friction meters. Beware, however, that *in vivo* measurements are often complicated by the fact that the static and dynamic friction coefficient of the stratum corneum surface increases because of hydration and associated swelling.

Having reviewed aesthetic product killers and their mechanisms and objective measurement, the importance of Sensory Science and the use of the human senses as calibrated instruments in their own right needs to be emphasised. Descriptive Analysis methodologies emerged in the 1950’s, as methods used first by the food industry (where the method is still most common). A complete methodology for descriptive analysis was first proposed in 1974 in the U.S.A. and, today, there are now published ANSI and ISO standards for skin creams and lotions [2], [3].

In the case of a topical product, the sensory chain proceeds in the following manner. The output of our sensory systems (vision, olfaction, somatosensory, audition) leads to Perception (e.g., "I see it", "I smell it", "I feel it", "I hear it") and, finally, to Judgement (e.g., "feels soft", "looks good", "I like it!"). Consumer judgement, therefore, is by nature *integrated* - involving integrated multiple sensory systems, integrated multiple sensory characteristics of a sensory system, the integration of liking with intensity. Sensory methods, in contrast, are *analytical*. They attempt to isolate the perception step, disentangling different sensory systems, defining discrete sensory attributes in a system and ignoring "hedonic" response, assessing intensity only (Figure 2).

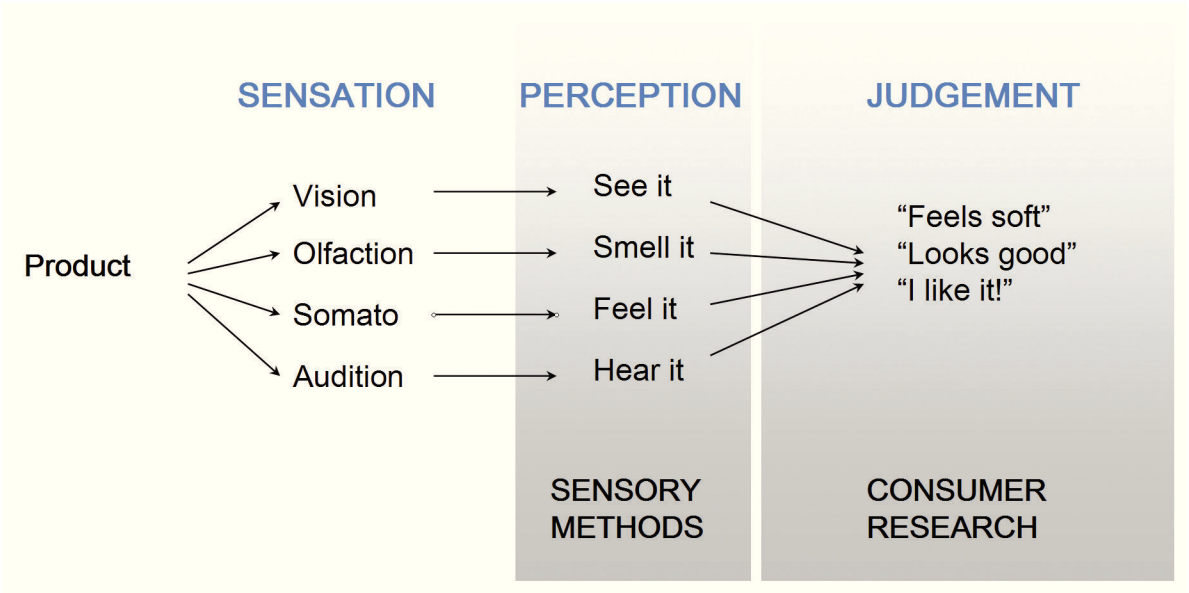

Figure 2. The flow of human sensory information.

A hierarchy of sensory methods can be drafted, therefore. Starting at the bottom of the pyramid, firstly, Consumer Panels output Liking in consumer terms. Second, Experienced Consumer Panels output Liking and Strength of Response in consumer terms. Thirdly, Laboratory Panels output Liking and Strength of Response in basic sensory terms (Figure 3). Finally, Descriptive Panels output Strength of sensory terms. Through the pyramid, therefore, one moves from integrated judgement to trained diagnosis - and it is this latter process, of course, that is the most useful to the R&D scientist.

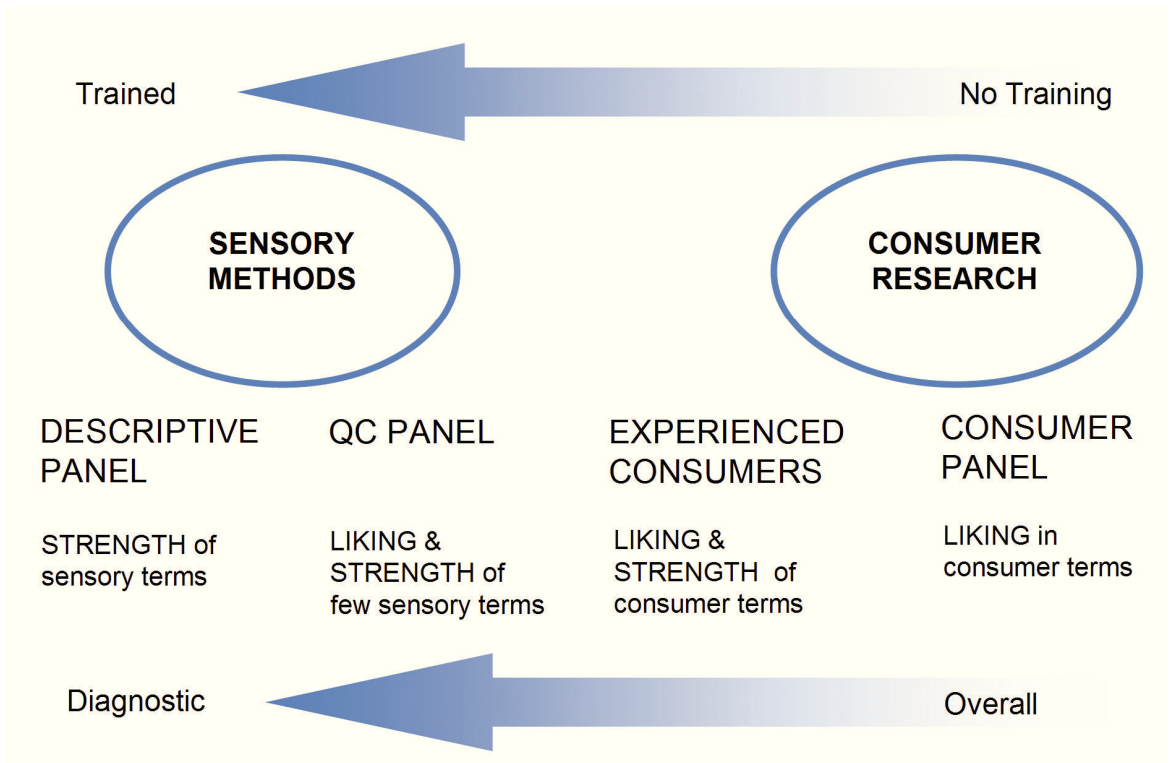

Figure 3. The unique characteristics of Sensory Methodology.

A simple case study illustrating the power of product application profile can be found in the development of Olay Daily UV Protectant (DUVP) in the early 1990's by the Procter & Gamble Company. DUVP was the first daily moisturiser to contain SPF15 protection from solar UVR. The drive to develop this technology was the growing body of data in peer-reviewed journals indicating that casual exposure to erythemally-effective UVR in ordinary daylight was responsible for the majority of skin cancer and ageing. The challenge in this project was developing a light daily moisturiser incorporating high concentrations of sunscreen raw materials with challenging aesthetics. Apart from issues with cost and skin compatibility, aesthetics and skin feel were a core focus of the development team as these are the key to compliance - and, in this case, compliance is critical as the SPF test is conducted at a given dosage rate ($2mg/cm^2$) that must be achieved to provide full protection. Taking the four main classes of sunscreen materials, polar oils are typically described by consumers as “greasy and heavy”, oil-soluble crystalline solids (requiring high levels of solvent) are typically “greasy”, water-soluble salts (countering thickeners and requiring more polymers) are typically “greasy and heavy" and insoluble particulates are typically “draggy and dry”.

Overcoming sunscreen compliance issues can be tackled via two main routes, firstly through the use of more efficient systems, that is, extracting more efficacy from lower levels of sunscreen. Greater efficiency may be achieved by, e.g., (i) the use of film-formers / shear-thinning emollients (ii) by combining oil and water-soluble sunscreens in one formulation (iii) the use of photostable sunscreens / sunscreen combinations. The second route to address sunscreen compliance is via improving skin feel by e.g., (i) the use of particulates or oil-soluble film-forming thickeners to reduce greasy skin-feel (ii) the use of silicone emollients to reduce the draggy skin-feel of ZnO, TiO_2 (iii) the use of alternative product forms (e.g., rub-free sprays).

Using a combination of these approaches, Olay DUVP was formulated to provide a skin feel profile parity with an equivalent moisturiser containing no sunscreens, with excellent consumer acceptance. The product remains a best-seller to this day and seminal longitudinal research performed by Dr Adele Green in Queensland, Australia [4] now confirms that compliant use of a daily moisturiser containing only a moderate level of sun protection (SPF15) is highly effective in the prevention of squamous cell carcinoma, malignant melanoma and photoageing.

2. Acute skin appearance

The majority of information used to make sense of the world around us is derived from vision and, unsurprisingly therefore, the battle for compliance can be won or lost within 5 minutes of the first application of a topical leave-on product due to undesirable acute changes in skin appearance. These changes include increased shine (due to increased specular reflection), matting (due to increased diffuse reflection), streaking (due to localised linear concentrations of optically-opaque product residue) or whitening (back-scatter of white light, often from metal oxides). A means of capturing and quantifying this appearance is, therefore, a very powerful aid to technology design to assure hard-won consumer trial is not squandered needlessly.

The invention of the Charge-Coupled Device and advent of the modern digital camera brings many benefits to the researcher including, (a) excellent quantum efficiency, giving superb sensitivity to low intensity light without loss of resolution, (b) instant access to the image, allowing real-time quality control, (c) potential black / white and colour calibration, allowing full confidence in image stability, even in studies spanning months or years, (d) a truly stable permanent record (in contrast with the inevitable degradation of celluloid film stock and prints over time) and (e) the effective elimination of unavoidable variation in the development process and celluloid film specification.

Theoretical technical digital image quality driven by either modern camera optics or CCD resolution is no guarantee, however, of faithfully capturing either (a) a true record of skin condition or (b) a treatment or time-related change in skin condition. Too many supposedly standardised image pairs that are meant to show a treatment or time-related difference are fundamentally flawed by combinations of poor lighting control, variable subject position, magnification changes, differing backgrounds or distractions within the image including clothing and jewellery.

If only one rule is adopted for effective use digital imaging in the Product Development process, it should be this – reproducibility. Put differently, when using digital imaging as a serious documentation and / or measurement tool, the only variable one actually desires is the passing of time or the effect of a treatment. Factors that need tight control include (a) incident angle of illumination (b) stability of flux and spectral power distribution of the light source (c) black / white / colour calibration (d) reproducibility of subject position. While there is much that could be written about this, the reader is directed to texts by this author [5] on the subject but also, more practically, to the variety of imaging systems available today which include all the above controls. In particular, this author recommends technology developed by the Canfield Scientific company (Figure 4).

Figure 4. The Canfield Scientific VISIA™ facial imaging system.

Digital images captured in such a reproducible manner may then be subjected to a variety of different measurement techniques, including subjective analysis by expert or naive judges when displayed on calibrated monitors or with a variety of objective image analysis techniques.

3. Fragrance

Anyone who has ever performed large-base consumer blind testing of topical product forms varying only in fragrance will know that this technology can drive passion and perceived technical performance to a very sobering extent. It is not uncommon for a Fragrance Rating to drive directly the Overall Product Rating of a given formulation and, upon closer inspection of internal rating scores, this often impacts profoundly apparent perceived technical endpoints such as "Skin Feels Moisturised" or "Shinier Hair". Fragrance, therefore, is another weapon in a formulator's arsenal that can be used to drive compliance.

Each “note” in a fragrance is a complex, carefully-balanced combination of ingredients. Indeed, there are more than 4000 chemicals that can be blended to create a unique fragrance, each with its own chemical structure, smell, volatility, affinity for skin / water / air and stability. A fragrance is, therefore, so much more than merely the "smell" of a product. A fragrance is a technology in its own right, usually a combination of hundreds of carefully-selected individual Perfume Raw Materials (PRMs). Formulating with fragrances thus presents unique and significant challenges, including PRM-PRM interactions, PRM-product matrix interactions, change in character display over time, the impact of usage conditions, stability issues, scale-up issues. The perfumer is, therefore, at once an artist, olfactive expert and expert scientist and their importance should never be under-estimated.

4. Packaging

Everything that has gone before is, of course, for *nothing* if the consumer does not trial the product in the very first place. In 2005, Procter & Gamble shared the results of research that showed that the consumer shopper makes his / her all-important purchase / no-purchase decision for an on-shelf product within a mere 3-7 seconds, this window being coined the "First Moment of Truth" (FMOT). Considering that typical trial rates for personal care products are around 5% or less, it would appear that the FMOT is one of the biggest opportunities available to place a technology in the consumer's hands, appealing fundamentally to a consumer's senses, values and emotions.

This brings the importance of packaging to the fore. In short, as offensive as it may seem to the R&D formulation scientist, innovative packaging materials, textures, colours, shapes, closures, signage are pivotal in winning in the FMOT window and allowing the consumer to experience the true benefit of the technology in-hand. Modern research techniques including an understanding of cognitive aspects of shopper behaviour and eye-tracking have proved breakthrough in the design of FMOT-winning packaging and on-shelf marketing.

5. Conclusion

We return to the wisdom in the statement, "*People remember experiences, they don't remember attributes or benefits...*". It is the firm opinion of this author that the question, "*What will make the use of my product a delightful experience…*?" is one which every R&D scientist needs to entertain seriously. Objective measures and metrics can be leveraged against the measurement of the otherwise ethereal concept of "delight" and, moreover, surprisingly complex technology can be used to drive trial and compliance. Without these tools, we truly "*labour in vain*".

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EARLY RECOGNITION OF ABSORPTION CHALLENGES FOR CONTEMPORARY TARGETS: KEY MOLECULAR PROPERTIES AND *IN SILICO* TOOLS

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Abstract

Oral route is the preferred option for the administration of small molecules due to convenience and good patient compliance. For absorption to occur, a drug compound needs to be dissolved in the gastrointestinal fluid to permeate the intestinal membrane. In recent times large efforts have been directed towards solubility enhancing strategies due to the poor solubility profile of the current pipeline of pharmaceutical companies. The reasons for the poor solubility, from a molecular perspective, are related to whether the compound has a solid-state limited or solvation limited solubility. Recent studies indicate that rather simple characterization of a molecule, including calculated molecular properties such as lipophilicity, charge, flexibility, planarity and size can provide information of whether the solubility is restricted by the strong crystal lattice or by poor hydration. Early assessment of these properties will allow the processes which limit solubility to be considered during the early formulation discussions, ultimately guiding toward optimal formulation approaches for new chemical entities (NCEs). Recently, it was shown that it is possible to predict, from molecular structure alone, i) the glass-forming ability of molecules (as an indicator of the possibility to manipulate the solid state as a means to increase dissolution rate/apparent solubility) and ii) drug solubility in commonly used pharmaceutical lipids (as an indicator of the possibility of utilizing lipids to increase the dissolved amount NCE delivered to the intestine). Through approaches like these, the future of formulation design will be transformed from experimental screening efforts to predictive science, allowing better understanding of the molecular interactions that result in successful performance *in vivo*.

Keywords

Computational pharmaceutics, glass-forming ability, lipid based formulation, solid-state, solubility, solvation.

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1. Definitions

Oral drug absorption is a function of solubility in the gastrointestinal tract (GIT) and permeability across the intestinal wall. Absorption of an orally administered drug largely takes place in the small intestine. In this compartment the pH under fasted condition is around 6.8 and the amount of naturally available lipids, such as phospholipids and bile salts excreted by the gall bladder, is relatively low. After a meal, the intestinal fluid becomes more acidic (pH of 6.1) and significantly higher amount of bile is excreted [1]. Intestinal fluid has been simulated *in vitro* with different biorelevant media, all of which are derived from the original fasted and fed state simulated intestinal fluid (FaSSIF and FeSSIF, respectively) developed in the late 90's [2]. Based on these simulated fluids it has been shown that the intestinal colloidal structures resulting from the bile secretion are rearranging when food is ingested and the larger (~60 nm in diameter) vesicle-like structures formed under fasted conditions are rearranging to small (<5 nm in diameter) mixed micelles in the fed state [3]. These aggregates have the capacity to solubilize drug molecules in the intestinal fluid to different extents, depending on the physicochemical properties of the molecule. The permeability of the intestinal wall is a function of passive and active transport. In the small intestine a number of membrane transport proteins are expressed that may aid the transport across the cell membrane (influx) or result in the compound, once it has diffused across the apical cell membrane, being immediately secreted back to the intestinal lumen (efflux). For the majority of drug molecules, active transport mechanisms are considered important in the distribution to organs once the compound has reached the blood circulation, but of minor importance for intestinal absorption. This is due to the high drug concentration in the intestine saturating the transporters leading to permeability becoming dependent on passive diffusion. However, for compounds with low passive diffusion and which are not well absorbed over the intestinal wall, e.g. hydrophilic compounds such as di- and tripeptides, or molecules with a poor solubility in the intestinal fluid, the drug concentration does not saturate the transporters, and therefore active transporter mechanisms will have an impact on the amount of drug absorbed. Although many factors impact on the amount of drug that is finally absorbed, this paper will focus on the impact of solubility. In particular, how project teams can obtain early information of the solubility hurdles to expect in a particular project and how this information can be used to better design formulations are reviewed.

2. What is poor solubility and does it matter?

A large majority of the compounds currently being discovered are poorly soluble; the percentage of recently discovered drug molecules with poor solubility has been estimated to be between 40-90% [4, 5]. From a clinical perspective, poor solubility can give rise to erratic, inadequate and non-reproducible absorption of the drug due to incomplete dissolution of the administered dose. From a discovery perspective, poor solubility may result in false interpretation of read-outs from *in vitro* screens, in the worst case resulting in the project team making the wrong decision during the selection of candidate drugs. In between the discovery and clinic, and at a relatively late stage in the drug discovery process, the formulators come on board.

The formulation scientists are key players for the success of the discovery program as they often are expected to deliver formulations in which the drug solubility is increased thousand-fold compared to that obtained in a buffer system.

Is there any quick fix solution for the solubility problem affecting discovery molecules? As solubility is determined by the physicochemical properties of the molecule, and these physicochemical properties, to a large extent, are associated with the target being explored, the answer unfortunately is 'no'. Although simple and rapid tools such as the Lipinski´s rule-of-5 have increased the awareness of the problems associated with 'unnecessarily high lipophilicity' [6], it is evident that some targets demand highly lipophilic ligands to interact [7-9]. More reasonable strategies to identify such targets, such as early computational predictions of the solubility of compound libraries already during the stage of virtual docking, would result in better informed decisions as the discovery project progresses. An important and unfortunately overlooked aspect is the possibility to connect medicinal chemists with formulation scientists during the early discovery phase. The molecular structure holds the key information regardless of which physiological property (pharmacological activity, stability, toxicology, metabolism, permeability, solubility etc) is being investigated and also impacts on the decisions made about formulation strategies (Figure 1). To efficiently communicate with the medicinal chemists involved during early discovery and successfully bridge between the cross-disciplinary activities taking place the formulation scientists need to learn the 'language of chemistry'. The potential of the formulators to early impact on the decisions made by the project team will likely increase if they use the same terminology as the medicinal chemists do.

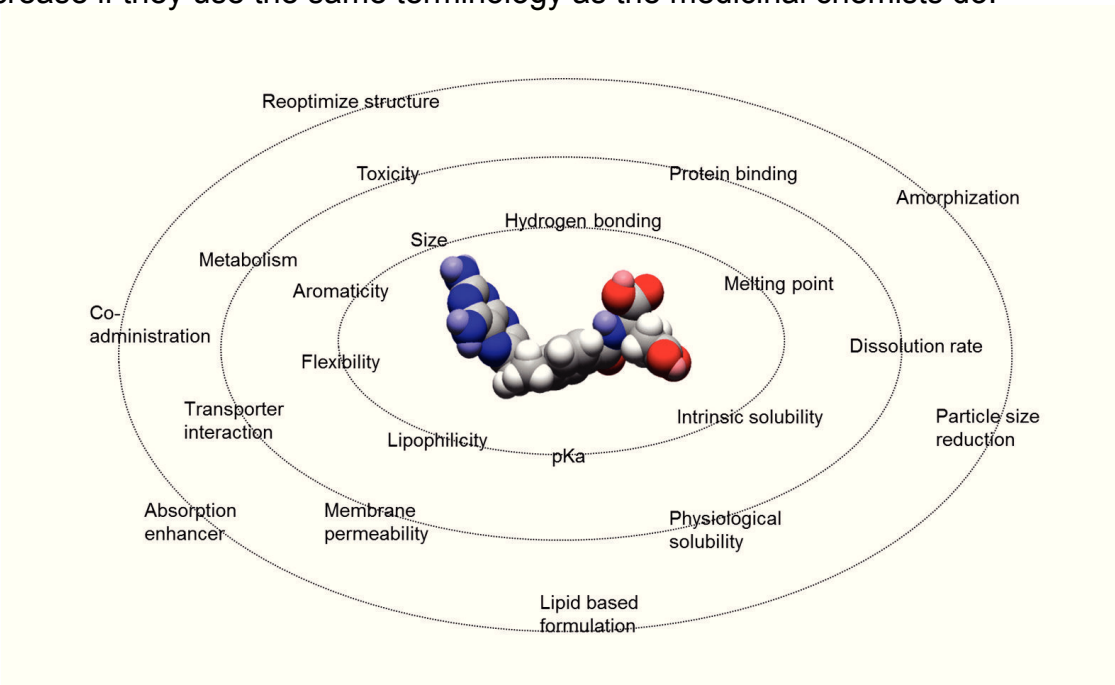

Figure 1. Interfaces between chemistry, physiology and pharmaceutics. The molecular structure of the drug has a number of physicochemical properties (inner layer) that can be measured, calculated or predicted. These compose the fundamental core on which physiological responses (exemplified in the mid-layer) and formulate-ability (outer layer) rely. Some of these physicochemical properties produce unacceptable physiological responses such as toxicity resulting in the compound needing to go through further chemical re-optimization.

3. Can we better understand the molecular features that determine poor solubility?

The poor solubility of drugs may be a result of them being solid-state limited or solvation limited in their solubility (Figure 2). These factors determine the concentration that is possible to reach in the GIT, but they will also impact on the formulate-ability and therefore which formulation strategy to apply. For solid-state limited compounds the solubility is mainly restricted by the strong intermolecular interactions in the crystal that limit the dissociation of the molecules from the solid material. Typically this can be assessed by a simple differential scanning calorimetry (DSC) experiment in which the melting point is measured. A melting point above 200ºC indicates that the solid state will be a major hurdle to overcome during dissolution. Molecular features, such as small molecular size and rigidity, have been identified as major molecular features for solid-state limited compounds [10]. For solvation limited compounds, it is the interaction with water that is the main hurdle and therefore the lipophilicity in form of the partition coefficient between octanol and water ($logP_{oct}$) can be used as an indicator for poor hydration. Other typical properties of solvation limited compounds are that they are larger molecules with a larger degree of flexibility [11]. The most problematic compounds are the drug molecules with mixed properties; such as those that are both high melting (solid-state limited) and highly lipophilic [12]. These will be restricted in their solubility both by the solid state and their poor hydration in water. The impact of these two properties can be assessed by the General Solubility Equation in which melting point and $logP_{oct}$ are used to calculate the aqueous solubility [13].

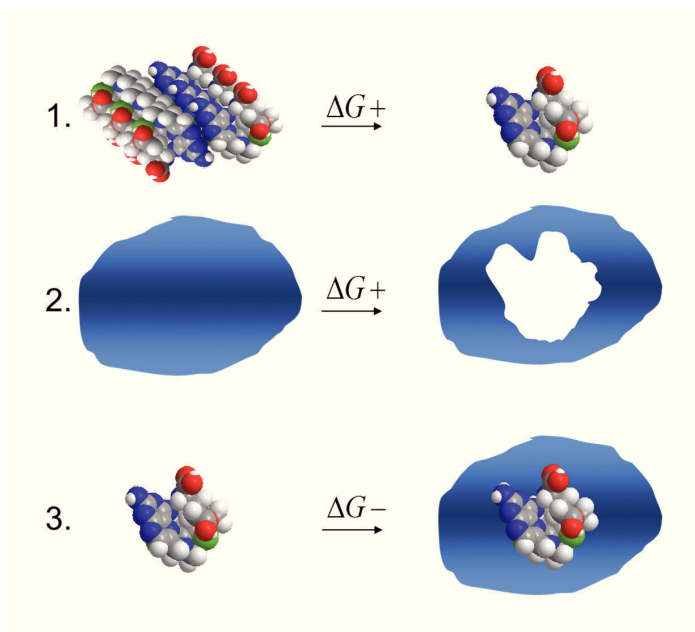

Figure 2. The thermodynamic principle of solubility. The drug molecule needs to dissociate from the crystal lattice (upper panel, demand energy) and the water has to loosen up its tight structure and form a cavity large enough to incorporate the drug molecule (mid panel, demand energy). Interactions are then formed between the water molecules and the drug (lower panel); a process that releases energy.

4. What can we learn from the information on solid-state versus solvation limited solubility?

A molecular understanding of the solubility and the processes possibly limiting solubility provide information on which enabling technique is likely to be successful. For active pharmaceutical ingredients (APIs) with solid-state limited solubility manipulation of the crystal structure is one approach to obtain a supersaturated solution. Common enabling strategies include pharmaceutical co-crystal production and amorphization and a major challenge is to design formulations which maintain supersaturation for a long enough time to enable absorption to occur. Another possibility is to re-optimize the chemical structure so that a more soluble pro-drug is synthesized. Structural features are then introduced to disturb the molecular packing in the crystal lattice thereby reducing the impact of the solid state on solubility. Solvation limited molecules on the other hand can be improved by increasing the solubilization in the GIT. These molecules are typically lipophilic APIs hence self-emulsifying lipid based formulations (LBFs) are attractive formulation approaches to reach a higher dissolved concentration of the drug in the GIT.

5. Can the successful formulation strategy for a compound be computationally predicted?

Currently there is little molecular understanding of the formulation characteristics required for a particular drug molecule. During the formulation stage, typically a number of standard formulations are tested for each new drug, an approach that is time, labour and material consuming [14, 15]. More importantly with this 'one size fits all' approach the best affinity between API and formulation may not be discovered and the final formulation is 'the best one of the formulations tested' rather than a 'custom' and optimized formulation for that particular API. In the same way as computational methods have been used to predict physiological responses (e.g. virtual docking, quantitative structure activity/property relationship etc) it is time to explore and develop computational pharmaceutics to transform the dosage form design process from an *in vitro* screening setting to predictive science, based on the understanding of fundamental molecular processes in these complex systems (Figure 3).

There are a large number of computational methods available to predict the aqueous solubility of a drug, and it is now also possible to discriminate between solid-state limited and solvation limited solubility by computational means [10,11]. The computational framework now needs to be expanded to encompass predictions and simulations of formulation design and formulation performance *in vivo* (Figure 3). Indeed, recent publications indicate that glass-forming ability, i.e. the intrinsic ability of a material to be transformed into its amorphous state, can be predicted from molecular structure. Although factors such as molecular size and hydrogen bonding capacity are generally accepted as features of importance for glass-forming ability, the datasets available in the open literature have historically been too small to allow any computational models using molecular descriptors as the main input to be developed. However, by using a dataset of 50 compounds it

was recently shown that the molecular weight could be used as a rapid indicator for glass-forming ability [16]. In this study, a molecular weight cut-off value of 300 correctly predicted 91% of the data-set used for the model development (i.e. the 50 compounds) and more importantly, the finding was confirmed using an additional 51 compounds to challenge the model obtained. In another study, the number of benzene rings, molecular symmetry and the capacity to form hydrogen bonds were also found to be important factors for glass-forming ability [17]. Based on these findings it should be possible to develop similar computational methods in order to predict the formulate-ability of compounds in other types of systems, e.g. lipid based formulations (LBFs). It was recently shown that the solubility of a drug compound in triglycerides (commonly used in LBFs) could be predicted from molecular descriptors using multivariate data analysis [18]. At the same time, solubility predictions in cosolvents and surfactants appear to be less accurate, and such *in silico* models currently provide predictions only at the qualitative level (high, intermediate, low solubility). LBFs are complex systems composed of several different excipients (lipid, surfactant and/or cosolvent) in different proportions and hence, future studies will show whether the loading capacity in such formulations can be predicted from molecular structure of the API.

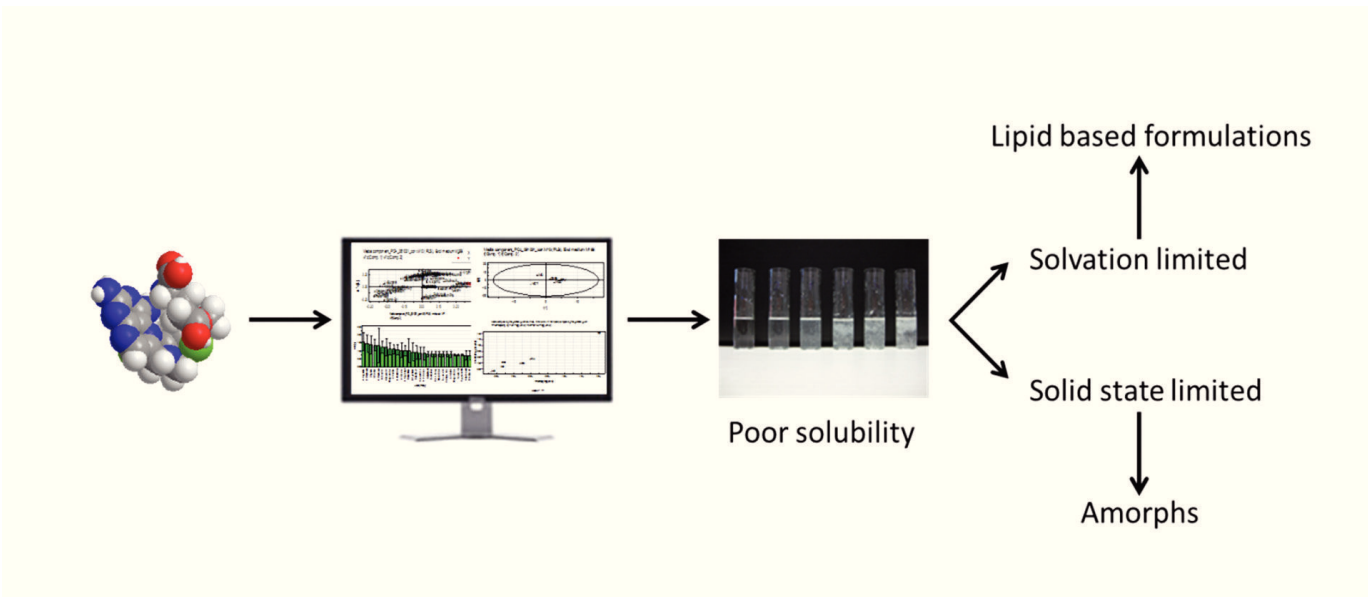

Figure 3. Computational pharmaceutics. Today it is possible to predict many properties using in silico tools such as multivariate data analysis (partial least squares projection to latent structures, neural network, support vector machine etc) and software for calculation of molecular descriptors. These models can now predict aqueous solubility - and interestingly - also identify the molecular cause of poor solubility (solvation or solid-state limited). In recent studies the solubility in excipients commonly used in lipid based formulations as well as the intrinsic glass-forming ability of drugs (ability to exist in its amorphous state) have been predicted with such computational tools indicating that also the field of pharmaceutics can be transformed from the current experimental setting to predictive science.

6. Conclusion

For current discovery programs to be successful an improved understanding of the underlying molecular causes of poor solubility is necessary. Formulation scientists should be involved early on in the discovery process and they should build bridges between the early discovery and early development stages. To do so successfully and efficiently, they need to learn the language of chemistry. Computational pharmaceutics in which classical pharmaceutical tasks such as preformulation and formulation selection are predicted with *in silico* tools using molecular descriptors of drugs is one possible pathway to increase the interaction between discovery and development. This strategy will equip interdisciplinary research teams to make better informed decisions and has the potential to increase the number of clinically successful projects also for the demanding targets currently being explored.

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IN SILICO PREDICTION AND MODELING OF TOPICAL ABSORPTION

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Abstract

(Trans)dermal delivery is based on diffusion and partitioning processes in the skin. A variety of models exist to predict transdermal flux and diffusion parameters. The simplest models base predictions on steady-state and allow estimation of lag time, maximum flux and permeability coefficient. More complex models separate lipid and transcellular pathway, take into account time dependency of skin penetration and/or include pharmacokinetic aspects relating to distribution and clearance in or from the body.

Key parameters arising from Fick's law of diffusion are the stratum corneum-vehicle partition coefficient, diffusion coefficient and diffusion path length. Critical physico-chemical properties of the drug are size/molecular weight, and the octanol-water partition coefficient, relating to the drugs solubility in the vehicle and stratum corneum.

This paper will review major concepts of predicting skin absorption and involve aspects of estimating solubility, contribution of pathways and pharmacokinetic concepts for rational formulation design.

Keywords

Diffusion, Hansen solubility parameters, modeling, skin permeation, stratum corneum, topical drug delivery.

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1. Introduction

The skin is an excellent barrier to the entry of chemicals and, at the same time, a target organ for the topical administration of drugs. This renders the administration of therapeutically relevant doses and its modeling a significant challenge.
Main transport processes include partitioning and diffusion of the drug from the formulation into the skin and into deeper tissue layers (Figure 1). Several pathways are relevant in drug diffusion: the intercellular pathways across lipid bilayers, the transcellular pathway through bilayers and corneocytes as well as shunt pathways via skin appendages. Depending on the physicochemical properties of the permeant, the relative contribution of each pathway differs. Further, the drug may bind to skin tissue and form a reservoir, for example, through binding to keratin or subcutaneous fat. Once the drug has entered the dermis, it diffuses into local blood circulation, which contributes to local redistribution and elimination from the site of delivery.
Amongst these processes, the partitioning and diffusion of the drug at the vehicle/stratum corneum interface has by far received most attention [1, 2], since it is often the rate-limiting step. More recent research indicates the importance of the other processes that also impact topical administration. To date, however, many of these remain poorly understood from a quantitative point of view. Further, solubility of the permeant is a critical parameter in any of these skin compartments.

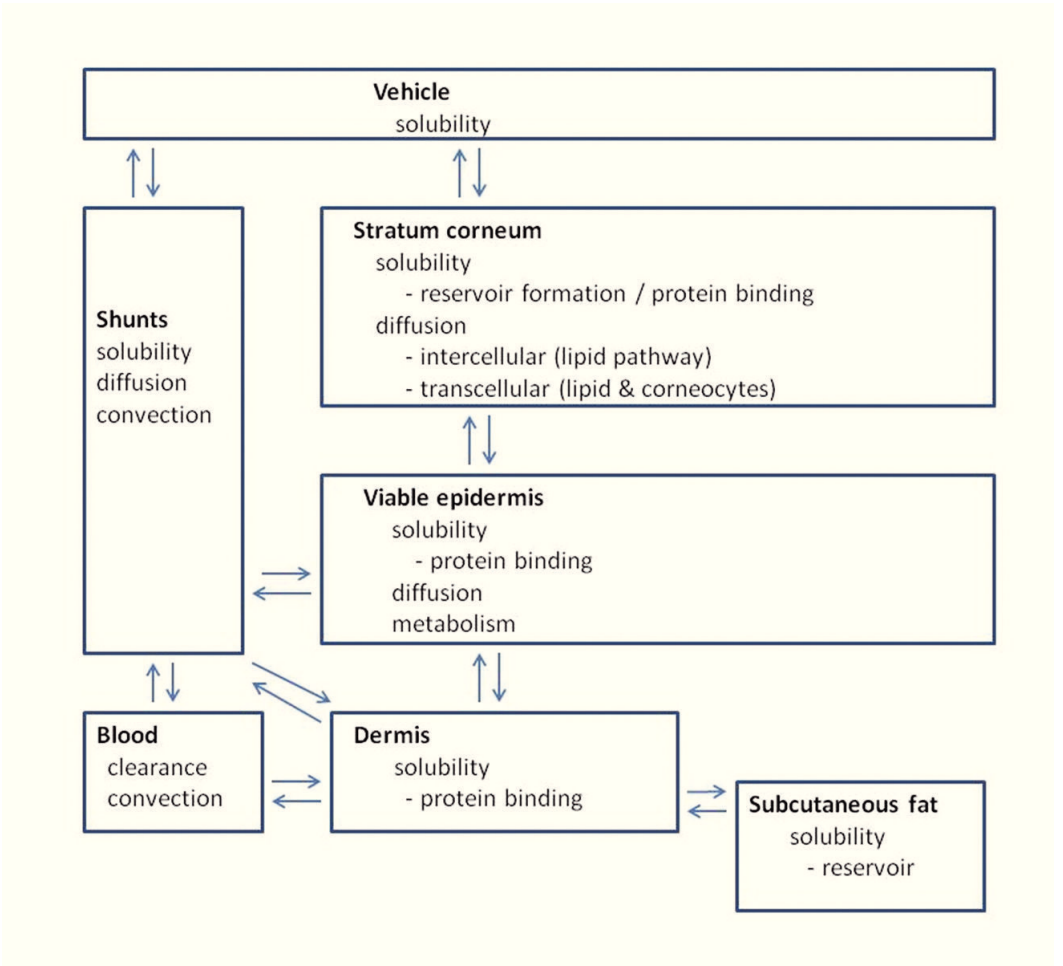

Figure 1. Global overview of transport processes for APIs delivered from a formulation to the skin.

The quality of models predicting skin permeation and therapeutic efficacy at the local level can only be as good as the quality of data used to build these models. Skilled users of the art are familiar with the challenge of producing reliable data generated via *in vitro* skin permeation tests. Despite efforts to harmonize test conditions [3], numerous differences in skin models, equipment and local practices exist and render data comparison between labs a challenging task [4].

2. Skin diffusion models

The simplest models describing skin diffusion assume steady-state conditions, under which Fick's 1st law of diffusion applies. The quantity of drug diffused *Q*, steady-state flux J_{SS} and lag time t_{lag} can be expressed with the following equations:

$$Q = \frac{DAt * (c_v - c_{SC})}{h} \qquad \textit{Equation 1}$$

$$J_{SS} = \frac{Q}{A * t} = \frac{D * \Delta c_s}{h} = \frac{K * D * \Delta c_v}{h} \qquad \textit{Equation 2}$$

$$t_{lag} = \frac{h^2}{6D} \qquad \textit{Equation 3}$$

where *D* is the diffusion coefficient, *A* the diffusion area, *t* the time, *c* the concentration of the drug in the vehicle *v*, stratum corneum *SC*, the concentration gradient Δc_S between both interfaces or within the vehicle Δc_v, , *K* the partition coefficient, and *h* the diffusion path length.
In practice, the partition coefficient between vehicle and stratum corneum, drug solubility and its diffusion coefficient in the stratum corneum is difficult to determine, so surrogate parameters describing equivalent phenomena in water and octanol are used. Plotting these parameters against drug diffusion data led to the Potts-Guy equation [5]:

$$\log k_p = -6.3 + 0.71 * \log P - 0.0061 * MW \qquad \textit{Equation 4}$$

where k_p is the permeability coefficient, *log P* the logarithmic expression of the octanol-water partition coefficient and *MW* the molecular weight of the drug.
The simplicity of this model employing only *log P* and *MW* makes it of the most popular models used to estimate skin permeability. Note that in oral drug delivery, the same concepts and parameters are used to predict the dissolution rate and solubility in the gastrointestinal tract (Anderson, separate chapter in this technical bulletin).

Some controversy exists as to whether the permeability coefficient k_p or the maximum achievable flux of a drug J_{max} should be used to predict skin diffusion [1, 6]. While k_p can be easily estimated *in silico* by many models, J_{max} is, similarly to systemic pharmacokinetics, the more practically relevant parameter. It is directly linked to toxicity, therapeutic efficacy and clinical efficacy.

3. Beyond steady-state diffusion modeling and the stratum corneum

In transdermal delivery systems, drugs that have been successfully commercialized present an optimal balance between physicochemical and pharmacological parameters [7], (Figure 2). On the physicochemical side, the molecular weight is well below 500 Dalton, the melting point lies below 300°C, and the log P ranges from -1 to 4. On the pharmacological side, drugs are potent enough to be delivered in therapeutically effective doses, present a short half-life, and have often low oral bioavailability, so that the transdermal route becomes a meaningful, alternative way of administration. These concepts also apply to topical formulation development [8], but require elucidation of the pharmacological parameters relevant to the local target, the skin.

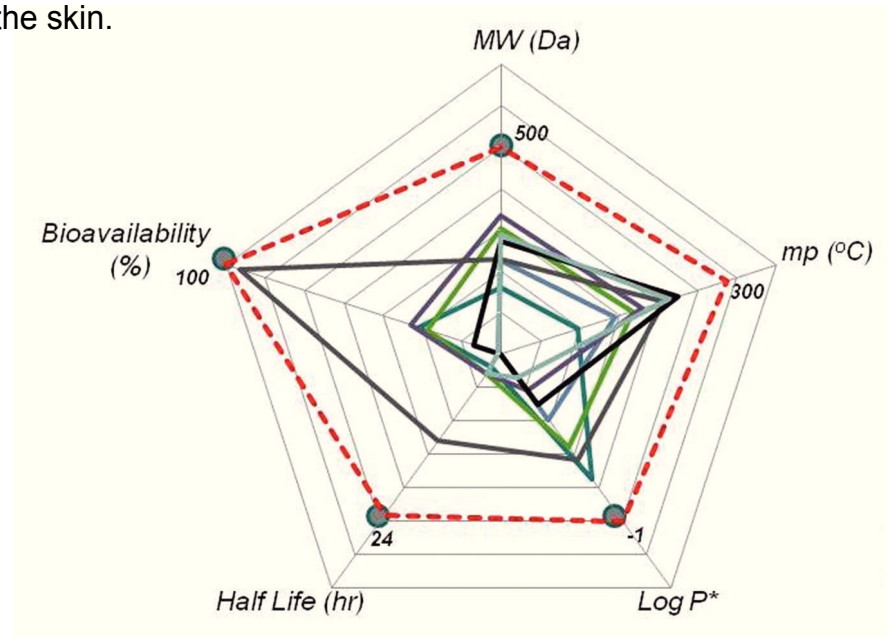

Figure 2. Graphical representation of key properties of transdermally delivered drugs nicotine, nitroglycerine, scopolamine, fentanyl, clonidine, estradiol, and testosterone. Log P is plotted in inverse scale to improve visualization.

Recently, binding to keratin has received increased attention highlighting the importance of drug diffusion into and across corneocytes [9]. Amongst several proteins, hoof, horn, callus and delipidized stratum corneum were identified as being suitable to predict corneocyte binding. This work also highlighted that binding coefficients can be predicted from log P.

Epidermal permeability results form two barriers in series, the lipophilic stratum corneum and the hydrophilic viable epidermis. For very lipophilic drugs, the barrier of the hydrophilic tissue may be significant. Therefore, it is convenient to include a correction factor into models like the Potts-Guy equation, as has been proposed by Cleek and Bunge [10].

The physicochemical properties of the drug also impact the extent of drug binding in epidermis and dermis, changing the available fraction of the drug at its target site of action. Further, local transport processes and metabolism may be significant. When pharmacokinetic concepts from systemic drug delivery are applied to topical delivery the skin, the local input flux, available fraction and clearance can be used to predict the effective steady-state concentration of the drug, which may be far lower than estimated from *in vitro* diffusion experiments [11, 12].

Overall, steady-state diffusion has been extensively modeled and experimental set-ups aim at generating data representative of these conditions [3]. However, many items remain poorly understood to a large base of scientists in the field: the relative contribution of pathways to diffusion of different types of drugs, effective ways of measuring drug solubility in semi-solid vehicles and stratum corneum, quantitative estimation of excipients' interaction with the drug and the stratum corneum altering its permeability, estimation of drug diffusion at finite dose conditions, *in vitro - in vivo* correlations, as well as rational formulation design using residual phase concepts. While the knowledge and tools are being developed and start to become available [12-14], more progress is to be made to enable these models to be effectively and broadly applied in the development of topical formulations. From a pharmacokinetic stand-point, the quantitative understanding of the locally available fraction of the drug, local transport phenomena such as active transport and convection, skin metabolism, and dermal clearance will be critical to estimate local drug levels and therapeutic targets.

4. Solubility parameters as formulation tool

Solubility is a key property in the formulation and delivery of a drug. It determines the thermodynamic activity of the drug in a formulation matrix and the extent of diffusion into and through stratum corneum. It is also linked to protein binding and reservoir formation in different skin layers and, therefore, impacts the pharmacologically available fraction of a drug. In this context, it is a little surprising that tools such as solubility parameters are not widely found in the literature relevant to topical formulation and drug delivery.
The Hansen Solubility Parameter concept is a three-dimensional approach which arose from the one-dimensional Hildebrand model [15]. It divides the total cohesive energy of a chemical into dispersive (atomic) δ_d, polar (dipole) δ_p and hydrogen bonding (molecular) δ_h forces, where the sum of squares of each Hansen parameter adds up to the total (Hildebrand) solubility parameter δ_t (equation 5).

$$\delta_t^{\,2} = \delta_d^{\,2} + \delta_p^{\,2} + \delta_h^{\,2} \qquad \textit{Equation 5}$$

Solvents compatible with the chemical are contained in a sphere when the dispersive component is plotted as $2\delta_d$ (Figure 3). The solubility sphere of a chemical is described by its center, e.g. the coordinates of the solubility parameters $2\delta_d$, δ_p, δ_h, and the radius R_0. If the relative energy difference (RED) to a solvent is lower than one, the chemical is likely to be compatible with that solvent, while a RED greater one would describe non-compatibility or, in other terms, non-solubility.

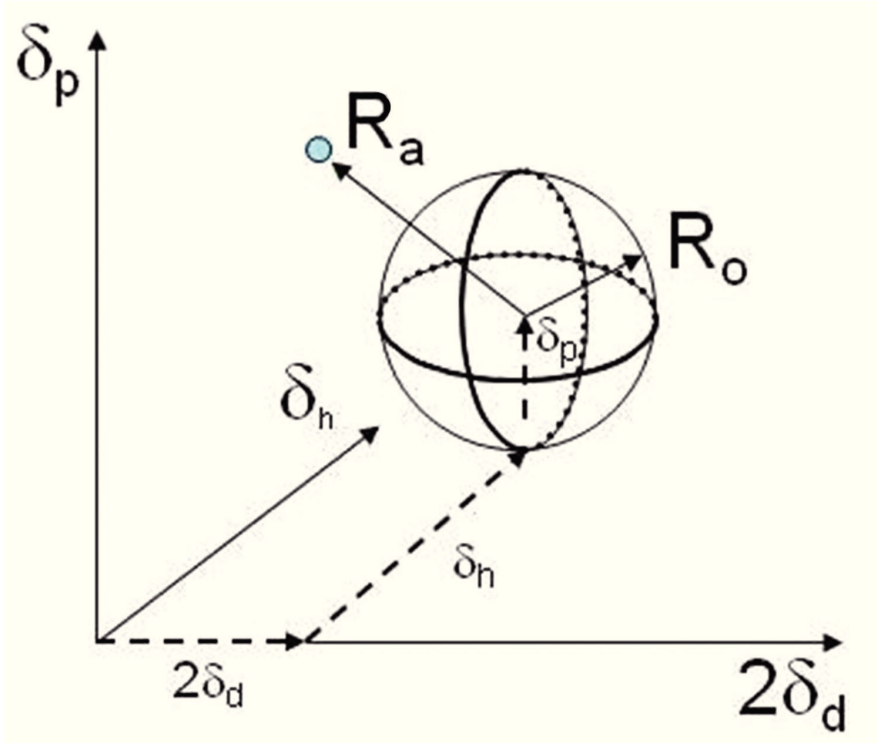

Figure 3. Graphical representation of the solubility sphere of a chemical using the 3D-Hansen solubility parameter model.

The Hansen model has found most widespread use in the coatings industry, but is also used in drug delivery applications [15-18]. In the field of (trans)dermal drug delivery, Gröning established a correlation between the exchange cohesive energy difference, i.e. the solubility parameter gap, of several drugs and ceramide with their *in vitro* steady-state fluxes across the skin [18]. This idea can be further developed to investigate if the solubility of a drug within different formulation matrices can be correlated to the experimentally measured *in vitro* fluxes. The step-wise approach includes the calculation or experimental determination of solubility parameters of each excipient, calculation of overall solubility parameter of the formulation matrices and their exchange cohesive energy gaps with ceramide, and the graphical plotting of the result against *in vitro* flux. For the example of ibuprofen, formulated into organic and silicone-based gels, a reasonable correlation was obtained. Since this example presents non-steady state conditions, a refinement of the model such as using the area under the curve instead of *in vitro* flux may be appropriate.

The Hansen solubility parameter concept equally provides the foundation of the "Formulating for Efficacy" software, which is designed to assist rational formulation design of cosmetic and pharmaceutical topical formulations. Open exchange between users and scientists in the field may help to extend the current use of solubility as well as pharmacokinetic tools to their full potential, so that topical formulation development succeeds in making the transition from being an art to being a well-understood science.

5. Acknowledgements

The author expresses her thanks to André Colas for stimulating discussions and for the courtesy of providing Figure 2.

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WORKING FROM INSIDE OUT: ORAL ADMINISTRATION FOR BEAUTY AND HEALTH OF SKIN AND HAIR

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Abstract

Food supplements are defined precisely as foodstuffs, constituted of a concentrated source of nutriments or substances having a nutritional or physiological effect alone or in combination, marketed in form of doses.

A complement is a product that provides nutrients as they exist in nature from their original food source.

These different ingredients act in different ways:

- Vitamins, minerals and trace elements are absorbed and conveyed by the blood to act directly on their target.
- Proteins and lipids are transformed into amino acids or fatty acids, among which the omega 3 are the most known.
- Numerous plants and preparation of plants can be used as food complements, e.g. fennel, artichoke, grape seed extract, guarana tea or ginger and black radish. When absorbed, plants release their active ingredients, which act on their targets. Recently we have shown that hesperidin, stemming from bitter oranges, ingested by oral route is metabolized in the intestine to hesperetin, which is absorbed into the blood. This metabolite is then conveyed up to the skin and exerts its global anti-aging properties.
- After sublingual ingestion, food aromas can be absorbed directly in the blood and can be released via sweat or sebum to influence the smell of the skin. It has been shown that certain food aromas positively modulate skin odor and might also be efficacious in decreasing malodor.
- Probiotics are live microorganisms, which, when ingested in adequate amounts, confer a beneficial health effects to the host. Probiotics contribute to maintaining the normal function of the intestine and are also endowed with numerous immunomodulatory functions. Current experimental and clinical data strengthen the assumption that certain probiotic strains exert their effects beyond the gut and confer benefits at the skin level. There are indeed emerging evidences that such probiotics can contribute to the reinforcement of skin barrier function and modulate the skin immune system: we have recently show that they are able to regenerate the skin immune system after UV damage and reduce skin reactivity. Altogether these data open the possibility to design new strategies for the maintenance of skin homeostasis based on probiotics.

By oral route, all these different active products could be efficacious for the health and beauty of skin and hair.

Keywords

Complement, food aroma, hesperidin, probiotic, supplement, vitamins.

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1. Introduction

A complement is a product that provides nutrients as they exist in nature from their original food source. You will find the naturally occurring vitamins, minerals, enzymes, essential fatty acids, fiber, protein, carbohydrates, probiotics, glycolipids, glycosaccarides, phytosterols and an array of antioxidants.

A supplement is a product that provides nutrients in a synthetic or isolated form. Isolated means that the vitamin or nutrient has been extracted from a whole food source.

Comprehension of bioavailability mechanisms are key for major nutritional science advances:

There are numerous ways for food skin supplement to act on skin and hair:

- Vitamins, polyphenols are directly absorbed and may go directly from the blood to the site of action in skin cells.
- After sublingual absorption, food aromas go directly to the blood and might be liberated through the skin by sweat and sebum.
- After absorption of some food extracts, metabolites can be formed by the intestinal microflora, which then can reach the skin.
- Probiotics stimulate intestinal cells and some mediators will pass through the blood to the skin.

2. Direct action on the skin: the example of photoprotection

The skin is the most important organ in contact with the environment. Hence, it is constantly exposed to external attacks such as physical, chemical, bacterial and fungal challenges.

The deleterious effects of the UV RADIATION on the skin are well known: alterations of keratinocytes and melanocytes, damage of collagen and elastin fibers, and dryness. In addition, a strong correlative relationship between chronic and intense UV exposure and photo aging and skin carcinogenesis has been established. Certain nutriments such as carotenoids, polyphenols, vitamin C and E or fatty acids have been described as being able to reduce ultraviolet light-induced erythema It has also been shown that carotenoids, dietary fish oil, combined with ascorbic acid (vitamin C) and tocopherol (vitamin E) and long-term ingestion of high flavanol cocoa protect against ultraviolet light-induced erythema [1, 2, 3, 4, 5, 6, 7, 8].

In addition, the antioxidants ascorbic acid and tocopherol have been shown to protect against DNA damage [9].

All these vitamins appear to be efficacious directly after ingestion.

3. Action through the skin: the example of perfume from food aroma

Food aromas act in a different way: they go directly through the blood and might be liberated through the skin via sweat and sebum. For example after administration of a chewing gum containing Rosa essential oil, a significant increase of geraniol is detected on the skin of each of the subjects tested. A person of 145 pounds (65 kg) would require 3.6 mg of geraniol for the desired fragrance effect. These examples illustrate that body odor can be improved by oral route with the addition of pleasant odors such as perfumes.

4. Action of Metabolites: the example of hesperidin as an anti aging agent

Hesperidin is a glycoside flavanon consisting of an aglycone (hesperetin) linked to a disaccharide, the rutinose (0-a-L-rhamnosyl-(1-6) glucose). Hesperidin structurally belongs to the polyphenol group, found abundantly in citrus fruits particularly in the peel. It is used in bitter orange jam since 1988, in healthcare products since 1995 and in several drinks since 1995. Hesperidin is hydrolyzed by the microflora in the lumen to hesperitin and other metabolites, which is absorbed into the blood [10, 11, 12]. We were interested to investigate if ingestion of hesperidin could be efficacious with respect to skin aging. To this end, we designed a double blind, placebo controlled clinical trial with 66 women (50 to 65 years old). This clinical trial included two groups supplemented for 6 months with 500 mg of Hesperidin or maltodextrin as placebo, respectively. In order to assess the beneficial effect of hesperidin supplementation on the appearance of skin aging, we evaluated skin sagging using a specific device named densiscore. This device reproduces the dermatologist evaluation with a standardized pressure on the skin and the use of a standardized scale from grade 1 to 6 to measure skin folds. This technology has been validated by demonstrating a perfect correlation between densiscore measurement and the chronological age [13]. Using the densiscore we observed a significant and relevant decrease in score skin folds in the group using hesperidin supplementation. Folding is decreased from 10% after 2 months, 14% after 4 months and 18% after 6 months. All these values are significantly different compared to baseline and to placebo. Reported on the correlation curve densiscore versus age, the results obtained after 6 months correspond to a 6 years improvement [13]. These data show that hesperidin and the metabolite produced from *Bifidobacteria* and *Lactobacillus* of the intestine as the main active compound are of particular interest in nutritional supplementation to fight skin aging.

5. Indirect activity *via* the release of mediators in the blood circulation: the example of probiotics for reactive skin

The term "probiotics" was first introduced in 1953. In contrast to antibiotics, probiotics were defined as *'live microorganism, which when administered in adequate amounts confer a health benefit on the host'*. In the last 10 years, scientific research on probiotics has progressed considerably and significant advances have been made in the selection and characterization of specific probiotic cultures and substantiation of health claims relating to their use. Many microbial types are used around the world to ferment milk, plant food, meat and other products. Two of the most widely known and characterized are *Lactobacillus delbreuckii subsp. bulgaricus* and *Streptococcus thermophilus*.

They were reported to positively influence the microbiota of the gastrointestinal tract. However, much progress has been made since in terms of the fermentation of dairy products. In this regard most probiotics fall into categories of lactic acid-producing bacterial organisms, including *Lactobacillus* and *Bifidobacterium*.

Probiotics are most often incorporated in yogurt and fermented milk, but other food lines are now available and numerous products are sold in tablet, capsule, and powder forms. As a common feature, after ingestion, probiotics, which should be able to survive through the stomach and small intestine, become transient constituents of the gut microbiota capable of exerting their biologic effects, thus giving a rationale for their use as a component of functional foods. Weaning, stress, dietary changes, use of antibiotics, and intestinal infections are all conditions that affect the natural balance of the intestinal microbiota for which the application of probiotics might be beneficial. Beyond their capacity to promote a healthy pattern of the intestinal microbiota, several lines of evidence also suggest that some probiotic bacteria can modulate the immune system in the gut and systemically, thereby improving immune defense mechanisms, and/or downregulate immune disorders such as allergies or intestinal inflammation.

Beyond the gut, probiotics might exert their benefit at the skin level. Indeed some specific probiotic strains, alive or in extract forms, can modulate skin immune system contributing to specific benefits.The mechanisms whereby probiotics may play a role in skin physiology are not fully elucidated. However, it is proposed that, as shown for other commensal bacteria, probiotics could be directly sampled in the lumen by mucosal dendritic cells, which express tight junction proteins and penetrate the gut epithelial monolayer. It is postulated that upon interaction of the probiotic bacteria (or their components) with the intestinal epithelium and/or direct interaction with dendritic cells, other immune cells, such as B and T lymphocytes may be activated (primed) and immune mediators, including cytokines, may subsequently be released. These cytokines, bacterial fractions, and primed immune cells may be transported *via* the blood to other organs, including the skin, where they could modulate the immune status and other physiological processes. The specific probiotic strain ST11 NCC 2461 has been identified and characterized by Nestle Research. ST11, or *Lactobacillus paracasei*, has been isolated from

human intestinal microbiota. It is a gram-positive, none motile, none spore forming lactic acid bacterium.

ST11 has been demonstrated to: survive to gastrointestinal conditions *in vitro*, persist transiently in the gastrointestinal tract, adhere to intestinal mucosa and epithelial cells in humans, display beneficial effects to the host (improves gut comfort, treatment of diarrhea, improvement of immune status and resistance of infectious diseases, and stimulate the synthesis of anti-inflammatory mediators. In order to evaluate the mechanism of action of ST11 *in vitro*, we elaborated a conditioned medium containing the mediators that might be produced in the intestine and might be found in the blood. For this purpose, a co-culture using CacO2 and PBMC was stimulated with alive probiotics [14]. Then we used an *ex vivo* skin explant model to evaluate the effect of ST11 on skin barrier function. Human skin from plastic surgery was placed on a specific device (classic diffusion cells) and pretreated with either a control medium or the same medium conditioned with ST11. After 24 hours, a solution of 10% of sodium lauryl sulfate (SLS) was applied to the skin surface to induce a reversible alteration of the barrier function. The aggression and the recovery of the barrier function were then assessed by measuring transepidermal water loss. We were able to show that after 1hr ST11 decreased the aggression induced by SLS and it also improved the speed of barrier function recovery after disruption(14].

We also demonstrated that ST11 mediators are able to protect *ex-vivo* against neurogenic inflammation [14].

On the basis of these data and considering the importance of neurogenic inflammation and the role of the barrier function as a major etiological factor for reactive skin, we evaluated this ingredient as a new approach for the management of reactive skin.

For this purpose, we conducted a randomized placebo-controlled double blind clinical study with 2 months supplementation of ST11 in 2 female treatment groups (n=32). In order to monitor the time course of skin sensitivity, a capsaicin test was performed. Moreover, in order to analyze the rate of skin barrier function recovery, the trans-epidermal water loss (TEWL) was assessed. Dryness of the leg and roughness of the cheeks was investigated by a dermatologist as well as by self assessment. The results of the clinical trial show that oral supplementation of ST11 decreases skin sensitivity and increases the rate of barrier function recovery. Therefore, the data provide evidence that daily intake of *Lactobacillus paracasei* ST11 could improve reactive skin condition [15].

The examples described in this article demonstrate that the ingestion of nutritional supplements and complements can have an effect on skin and hair. Efficacy is associated with the intrinsic bioavailability of the compounds themselves, their metabolites or by the activation of other mediators.

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SOLAR UV DAMAGE AND SKIN PROTECTION: THE BOOSTING OF NATURAL DEFENCES AND HEALING BY COSMECEUTICALS

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Abstract

The electromagnetic spectrum of solar radiations has been divided into the UVC region (below 290 nm, not incident on the earth's surface) and the UVB (290-320 nm) and UVA (320-400 nm) regions. Wavelengths below 290 nm are blocked by the stratospheric ozone layer. Both UVA and UVB radiations cause damage to skin cells and skin tissue and these events have been linked to acute damage such as sunburn as well as the chronic occurrence of skin cancer and inevitable photoaging. UVA generates distinct types of damage often associated with oxidative stress which is mediated by reactive oxygen species (ROS). UVA also elicits quite distinct stress pathways. The oxidising nature of the interaction of UVA radiation with human skin cells and the implications of this for endogenous and exogenous antioxidant defence will be considered in this overview.

Keywords

Antioxidants, antioxidant enzymes, cancer, cosmeceuticals, formulation, oxidative, photoaging, protection, reactive oxygen species stress, skin, solar, stress proteins, UVA, UVB.

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1. The solar spectrum

The spectrum for absorption of DNA overlaps the region of the solar spectrum which reaches the earth. This region of overlap is indicated in Figure 1 and defines the UVB region of sunlight which has been recognised as dangerous for many years.

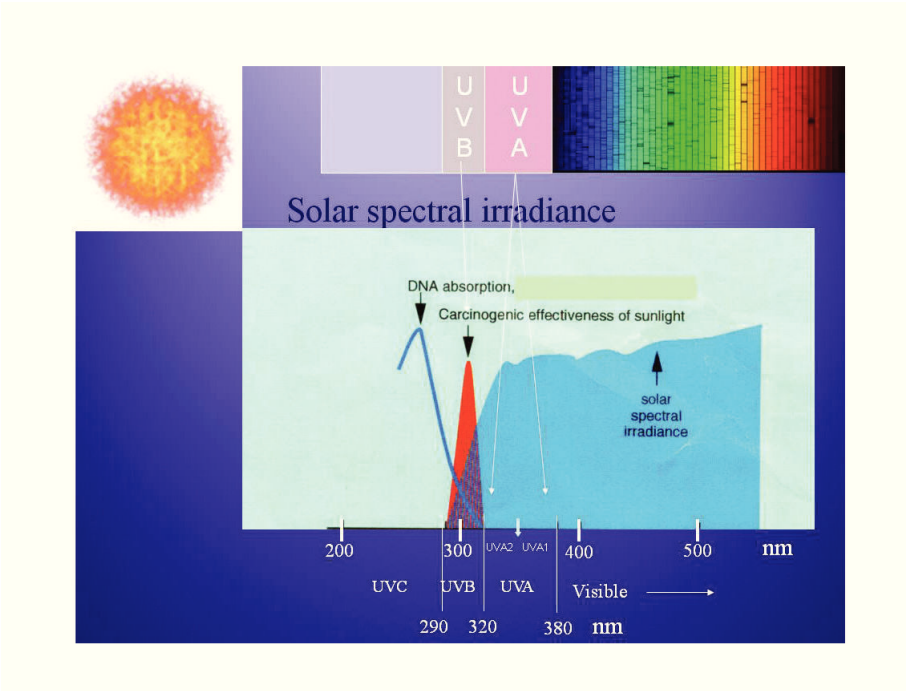

Figure 1. The spectrum of solar UV and visible radiation reaching the surface of the earth and the overlap with DNA absorption.

Because of this absorption overlap, UVB radiations constitute the key cancer–inducing wavelengths in sunlight (Figure 2) and is consequently the region attenuated by conventional optical sunscreens. However, it is now well recognised that the UVA region causes a variety of damage and is also potentially carcinogenic and involved in skin photoaging. Importantly this UVA region interacts with cells and tissue quite differently from UVB and constitutes a much higher percentage (95 %) of the total solar UV radiation reaching the earth's surface.

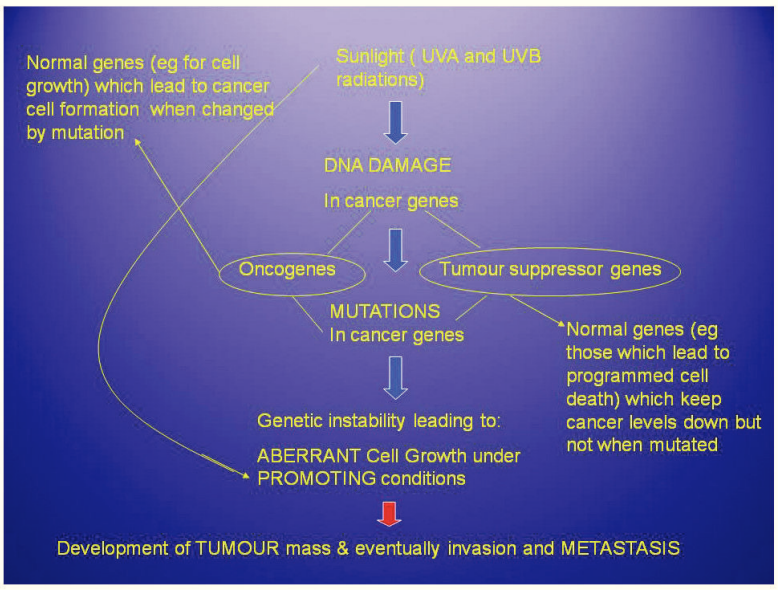

Figure 2. An outline of the carcinogenic pathway following solar UV irradiation of skin.

2. Skin penetration

The longer the wavelength of radiation, the further the penetration in to tissue, as described in Figure 3. Evidently UVA radiation penetrates much further than UVB in to skin and a significant percentage of UVA radiations can penetrate right through the dermal layer and even in to the subcutaneous layer.

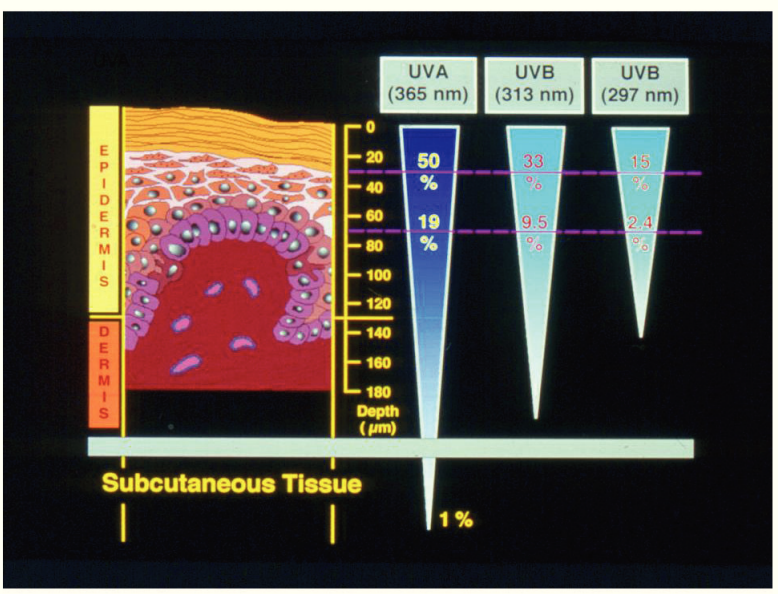

Figure 3. The relative penetration of UVA and UVB radiations through human skin.

3. UVA-induced oxidative stress

The most important characteristic of the interaction of UVA with biological material is that it generates a very significant oxidative stress in cells (Figure 4 and reference 1). The picture is quite complex because there are many cellular molecules which absorb UVA and generate reactive oxygen species (eg tryptophan, nicotinamide adenine dinucleotide phosphate (NADPH), porphyrins etc). Singlet oxygen is undoubtedly the major species generated directly by UVA but other species such as superoxide anion and hydrogen peroxide are also generated and there are many ways in which these species can interconvert to end up with the highly diffusible and reactive oxidant, hydrogen peroxide. UVA also leads to the release of free iron and free heme in cells and these are pro-oxidant catalysts which further exacerbate the oxidative stress [2]. For example, free iron is the catalyst in Fenton chemistry which accelerates the production of the highly reactive hydroxyl radical from hydrogen peroxide. Superoxide anion can also drive this reaction forward by continuously regenerating the ferrous form of iron. Several other reactions are worth noting: Importantly, UVA radiation is able to activate nicotinamide adenine dinucleotide phosphate (NADPH) Oxidase (Nox1) which generates superoxide anion [3]. Furthermore superoxide dismutase can then convert superoxide anion to hydrogen peroxide.

Another point to note is that an important class of cellular molecules which absorb UVA are the porphyrins and these absorb in the longer wavelength UVA region of the spectrum. Since it is this particular molecular interaction with cells that leads to singlet oxygen, the UVA region of sunlight will be of crucial importance to creating ROS and therefore cell damage.

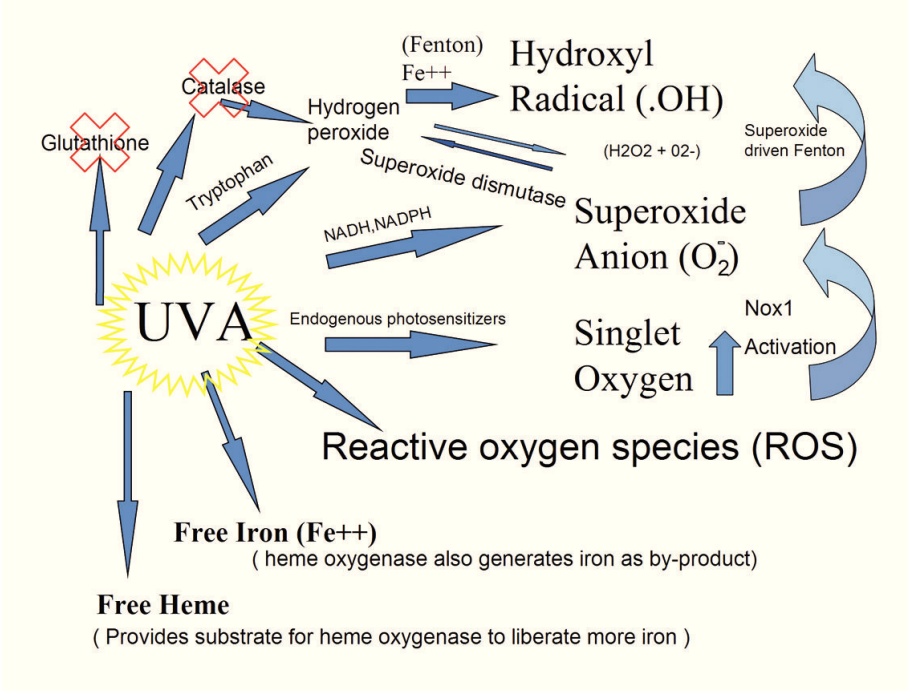

Figure 4. A schematic representation of the reactive oxygen species generated and pro-oxidant moieties released following UVA irradiation of cells and tissue.

As mentioned in the introduction, a major effect of UVB at biologically relevant doses is damage to DNA. However, an important consequence of the dramatic UVA-mediated oxidative stress is that, unlike UVB, a major effect of UVA radiation at the doses which cause observable damage to skin is to oxidise lipids and proteins throughout the epidermis and the dermis.

Damage to proteins will clearly involve those of the extracellular matrix, such as fibrillin, and since these will not always be repaired or replaced, long periods of sustained low level UVA exposure are likely to lead to a slow oxidation of these crucial structures. Lipids are also oxidised by low levels of UVA and this can set off chain reactions which can be sustained. Here it is important to note that this process can generate many lipid messenger molecules (such as ceramides and 4-hydroxynonenal). These signalling intermediates activate other proteins and enzymes and this includes not only enzymes such as oxidases which generate additional ROS but crucially, metalloproteinases. The sustained activation of these metalloproteinases, in addition to the accumulation of protein damage, is clearly going to be central to the photoaging process [4].

4. UVA activation of gene expression

Several genes/proteins are activated, some very strongly, as a result of irradiation of skin cells with UVB and UVA (Figure 5 and reference 5) and although most observations were originally made in cells, similar data was later obtained in human skin. By virtue of the oxidative stress generated by UVA, wavelengths in this range activate a unique set of enzymes. The first and strongest activation of gene expression to be observed was the activation of heme oxygenase 1 in human skin fibroblasts (reviewed in reference 6). This activation is due to the strong transcriptional up-regulation of the gene which is at least 15-20 fold over basal levels even at sub-lethal does and can reach 100 times the basal level transcription rate of the gene. This is clearly an oxidative stress response since the activation is strongly dependent on the levels of endogenous glutathione. Furthermore the activation was the first demonstration of gene activation by singlet oxygen (already known to be generated by UVA). Activation of this gene was soon shown to protect against oxidative membrane damage and there is now a considerable interest in the protein since this oxidative stress response is known to be anti-inflammatory as well as antioxidant and has been implicated in many human pathologies. One of the by-products of heme oxygenase catabolism of heme is the release of iron which together with the iron released directly by UVA radiation leads to the post-transcriptional activation of ferritin, the major iron scavenging protein in cells. Clearly a major effect of UVA radiation is to disturb heme and iron homeostasis and the resultant gene activation would appear to be a strong cellular response to restore homeostasis [2]). Activation of heme oxygenase 1 only occurs in fibroblasts and not in human skin keratinocytes and it has been shown recently by gene silencing experiments that this diference is entirely due to the activity of the transcriptional suppressor protein, Bach1 [7].

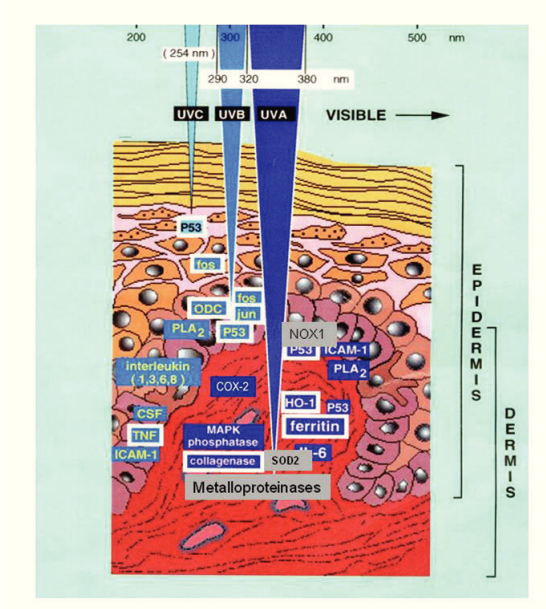

Figure 5. Differential activation of gene expression as a function of UV wavelength range (adapted from reference 5). There is major induction of the stress protein heme oxygenase 1 (HO-1) in the dermal layer of human skin.

UVB and UVA radiation were both shown to activate interstitial collagenase (metalloproteinase 1, MMP1) in human skin fibroblasts. It is now known that UVA irradiation activates a series of metalloproteinases in human skin fibroblasts and that these will play a key role in elimination of damaged/oxidised proteins and in remodelling of damaged skin [4]. Chronic activation of these multiple proteases in the dermis together with sustained oxidative protein damage will undoubtedly lead to irreversible damage to the extracellular matrix and contribute to the photoaging process.

An interesting recent observation is the UVA activation of NADPH oxidase (Nox1) in human keratinocytes [3]. Importantly this activation leads to the generation of reactive oxygen species (presumably superoxide anion) and this UVA generation of ROS is entirely prevented by using SiRNA targeted at the Nox1 gene. Our own recent experiments have shown that, although originally observed in keratinocytes, this activation occurs to an even greater extent in cultured fibroblasts (Zhang and Tyrrell, unpublished data).

In addition to these proteins, UVA also activates superoxide dismutase 2 (SOD2) which generates hydrogen peroxide from superoxide anion), intercellular adhesion molecule 1 and a protein that repairs oxidised protein, methionine-S-sulfoxide reductase [8]. It should be noted that the activation of these stress proteins is an emergency response to restore cellular homeostasis and this can have damaging side effects which further exacerbate the oxidative stress generated by UVA. For example, Nox1 generates superoxide which, in turn can be converted to hydrogen peroxide by the induced SOD2 and other SODs. The release of free iron by heme oxygenase can then contribute to the catalytic breakdown of hydrogen peroxide to generate hydroxyl radical.

5. Strategies for added protection

While constitutive and inducible pathways are able to strongly protect skin against oxidative insult, there are arguments that the supplementation of standard UV absorbing optical sunscreens with antioxidants could provide added protection. Given the large choice of antioxidants available, a key factor in selecting an antioxidant mix is to ensure that it is possible to formulate these such that the active compounds reach the target sites. This crucial aspect is often overlooked but there are also several non-formulation issues to be considered when deciding on the appropriate antioxidants to add to the mix as outlined below.

5.1 Do the selected compounds give added protection against ROS and how do you measure this?

A useful measure of protection against ROS in skin is provided by Electron Spin Resonance (ESR) technology. A study by Wang *et al* [9] compares ESR signals between UVA treated porcine skin (*ex vivo*) which had been pre-treated or not with a series of protective topical preparations already on the market. These were mostly optical sunscreens plus tocopheryl acetate although some preparations had added flavonoid-containing plant extracts. Almost no reduction in ROS as measured by ESR was observed over and above that provided by the optical absorption (SPF) provided by the preparation. Since at present no product could be marketed as a sunscreen without the optical absorbing component, these observations provide an interesting challenge.

Another useful marker of oxidative stress is activation of gene expression. An EU project from a decade ago (Prevention Biomarkers QLK4-1999-01590) included a closing study which exploited several marker genes (heme oxygenase, intracellular adhesion molecule 1 and metalloproteinase 1) in a cross-over study in humans fed either a low or a high flavonoid–rich diet (green tea polyphenols plus oranges). After a suitable time on the diet the skin of subjects was irradiated with a standard dose of UVA radiation. Biopsies were taken 24 hours later and gene activation measured. A significant number of subjects showed suppressed gene activation when on a flavonoid rich diet. Although this study was an indication that such a flavonoid diet may provide health benefits, the study was too small to reach definitive conclusions. The key point to stress is that it did demonstrate the feasibility of using such markers to measure protection in human skin.

5.2 Does the antioxidant mix protect against all species?

There is now a large body of literature which describes scavenging of both radical and non-radical species by a variety of natural antioxidants, usually flavonoids and carotenoids. These can be supplemented with both vitamin C and Vitamin E analogues with the appropriate lipid/aqueous partition coefficients. It is therefore possible to design relatively simple mixtures with the potential to scavenge all solar UV generated ROS and with properties that allow functional formulation.

5.3 Is excess free iron taken care of?

Flavonoids are polyphenolic compounds and since two adjacent hydroxyl groups will confer various levels of iron chelation, the addition of flavonoids in a formulation intended for protection will also confer iron scavenging potential. This can be examined by the measurement of free iron levels with and without the addition of the protective compound(s). The example in Figure 6 (adapted from reference 10) shows the dose-dependent release of labile iron in cultured human skin fibroblasts as a function of increasing fluence. The results with epicatechin, a common flavonoid found in green tea and red wine etc, demonstrates that there is a concentration-dependent reduction in the levels of labile iron detected. Even at 1 and 3 micromolar concentrations of the polyphenolic compound, the protection is very significant.

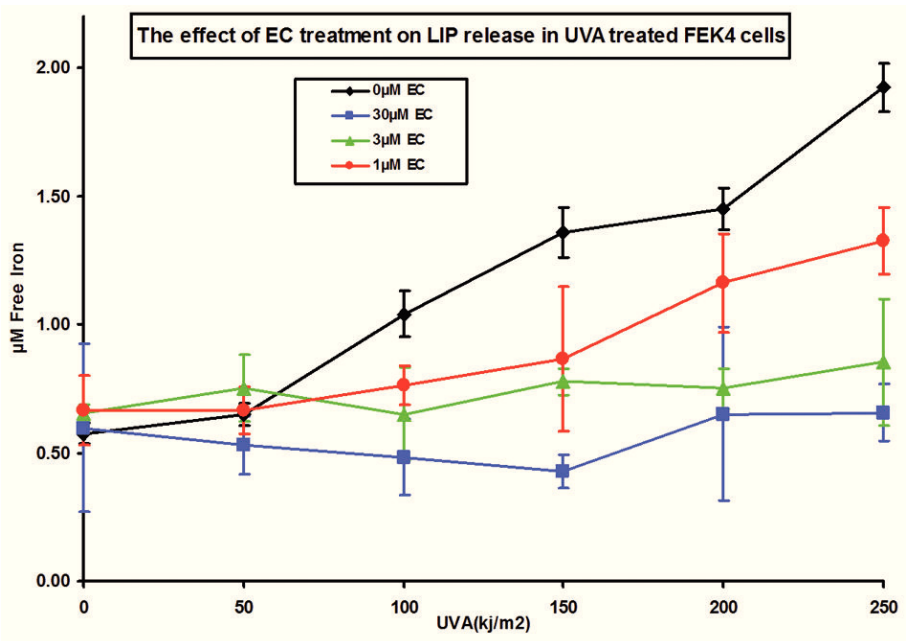

Figure 6. UVA–mediated release of labile iron as a function of UVA fluence and its suppression by a series of concentrations of epicatechin (EC, adapted from reference 10).

5.4 Are the active ingredients doing what is intended and do they have other properties?

The data shown in Figure 6 could lead to the conclusion that epicatechin is acting as an iron chelator. However, additional experiments [10] have shown that the reduction in labile iron levels is not due to iron chelation but results from protection of lysosomal membranes against oxidising damage. The iron reduction and protection occurs regardless of whether one of the hydroxyl groups of epicatechin is substituted by a methyl group, a modification that would be expected to compromise iron chelating efficiency.

Indeed, although polyphenolic flavonoids are used as antioxidants in numerous topical preparations, most of these are powerful cell signalling agents and exert effects at much lower concentrations than the concentrations that would endow them with significant antioxidant properties. When developing products intended for protection, it is essential to be aware of the often complex pharmacology of the components.

5.5 What are the best compounds to use other than vitamins A and C and derivatives?

In practice, many types of preparation have now been shown to provide in vivo protection against UV-mediated skin damage in both rodent models and humans and complement endogenous protection [11]. For example, carotenoids have been shown to protect both topically and systemically against UV damage to humans and rodents [12]. Several polyphenols (notably catechins from green tea)have been shown to provide protection often in combination with Vitamins E and C (eg. reference 13) or analogues. This remains an active area of development with many possibilities and formulation is likely to be the limiting factor in generating new and effective photo-protective agents using these natural ingredients [14].

6. Concluding remarks

The UVA region of sunlight induces a major oxidative stress in cells that is exacerbated by the UVA-mediated release of the pro-oxidant catalysts, iron and heme. This substantially enhances the potential of sunlight to cause major structural damage in skin so that UVA is implicated in both the photoaging and the photocarcinogenic processes. Skin cells and tissue contain a panoply of complementary antioxidant defence mechanisms, both constitutive and induced, which can neutralise the UVA-mediated oxidative stress. There is a view that it would be beneficial to complement these defences by topical (or even systemic) treatment with natural products with antioxidant properties. There is now a good background for choosing such compounds and a primary issue will be the generation of suitable formulations to ensure their efficacy at damaged sites in the skin.

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TRIGGERED AND PROGRAMMABLE ORAL AND PARENTERAL FORMULATIONS EMPLOYING STRUCTURED AND COMPLEX LIPIDS

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Abstract

The advent of new technologies is providing opportunities to better understand structure and kinetic processes across a range of materials science fields, with lipids being one example. In particular, scattering-based techniques can now be employed to study fast transformation processes resulting from either biological processing, such as the action of enzymes on lipid structures and composition, the effects of formulation on skin structure or on 'responsive' lipid materials specifically designed to respond to external stimuli for localization and/or controlled release. We have a strong interest in designing responsive materials using lipids to selectively and specifically control the release of drug 'on-demand'. In order to control and understand the kinetic processes in such materials, we have utilized advanced synchrotron-based techniques, which enable millisecond resolution of nano-scale structure to be determined in such systems. Specifically, by controlling the nano-scale structure in self-assembled lipid materials we effectively provide an on-off switch to control drug release. Such new pulsatile release systems have applications in reducing frequency of administration for frequently or repeatedly injected therapies, such as short-acting biologicals for macular degeneration, where repeated intravitreal injections may be replaced with light-activated pulsatile release systems. A number of different approaches varying in complexity can be taken to render lipid systems responsive to light, but all revolve around controlling lipid packing at the molecular level.

Keywords

Digestion, lipids, liquid crystals, small angle x-ray scattering, stimuli responsive, structure.

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1. Introduction

Lipid-based drug delivery systems are a highly versatile platform for building new technologies. Lipid systems designed for use in drug delivery can be classified into two main classes for the sake of this article – programmable or triggerable. Programmable systems could be defined as systems where the starting composition and subsequent biological processing dictate the behaviour of the systems. The best example would be lipid-based oral delivery systems for poorly water soluble compounds. On the other hand triggerable systems are designed to enable external control or activation of drug release, for example for repeated pulsatile delivery. In both cases, controlling the formation of structure and measuring the structural attributes under different physiologically relevant or stimulus conditions is imperative. In this article some emerging techniques for understanding structure in these systems and application to developing technologies in the programmable and triggered systems are described.

2. Programmable systems

The most common - of what could be termed programmable systems - would be classical lipid-based oral delivery systems typically employed for poorly water soluble, highly lipophilic compounds for which solubility in the gastrointestinal tract is the major limitation to absorption and bioavailability. Lipids, surfactants and co-solvents may be included to improve drug solubility in the formulation, or to maintain drug in solution during dispersion and digestion of the lipids. The number and nature of these three major excipient classes is immense, leading to difficulties in predicting appropriate formulation strategies for particular compounds. The situation becomes even more complex when one considers that the digestion of formulation components *in vivo* tends to further increase the number of components present, for example the digestion of triglycerides to form diglycerides, monoglycerides, fatty acids and potentially glycerol.

It has long been recognised that the processes of dispersion in endogenous bile and digestion of lipid formulations results in the generation of colloidal structures both at the interface of oily droplets [1], and in the dilute 'bulk' aqueous medium (Figure 1). The structures can include bulk liquid crystalline structures such as lamellar, cubic and hexagonal structures, as well as vesicles and micelles in the dilute fluid. These structures can all contribute to drug solubilisation at various stages of digestion and dilution of co-administered drug. Despite the likely importance of such structure generation during *in vivo* processing of lipid based formulations, relatively little is understood about the nature of these structures and how they ultimately impact drug absorption.

The lack of emphasis on structure formation has arisen due to a number of factors. Firstly, there is an industry driver to obtain a rapid 'answer' to the problem of how lipid based formulations will perform *in vivo*. This focus on performance has led to a paradigm where outcome, in terms of drug absorption in an *in vivo* model, possibly indicated or contraindicated by an *in vitro* test [2, 3] for dispersion or digestion (or both), is used as the design criteria for formulation development.

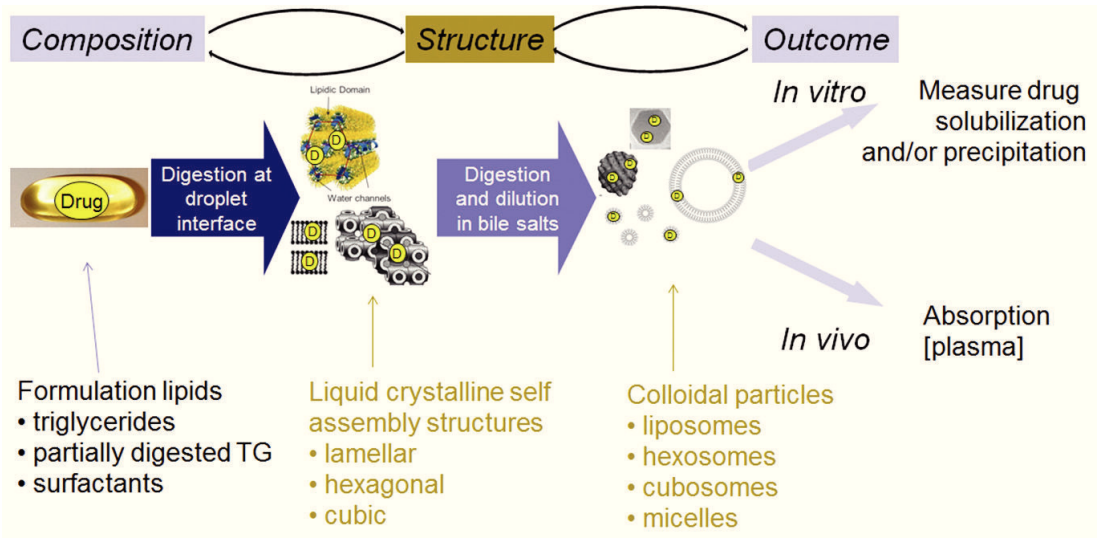

Figure 1. Diagram illustrating the complexity in structure formation and distribution of drug during digestion of lipid-based formulation that will ultimately dictate absorption profile for a co-administered poorly water-soluble drug.

The provision of rules, or classification systems based on the constituent components of the formulation has partly enabled an understanding of their likely behaviour *in vivo* [4]. However, given the aforementioned increase in compositional complexity during digestion, the rational selection of lipid formulations to optimise absorption arguably will not be achieved until the necessary structural aspects of the gastrointestinal milieu immediately prior to absorption are completely understood. It could be further proposed that a classification system based on structure formation and interaction with drug candidates with specific sets of physicochemical properties will ultimately enable rational design of formulations. However, a number of major hurdles must be overcome to achieve such a system:

1. The link between transient/non-equilibrium composition and structure formation must be established.
2. Prediction and confirmation of structure *in vivo* must be established.
3. The link between pre-absorptive structure and absorption must be determined.

Lipid formulations 'programmed' to deliver structure, which is then known to deliver the absorption outcome would streamline development approaches for optimal formulations, and thereby facilitate the rational design of formulations rather than the semi-empirical approaches that have served the industry to date, albeit at a suboptimal level. As a necessary first step, we have recently made steps towards addressing point 1. above. By developing advanced scattering based approaches to start to understand the nexus between composition and structure formation during digestion.

3. Towards understanding structure in digesting lipid systems

Small angle x-ray scattering (SAXS) has long been recognised as the gold standard method for quantitative structure determination in colloidal systems. It stands to reason then that the application of SAXS to understand structural evolution has received some attention. SAXS is a powerful technique in discriminating not only the presence of ordered structures such as the liquid crystalline cubic and hexagonal structures, but also in discriminating between vesicular structures and micelles, and with appropriate modelling approaches can elucidate the fine structure in such systems such as size, shape and bilayer thickness [5].

Although most of the studies e.g. [6 & 7] have involved 'equilibrium' assemblies of components likely to be present during digestion rather than complex non-equilibrium systems more likely to represent the pre-absorptive matrix in the gut, some recent attempts have been made to apply SAXS to dynamic digestion systems. Fatouros *et al*. have removed samples taken during the *in vitro* digestion test mentioned earlier and studied them using SAXS, which revealed the presence of ordered liquid crystalline structures [8]. The need to inhibit the digestion process and subsequently handle and treat the sample before structural interrogation makes kinetic resolution difficult with such an approach. Subsequently Salentinig *et al*. have approached the problem using a flow through cell fitted to a simplified version of the digestion model usually used in pharmaceutical formulation interrogation, to enable the scattering to be acquired in real time [9]. However, the laboratory source utilised in the study limited the kinetic resolution to several minutes with very weak scattering, again providing an advance in the field but with albeit limited potential to capture the true structural transformations in necessary detail to describe the subtle and not so subtle changes to colloidal structure occurring dynamically during digestion.

Concurrent with the studies of Salentinig *et al.*, our group developed a similar approach illustrated in Figure 2, instead utilizing a synchrotron x-ray source and coupled to the typical *in vitro* digestion format utilised by a number of groups specifically for the digestion of pharmaceutical formulations, to enable more direct correlations with past studies to be made [10]. The use of the synchrotron source provides orders of magnitude increase in intensity, which consequently allows adequate collection of structural information on the seconds rather than minutes timescale, thereby enabling true 'real time' detection of structure during digestion. Although it is still early in our application of this flow through model towards resolving point 1., by way of illustration, a recent case study published during the Gattefossé Foundation Journées Galéniques meeting is described briefly below [11].

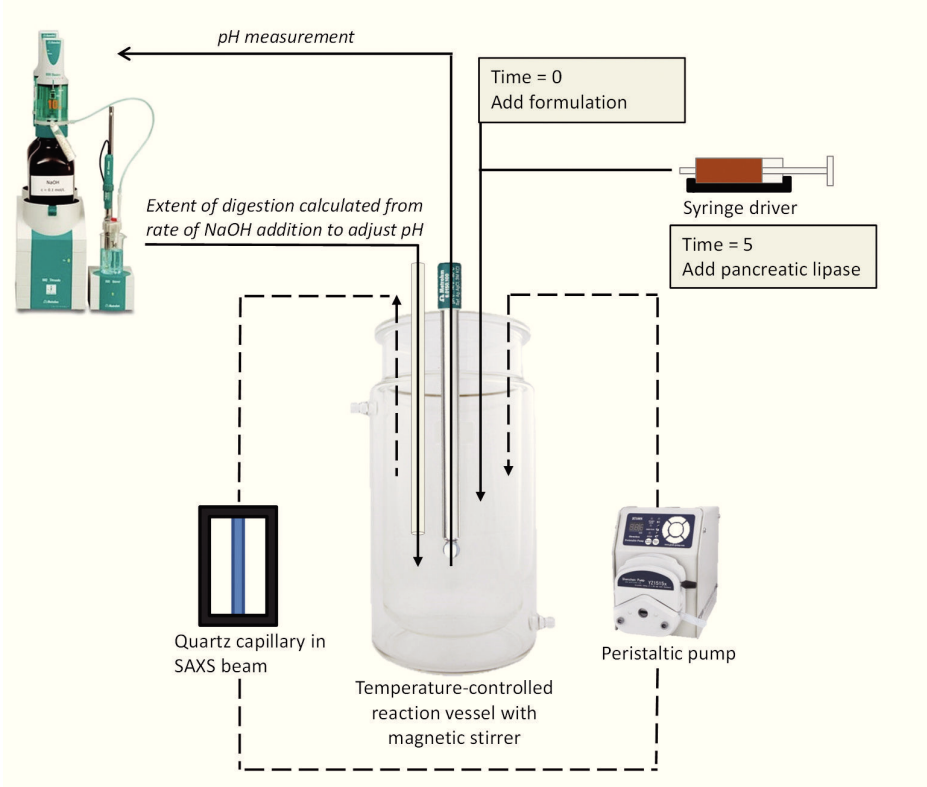

Figure 2. Schematic of in vitro digestion model coupled to a flow-through quartz capillary for time-resolved synchrotron SAXS.

The *in vitro* digestion model used to assess drug concentrations in the aqueous phase on digestion of medium chain triglycerides has revealed a supersaturation effect when a sufficiently high concentration of lipid is present, with drugs of sufficiently high lipophilicity such as halofantrine or cinnarizine(left panel of Figure 3) [12]. Curiously, the titration curves obtained for this system, produced by profiling the consumption of sodium hydroxide added by the pH stat to counter fatty acid production, showed a 'kink' not evident at low lipid concentrations (right panel of Figure 3). It was proposed that a solubilising vesicular phase was present that supports supersaturation, although this was never structurally demonstrated.

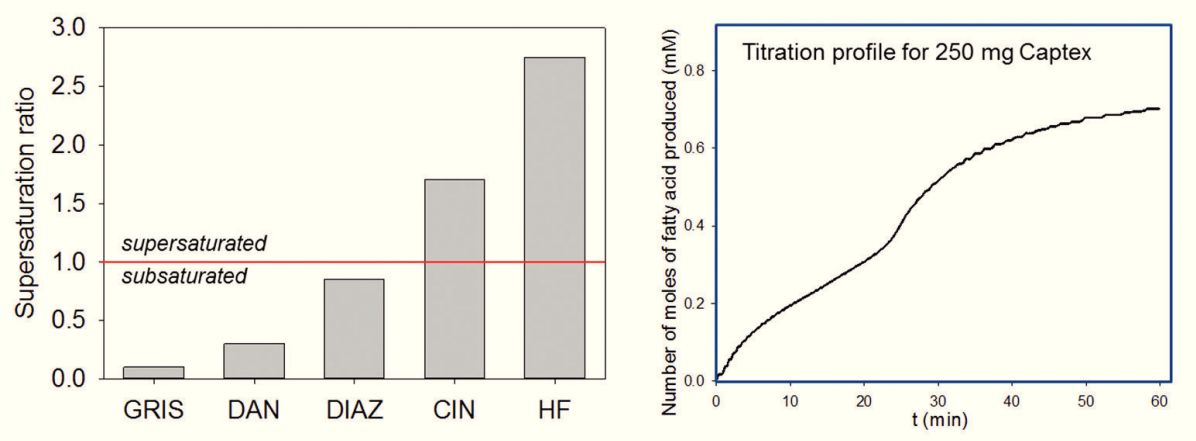

Figure 3. Supersaturation effect with increasing drug lipophilicity when digesting 250 mg medium chain triglyceride (MCT, left hand panel, reproduced from [12]) and coincident 'kink' in the titration profile at 250 mg lipid load (right hand panel). The 'Supersaturation ratio' is calculated from the concentration in the separated aqueous phase after digestion is complete, divided by the solubility of drug in a pre-digested aqueous phase.

Using the scattering obtained over time (left panel of Figure 4), and verification using cryo-TEM (right side of Figure 4) we showed that there is a transformation from undigested oil to micelles to vesicles during digestion, with the transition to vesicles occur at the 'kink' in the titration profile, and that the kinetics of changes in the structural dimensions of the lamellar structures correlated well with the kinetics of digestion.

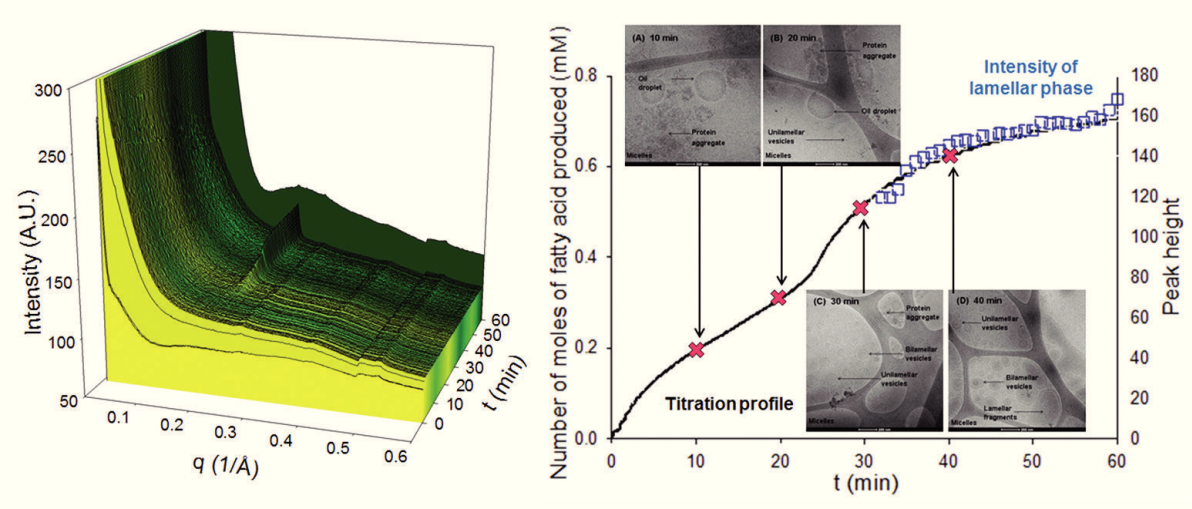

Figure 4. Correlation between micellar to vesicle transition from scattering data and cryoTEM, and titration kinetics (modified from [11]).

Thus, using advanced emerging techniques such as synchrotron SAXS, it is becoming evident that we may be able to now link:

1. Initial composition (in the formulation) with
2. Dynamic composition (dynamic, from titration curve and HPLC) with
3. STRUCTURE (sSAXS – cryoTEM) and
4. Outcome (in this case supersaturation).

Such correlations have in the past been very difficult to establish because of the lack of ability to interrogate the structural aspects appropriately. With the advent of increasing numbers of synchrotron sources worldwide and the approach described here it is hoped that more groups will take up the challenge to enable more rapid convergence in our understanding of the impact of formulation variable on structure formation.

4. Triggered systems

The potential to trigger the release of repeated doses of drug on demand after administration of lipid-based delivery systems has potential for application in areas such as reducing the frequency of regularly administered injections. Drugs with short half-lives would be amenable to this type of system, particularly where pulsatile release rather than slow continual release are favourable for treatment. Drugs with acute toxic effect at low doses might also be suitable, providing a means to titrate the patient dose without individual administration. Many short acting biological

drugs, where the administration is dictated by a diagnostic test, or where using a long acting polymer formulation is not possible due to incompatibility or degradation would be candidates.

In order to address such a need, a system that possesses an on-off 'switch' is required that enables a dose of drug to be released when the switch is 'on', then for release to stop when the switch is 'off'. To achieve such an effect using lipids we have been investigating the potential to switch between different liquid crystalline structures such as those in Figure 1, with dramatically differing drug release behaviour. By addition of photosensitizing agents that respond to near-infrared [13] or UV light [14], reversible control over such structures has been achieved.

In one example, lipids derivatised with a UV active spiropyran group were incorporated into a liquid crystalline structure formed using the lipid phytantriol. Irradiation of the matrix was shown to disrupt the lipid packing reversibly (indicated by the derived quantity 'T equiv' to indicate the level of disruption of the structure), and the magnitude of the effect was dependent on time of irradiation [15] (Figure 5).

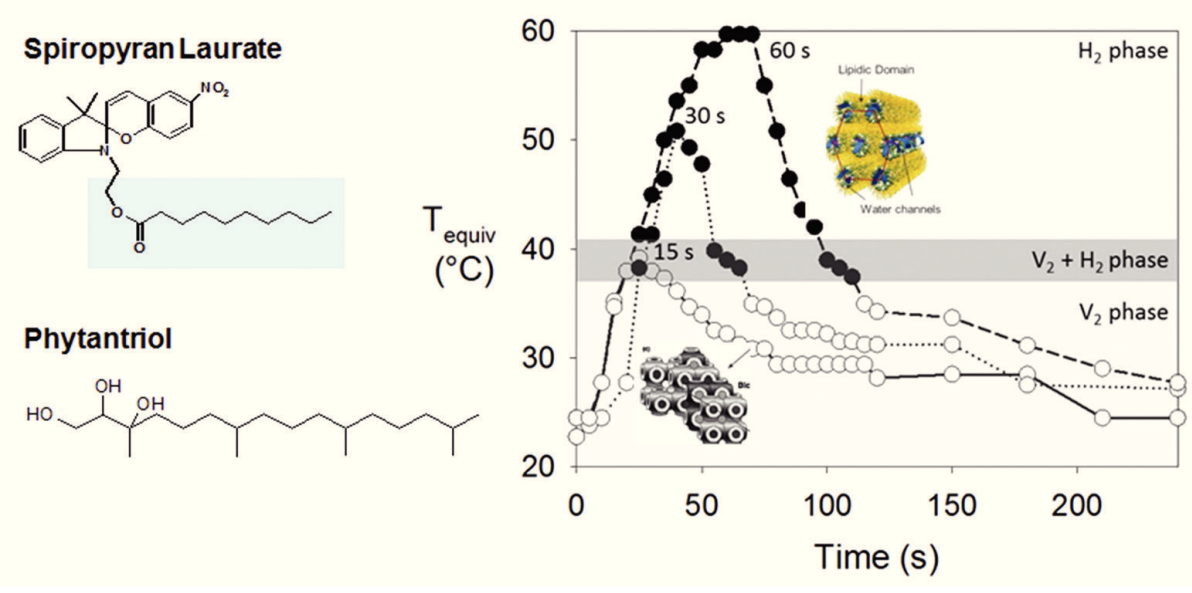

Figure 5. Incorporation of the UV active lipid, spiropyran laurate, into the liquid crystal structure formed by the lipid phytantriol, induces a reversible change in nanostructure on irradiation with >15 s of UV light. Irradiation for 30 s or 60 s was sufficient to change the nanostructure. The term 'Tequiv' indicates the level of disruption induced by spiropyran laurate isomerisation on UV irradiation.

Importantly, this work again was facilitated by the use of fast synchrotron acquisition of the scattering from the liquid crystalline phase as the structure developed over seconds timeframes. Switching between these types of structures using temperature directly has previously been shown to enable control over drug release in an 'on-off' manner (Figure 6) [16], thus opening new opportunities for pulsatile release systems.

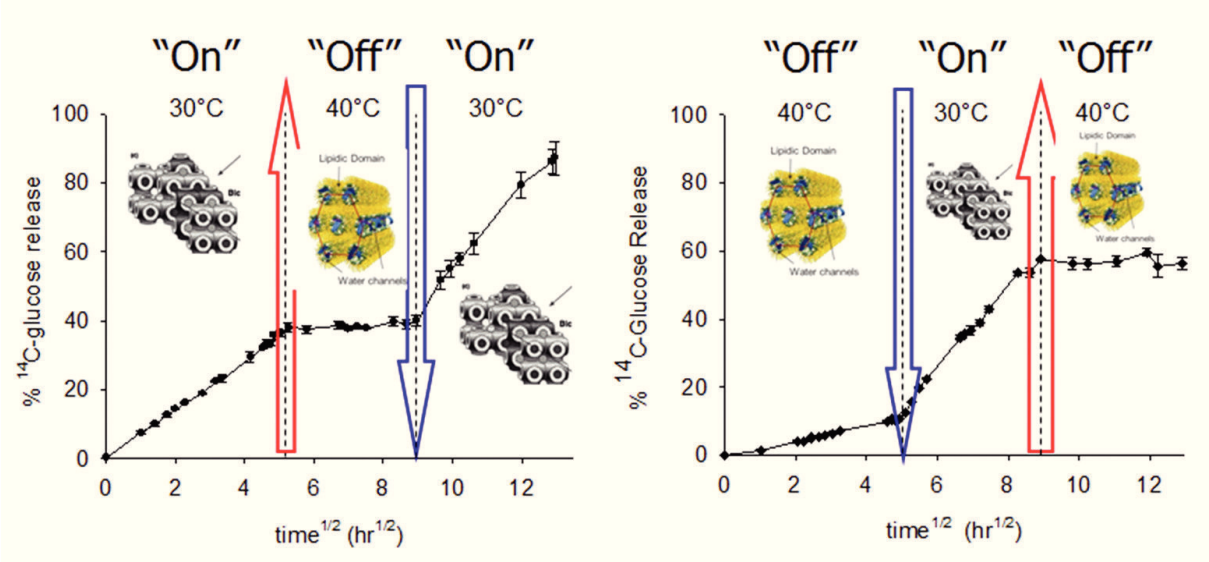

Figure 6. Reversible control over drug release is dictated by controlling the nanostructure adopted by the lipids at differing temperature.

In vivo studies are currently underway, with hopes that the technology may help to reduce the need for frequent intravitreal injections in the treatment of macular degeneration, as one application.

6. Conclusion

Great opportunities are presented to the field of lipid-based drug delivery through the availability of new techniques for probing structure formation and transformation. When we have sufficient understanding of such structural aspects, we will be in a strong position to more rationally design lipid systems to optimise performance where structure formation is key to their application. Systems where structure formation is 'programmed' into the initial composition, or where structural changes are 'triggered' externally to impart specific functional both offer such opportunities, and exciting times await at the interface of lipid chemistry, self-assembly and structural control.

7. Acknowledgments

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TOPICAL AND TRANSDERMAL DELIVERY – TODAY AND TOMORROW

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Abstract

The number of drugs available as successful commercial topical and transdermal products is currently limited to those that exhibit the established and proven physicochemical properties enabling their effective passive delivery to or through the skin. This article will review some of the successes and failures of the past few decades in these two areas of drug delivery as well as examining what the future may hold in terms of new products, novel formulation approaches and regulatory and commercial challenges. The article will hopefully persuade the reader that whilst having a clear eye on the future is important, understanding the lessons of the past is of equal value and should impart a clear warning that physical pharmacy and biology will almost always thwart miss-placed ambition and/or company dogma.

Keywords

Drug delivery, topical, transdermal.

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1. Passive topical and transdermal delivery – today

For the purpose of this article, topical delivery is defined as non-systemic delivery of drugs to or through the skin and transdermal delivery as systemic delivery of drugs through the skin. Furthermore, passive delivery is defined as delivery requiring no physical disruption of the stratum corneum and active delivery as delivery utilizing physical disruption of the stratum corneum or use of an external driving force other than simple diffusion. This article, unless stated otherwise, deals with the United States of America (USA) pharmaceutical market.

There are many marketed topical drug products (that utilize in excess of 50 drugs), mostly for the treatment of dermatological conditions. The vast majority of these products are non-occlusive systems such as gels, ointments and creams but there are a couple of notable exceptions. Lidoderm® (marketed by Endo) is a large (10 cm x 14 cm) lidocaine occlusive patch indicated for relief of pain associated with post-herpetic neuralgia. Lidoderm® was approved by FDA in 1999 and has annual sales of over $1 billion. However, a generic version of the product was launched by Actavis in September 2013 and this will probably impact sales of Lidoderm® moving forward. The only other occlusive topical marketed in the USA is Flector®, an occlusive diclofenac patch indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions that was approved in the USA in 1999.

Table 1 contains details of the drug products currently available as occlusive transdermal systems in the US and the EU. There are only 17 drugs that are formulated in this manner and the sector represents a very small proportion of the overall pharmaceutical market by both number of products and US dollar value. The reason the transdermal market is so limited is that drugs require some very specific physicochemical properties and a low therapeutic dose to enable their successful and efficacious delivery through skin. Table 2 summarizes these characteristics for those drugs that are marketed as transdermal products. A quick scan of this table will tell the reader that they are all small (low molecular weight), reasonably lipophilic (as measured by their log P values) molecules that have a low melting point (representative of reasonable solubility) and usually a high potency. These molecular features are required simply because human skin has evolved as a very good barrier and is generally very impermeable to anything that is large and/or hydrophilic in nature.

Table 1. Passive transdermal drugs for systemic delivery launched in the USA.

Drug	USA approval	Indication
Scopolamine	1979	Travel sickness
Nitroglycerin	1982	Angina
Clonidine	1984	Hypertension
Estradiol	1986	Female HRT
Fentanyl	1990	Chronic pain
Testosterone	1995	Hypogonadism
Nicotine	1996	Smoking cessation
Estradiol and norethindrone acetate	1998	Female HRT
Ethinyl estradiol & norelgestromin	2001	Female contraception
Oxybutynin	2003	Enuresis
Methylphenidate	2006	ADHD
Selegiline	2006	Depression
Rivastigmine	2007	Alzheimer's disease
Rotigotine	2007 & 2012*	Parkinson's disease & restless leg syndrome
Granisetron	2008	Chemotherapy-induced emesis
Buprenorphine	2010	Moderate to severe pain

*Withdrawn from the USA in 2008, reformulated product approved by FDA in April 2012 and re-launched in July 2012; withdrawal not requested in EU.

In addition to the occlusive transdermal patches available in the USA there are a limited number of non-occlusive transdermal systems available. Table 3 contains these and, because there are so few drugs delivered in this way, they are listed as individual products rather than by their active ingredients. These products are predominantly made up of testosterone and estradiol products for male and female hormone replacement therapy (HRT) respectively.

The non-occlusive application of these formulations necessitates the use of very large areas of application (where a patch might be 20-60 cm^2 these formulations are applied to areas in excess of 100-200 cm^2). This has led to the recognition by FDA of an issue relating to the widespread use of such formulations. All such transdermal testosterone formulations now come with 'black box' warnings in the labeling pointing out the potential for product to transfer from the skin of a patient to another person. This poses particular danger if the other person is a female and/or child. The developers of these products have had to conduct several additional clinical studies to demonstrate the propensity for transfer and also the effectiveness of washing procedures to mitigate it.

Table 2. Physicochemical properties and doses of marketed transdermal drugs.

Drug	Example of product	Max daily systemic dose (mg)	RMM	Log P[a]	Melting point[b] (°C)
Methylphenidate	Daytrana	30	233	2.3	Liquid
Nicotine	Nicoderm	21	162	0.57	Liquid
Nitroglycerin	Nitro-Dur	20	227	2.2	Liquid
Selegiline	Emsam	12	187	2.7	Liquid
Rivastigmine	Exelon	9.5	250	2.1	89[c]
Testosterone	Androderm	10	288	3.2	155
Rotigotine	Neupro	8	316	4.4	177[c]
Oxybutynin	Oxytrol	3.9	358	5.1	186[c]
Granisetron	Sancuso	3.1	312	1.5	210[c]
Fentanyl	Duragesic	2.4	337	3.9	83-84
Buprenorphine	Butrans	1.7	468	2.8	209
Clonidine	Catapres-TTS	0.3	230	2.4	130
Scopolamine	Transderm Scop	0.3	303	0.76	Liquid
Norethindrone acetate	Combipatch	0.25	341	3.8	161-162
Norelgestromin	Ortho Evra	0.15	327	4.4	112
Estradiol	VivelleDot	0.1	272	4.1	173-179
Ethinyl estradiol	Ortho Evra	0.02	296	4.1	141-146
Median value	**-**	**3.1**	**296**	**2.8**	**-**

[a]ACD/Log P values from www.chemspider.com: [b]Merck Index except where indicated otherwise; [c]Predicted value using EPISuite from www.chemspider.com

Table 3. Non-occlusive transdermal products approved in the USA.

Product	Drug	Form	Indication	Year Approved
Nitroglycerin	Nitroglycerin	Ointment	Angina	1988
Androgel	Testosterone	Gel	Hypogonadism	2000
Testim	Testosterone	Gel	Hypogonadism	2002
Fortesta	Testosterone	Gel	Hypogonadism	2010
Axiron	Testosterone	Gel	Hypogonadism	2011
Estosorb	Estradiol	Emulsion	Female HRT	2003
Estrogel	Estradiol	Gel	Female HRT	2004
Elestrin	Estradiol	Gel	Female HRT	2006
Divigel	Estradiol	Gel	Female HRT	2007
Evamist	Estradiol	Spray	Female HRT	2007
Gelnique	Oxybutynin	Gel	Enuresis	2009

2. Passive topical and transdermal delivery – tomorrow

There are several issues with passive occlusive transdermal delivery now and moving forward. These include the following:

- A lack of suitable molecules for delivery modality
- Incomplete bioavailability (1-40%) = high unabsorbed dose remains in patch
- High unabsorbed dose in patch = diversion & abuse problems for some drugs
- Requirement for drug potency for delivery exacerbates these problems
- Litigation around safety e.g. fentanyl
- Irritation issues with products e.g. Oxytrol® (14-17%), Androderm® (17%)
- Poor adhesion of patches especially under stressed conditions

To tackle these and other issues there is a need for research and development in several different areas but the first issue that needs to be addressed is to simply be sensible about what can be delivered transdermally using passive methods. History has shown us what works and yet despite this there are still efforts expended in the pursuit of product ideas that will simply not work because the drug molecules involved will not pass through intact human skin. It is not the purpose of this article to 'point fingers' at specific drug developers but being very aware of the limitations associated with passive transdermal delivery may save some investors time and ultimately money. Some other questions and suggestions for future research are given below:

- Is the record of failure in development of enhancers off-putting for the sector? SEPA® and Azone® were both developed with the intention of being commercially available enhancers and yet neither has made it in to a product.

- Is there a possibility of developing better adhesives with less detachment, higher drug loading and less skin residue?
- Can we develop mechanisms to combat skin irritation that are not reliant on the use of topical steroids?
- Can patches become smaller and more discrete?
- Shorter lag times may allow more acute therapies to be developed?
- Better design/selection of drug candidates for transdermal delivery? Most transdermal drugs were not initially developed with that route in mind so attempting to design in delivery as well as potency may be an approach that adds value. In this respect, can drug discovery groups work more closely with drug delivery groups?
- Modification of existing drugs to improve delivery eg. pro-drugs?
- There is a social need and regulatory desire for anti-abuse systems in formulations that are subject to diversion and abuse e.g. fentanyl patches

As far as passive non-occlusive topical and transdermal delivery is concerned there are several issues that research could attempt to address:

- Poor bioavailability (<10%) = high unabsorbed dose
- High unabsorbed dose = where is the unabsorbed drug?
- Where is the unabsorbed drug ? = possible transfer to other people
- Where is the unabsorbed drug ? = possible transfer to the environment
- Possible transfer = additional clinical studies and labelling to minimise risk
- Possible transfer = ‘black box’ warnings on some products e.g. testosterone
- Large application areas e.g. torso, arms, thighs = exacerbation of transfer?
- How to conduct bioequivalence studies? Tape stripping or other methods?
- Formulation development is still in the dark ages?
- Formulations are often very inelegant and deliver very poorly

3. Active topical and transdermal delivery – today

There have been several active topical and transdermal delivery products approved by the FDA over the last 20 or so years. Unfortunately, most of these products are not currently available, having been withdrawn from the market for a variety of reasons. The majority of the products in this category that the FDA have approved were lidocaine delivery systems for local anesthesia and Table 4 briefly summarizes details of these and their history.

Table 4. Active topical and transdermal products approved by FDA.

Product name	Drug(s)	FDA approval	Withdrawal	Technology	Indication
Iontocaine®	Lidocaine & epinephrine	1995	2005	Iontophoresis	Local anaesthesia
Glucowatch®	n/a	2001	2007	'Reverse' iontophoresis	Glucose monitoring
Lidosite®	Lidocaine & epinephrine	2004	Listed as discontinued by FDA	Iontophoresis	Local anaesthesia
Sonoprep®	Lidocaine	2004	2007	Ultrasound	Local anaesthesia
Ionsys®	Fentanyl	2006	Listed as discontinued by FDA	Iontophoresis	Pain relief
Zingo®	Lidocaine	2007	2008	Needle free powder injector	Local anaesthesia
Synera®	Lidocaine & tetracaine	2005	Marketed	Heated patch	Local anaesthesia
Sumavel DosePro®	Sumatriptan	2009	Marketed	Needle free liquid injector	Migraine
Zecuity®	Sumatriptan	2013	Yet to be marketed	Iontophoresis	Migraine

Unfortunately there have been a couple of high profile companies with reasonably well-developed technologies in this sector that have failed in the last couple of years. It appears that these failures were more to do with 'business' reasons and perhaps capital availability, rather than the pure technical merits of the technologies in question. However, they have not done the sector any favours in terms of its external perception as both failures have ultimately lost their investors money.

Transpharma was founded in 2000 and was developing a radio frequency micro-channeling product for the delivery of a number of actives. The company raised substantial sums to cover development and conducted several successful phase I studies including a collaboration with Lilly for the delivery of parathyroid hormone (PTH). Unfortunately, the PTH phase II trial failed in 2011 and Lilly terminated the agreement, which left Transpharma looking for investment from elsewhere. This investment was not forthcoming and the assets and IP of the company were sold for $3.6 million in 2012 to Syneron who appear to have done little with them to date.

Altea Therapeutics (founded in 1998) developed a system that used thermal ablation to create channels through the stratum corneum which were then used to deliver

drugs from patches through the skin. They raised in excess of $60 million in venture capital and had a significant collaboration with Amylin and Lilly but folded in 2011 after essentially running out of capital. All the assets of Altea were acquired by Nitto Denko in 2012 for an undisclosed fee.

It is not really the place of this article to speculate on the specific reasons for the withdrawal of most of the active products that have been approved by FDA and it is not always clear why they have been withdrawn from the market. Suffice to say, some products simply did not sell in sufficient numbers to warrant their place on the market and others were deemed as possibly unsafe and withdrawn because of that. What is clear is that none of these products has yet proved to be anywhere near a commercial success for their developers and that this area is a difficult one to make profitable headway in.

4. Active topical and transdermal delivery – tomorrow

There are several companies and academic institutions still pursuing the development of active topical and transdermal technologies and some of these are summarized in Table 5. In addition to those listed in Table 5 it is hoped that the new owners of the technologies discussed in the previous section can continue their development towards a product.

Table 5. Examples of companies and institutions developing active topical and transdermal delivery technologies.

Company	Technology	Development programs
Nitric Bio	Iontophoresis	Onychomycosis, Warts
Transcu Group	Iontophoresis & 'ionic passive'	Unclear if internal development is on-going
Power Paper	Iontophoresis	Onychomycosis phase 2 Psoriasis, Local pain
Iomed	Providers of inotophoretic technology, components & hardware	n/a
Travanti Pharma		
Isis Biopolymer	Iontophoresis	Anti-aging
OBJ	Magnetophoresis	Numerous
Phosphagenics	TPM enhancers	Pain, diabetes, acne
Zosano	Coated microneedles	Osteoporosis
Corium	Biodegradable microneedles	Osteoporosis
Theraject	Dissolvable microneedles	Vaccines, proteins, pain
3M	Silicone hollow & solid miconeedles	Numerous
Vaxxas	Coated microneedles	Vaccines

Company	Technology	Development programs
Queens University Belfast	Swellable microneedles	Numerous
AdminMed	Steel microneedles	Unclear if internal development is on-going
Georgia Inst. of Technology	Microneedles	Numerous
Emroy University	Microneedles	Numerous
Cardiff University	Microneedles	Gene delivery
University of Queensland	Coated microneedles	Vaccines
University College Cork	Silicon microneedles	Vaccines
University of Maryland	Microneedles	Numerous
Mercer University	Microneedles	Numerous
University of Leiden	Microneedles	Numerous

It is of note that the most common technologies listed in Table 5 are various versions (coated, biodegradable, dissolvable, hollow, silicone and swellable) of microneedles. There are at least five companies and five university based research groups in this space and the hope must be that this concentration of research effort is enough to deliver a successful product. There are a number of key questions that those developing microneedle delivery systems will probably need to address at some point and these include the following:

- Intellectual property – is there a clear position?
- Fragmented development efforts in industry and academia - is some consolidation needed?
- Safety (infection) – still unanswered? Anecdotal evidence suggests it's OK?
- Safety (dose dumping) – risk depends on drug and technology?
- Utility – drug delivery (how much?) limitations?
- Utility – patient acceptance studies, ease of use?
- Scale up of manufacturing – possibly the greatest challenge?

Because the exact reasons for past product and development failures are difficult to pin down it is perhaps easier to list some general possible pit-falls that those involved in current development programmes should look out for. The reasons that products have been withdrawn in the past probably include:

- Technical failures
- Safety concerns
- Manufacturing difficulties & high cost of goods
- Poor acceptance by end users
- Poor perceived benefit over existing options
- Poor sales
- Reimbursement issues

In addition to understanding the failures of the past there are certainly a number of questions and truisms that must be considered by those developing any new technology:

- Technology has a habit of running away with itself
- Technology can inspire (sometimes) misguided devotion
- The technology is not the product – the 'medicine' is
- Give equal weighting to the engineering and the drug delivery
- The technology may be impressive but is there an unmet need for it?
- The technology has to be easy to use
- Get the costs right upfront
- Can't use the market place as a test run – technical failure breeds mistrust
- If a new product gets a bad reputation it will fail quickly
- Keep it simple

5. Conclusions

It is practically impossible to predict where topical and transdermal delivery may be in 20 years time. One approach is to attempt to view it in two ways, both pessimistically and optimistically, and conclude that the truth will perhaps be somewhere between the two.

As a pessimist, one might at least hope for the introduction of a new passive transdermal system every few years, but the bulk of these may well be generic forms of those that already exist. The problem could be that the collection of existing drugs, from which nearly all current transdermals are drawn, that posses the right physicochemical and pharmacokinetic properties, and for which a compelling commercial case can be made has diminished significantly and will soon run dry. Furthermore, the rise of biotechnology has yielded more and more drugs that are never going to be delivered through the skin using passive techniques. As far as passive topical systems are concerned, the pessimist may conclude we face the recurring 'same old' problem of inefficient delivery and often poor cosmetic acceptability. If one had a negative outlook on active delivery one could conclude that the lessons of the past will go unheeded and they run into further trouble with investors ultimately loosing faith in them.

Finishing on a more positive note, an optimist may see possibilities for the introduction of more novel passive transdermal systems and improvements in the efficiency and aesthetics of topical formulations. There must be hope that the effort currently invested in microneedle research delivers a viable product within the next five or six years and that one or more of the other active approaches has sufficient 'legs' to yield a commercially successful product in a similar time frame. The continued progress that will surely be made in the miniaturization of electronics and technology in general must help the cause of the active topical and transdermal approaches currently under development.

As stated above, the realist will probably conclude the truth to be somewhere between the two scenarios outlined. It's going to be an interesting ride…

WHAT ARE THE FUTURE FORMULATIONS AND TECHNOLOGIES THAT WILL ADVANCE ORAL, TOPICAL AND COSMETIC PRODUCTS BY 2030?

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Abstract

Advances in technology are normally driven either by consumer/patient need or sometimes by creating that need. Developments in formulations and related technology are no different. The drivers over the next 15 years will be:

- a) continuing unmet therapeutic and consumer need. These are and will continue to be different in the developed markets and the resource poor settings of developing countries. Formulations will be required for new treatments to access difficult targets or to facilitate widespread distribution of existing therapies and treatments.
- b) advanced administration to refine existing and new therapies to be both more selective and to deliver individual point of therapy or tailored dose manufacture.
- c) consumer/patient convenience, in the world of polypills and multiple therapies, ease of application and administration will become a key market differentiator.
- d) changing market dynamics, where the challenge of treating the elderly and the very young are coming into greater focus.

The author will provide thoughts on how these drivers may influence the development of existing and novel formulations up to 2030.

Keywords

Adherence, age related medicines, market dynamics, novel technology, oral dosage forms, stratified medicine, topical delivery.

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1. Introduction

Innovation is primarily driven by need or want. That is, there generally has to be a pull for a technology or therapy in order to initiate its design and fulfill its development. New development through innovation come largely through two types of change in product realization: a. evolution via continuous improvement, or b. step change or quantum leap. In science and engineering the latter is generally when you have access to a new material or a new process to help enable products that will fill a need. Note, here the word 'new' is a relative term specific to a field of science: many innovations, especially in the pharmaceutical sector, come from other disciplines where they are already common place. To predict what changes may occur in an area, one has to look at both the technology status but also at what the driving forces are that will precipitate innovation.

Over the last 30 years, the pharmaceutical market has been dominated, in terms of sales, by solid oral dosage forms being sold into the so called traditional markets of the United States, Western Europe and Japan. This has been the major target for both innovator drug companies, biotechs and generic manufacturers and has been the source of the majority of 'blockbuster drugs' sales. In the last 10 years there have been subtle changes to the market which are challenging this model. The advent of drugs based on biological macromolecules has changed this picture. In the second quarter of 2013, 4 out of the top 10 drugs, by sales, were injectable macromolecule therapies and an additional one delivered by inhalation [1]. This change is being accompanied by more targeted, specific therapies e.g. the highly segmented anticancer market. In addition to the variation in therapeutic moiety, the world market place and age demographic is also changing and adding additional challenges to the development of medicines.

This modification of the market will continue over the next 15 years and will guide many of the innovative changes both in the design of medicines and their manufacture. This text will look at some of the major market forces in the pharmaceutical arena where innovation is required to sustain development and highlight the type of technology that can be used to meet that need.

2. The world market and access

In 2013 much of the focus of pharmaceutical companies has been on the 'emerging markets' particularly those of the BRIC countries: Brazil, Russia India and China (see Figure 1). These countries, along with Turkey, the middle east and those in Eastern Europe, have the most rapidly growing economies and a large population who can now afford medicines and are deemed potential customers by the pharmaceutical companies. There are still, however, many people in the world who are too poor to afford the cost of many therapies. These are predominantly in resource poor countries where lack of money is compounded with both climatic and infrastructure challenges that can restrict medicine supply [2]. However, the problem of access is not restricted to the resource poor settings. Many individuals in developed countries are unable to obtain their required medication due to monetary constraints.

In the US in 2011, 46.8 million people, 17.5% of the population, do not have vital medical insurance [3] potentially restricting their access to many medications. This includes 12.7% of children who were below the poverty line.

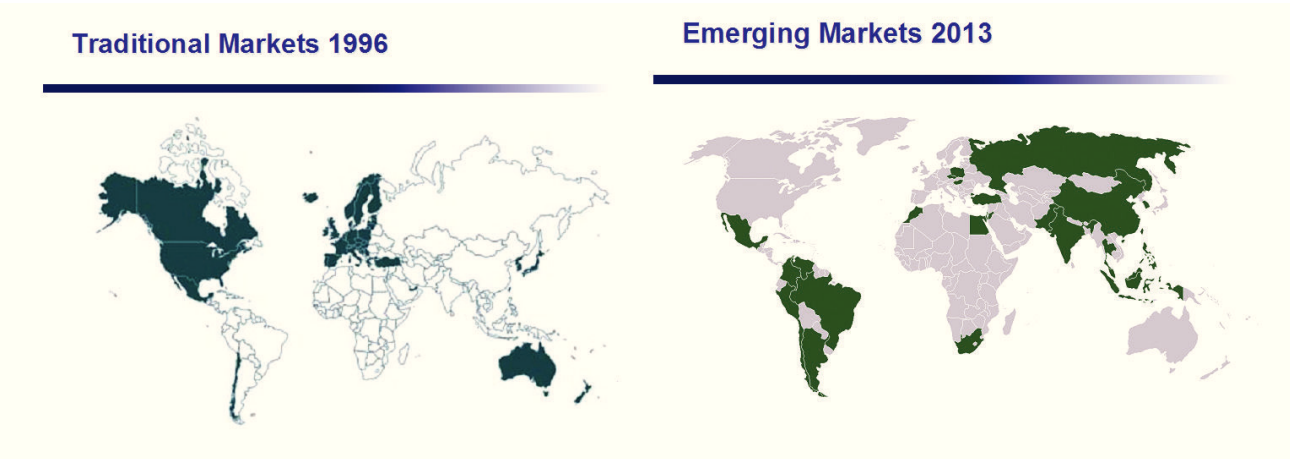

Figure 1. A comparison of the traditional and emerging pharmaceutical markets.

In order to meet the challenge of increased low cost supply, both generic and innovator companies are looking at the ways of reducing cost of manufacture. By the time most compounds reach generic status, the cost of the active pharmaceutical ingredient (API) is generally relatively low and not restrictive. For many oral dosage forms, the major part of the cost is associated with plant time and testing of intermediates and release of final product. Changes in production methods from batch to continuous manufacture could have a potentially big impact, estimated in a recent study between the Massachusetts Institute of Technology and Norvatis to be up to a 30% reduction in total production cost [4]. Many companies are investing in developmental technology to produce a continuous manufacturing system. This is either by telescoping unit operations or by flowing one operation into the next. New flow systems are being investigated for blending, granulation, milling, pre-compression, and compression (see figure 2). This can all be controlled by feedback loops from process analytical technology built within the system [5].

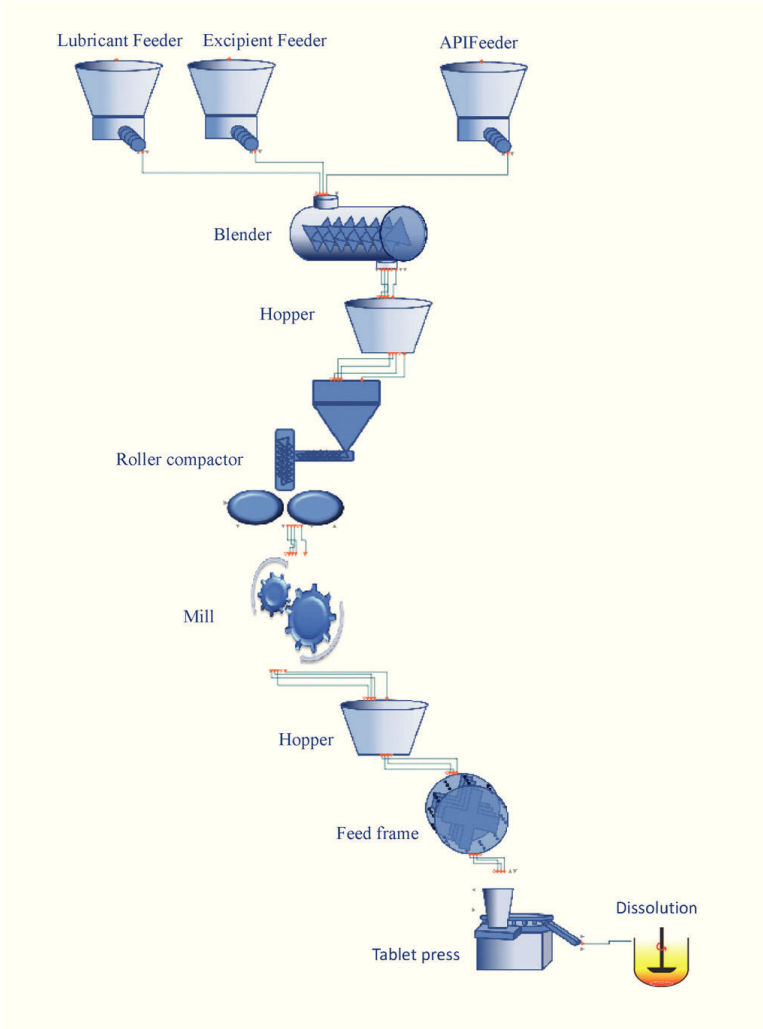

Figure 2. Schematic of a continuous tablet manufacturing process via roller compaction reproduced from R. Singh et al [5].

To enable this technology may require some product reformulation to accommodate this move to simplify the formulations. The potential for the development of novel multifunctional excipients, e.g. those which can act as a lubricant and a binder, still exists to build on the properties derived from traditional single excipients and co-processed excipients [6]. This would reduce the number of processing steps and could aid continuous processing. Continuous manufacture will also challenge the current QC/QA release testing and the regulatory paradigms, which are established around a batch release and review system. Expanded use of process analytical technology for in line testing would form a large part of the manufacturing strategy. This, coupled with parametric release testing, could enable a large reduction in product cost and enable lower price dosage forms.

3. Population demographics: age related concerns

The population of the world is set to continue growing over the next 30-40 years. With increases in the standard of living, higher quality food, and better sanitation and healthcare, the proportion of the population living to a far older age in developed nations is set to increase greatly. This change in the number of people over the age of 65 is set to have an effect on the requirements for medicines and the type of formulations that needs to be produced. Table 1 shows the projection and distribution of the total population for the United States by age. Specifically, over the next 20 years the number of people in the age group 65-84 is set to double to be over 63 million by 2030 [7]. Similarly, data according to Eurostat suggests that the number of older adults (aged over 65 years) will increase in the EU from 87 million in 2010 to 123 million in 2030 [8]. In the UK for example, older adults aged 80+ will represent 9% of the population in 2050 compared with 4.8% in 2012 [9].

Table 1. Population estimates and projections of the older population in the United States: 2010 to 2050. Numbers in thousands. Reproduced from [7].

Age	2010	2020	2030	2040	2050
Number Total	310,233	341,387	373,504	405,655	439,010
Under 20 years	84,150	90,703	97,682	104,616	112,940
20 to 64 years	185,854	195,880	203,729	219,801	237,523
65 years and over	40,229	54,804	72,092	81,238	88,547
65 to 69 years	12,261	17,861	20,381	18,989	21,543
70 to 74 years	9,202	14,452	18,404	17,906	18,570
75 to 79 years	7,282	9,656	14,390	16,771	15,964
80 to 84 years	5,733	6,239	10,173	13,375	13,429
85 to 89 years	3,650	3,817	5,383	8,450	10,303
90 and over	2,101	2,780	3,362	5,748	8,738
Percent Total	100.0	100.0	100.0	100.0	100.0
Under 20 years	27.1	26.6	26.2	25.8	25.7
20 to 64 years	59.9	57.4	54.5	54.2	54.1
65 years and over	13.0	16.1	19.3	20.0	20.2
65 to 69 years	4.0	5.2	5.5	4.7	4.9
70 to 74 years	3.0	4.2	4.9	4.4	4.2
75 to 79 years	2.3	2.8	3.9	4.1	3.6
80 to 84 years	1.8	1.8	2.7	3.3	3.1
85 to 89 years	1.2	1.1	1.4	2.1	2.3
90 and over	0.7	0.8	0.9	1.4	2.0

Already, older adults are by far the main users of drug products and currently whilst individuals over 65 represent 16% of the population they consume 31% of all of the medicines. Despite this, in many cases the old and very old are currently not well catered for in terms of their needs. This may be related to changes in physiology or in terms of capability or comorbidities. A prime example of this is swallowing. A recent review showed that up to a third of older patients can have problems swallowing and opening of capsules or crushing of tablets is considered common practice [10]. This can lead to incorrect dosing and compromising delivery systems. Problems with decreasing cognition, visual recognition and dexterity can also impede an older adults ability to adhere to what is an often complex poly-pharmacy regime.

In addition to the challenges in taking medication, the changes in older adults physiology can impact on medicines performance. The body's metabolism will change with age; drug absorption and distribution within the body will alter as body fat and blood supply changes. This can be compounded by impaired renal clearance and heightened drug interactions, all of which can effect relative toxicities and efficacies. [11]. For transdermal and topical systems the skin structure and integrity is known to change with age [12] which, could have significant effects on drug delivery to the skin. Many of these are interacting factors which means that there is no such thing as a standard older person and tailored approaches may be required to meet individual's needs. (see stratified medicine section below).

Even with the size of the current elderly population, the design of age specific dosage forms has to date been limited to paediatrics, where legislation and the enticement of increased patent exclusivity has led pharmaceutical companies to develop specific formulations. The European Medicines Agency (EMA) are now taking far more consideration over the dosing of medicines to older adults and have recently published a quality reflection paper on geriatric medicine [13].

To initiate changes in the strategy for provision of medicines for older adults, new technology is required to facilitate it. Some recent novel approaches have been suggested. Glaxo Smith Kline (GSK) recently presented a case study on a novel tablet design for enabling simple adherence to polypills [14]. This technology joins or glues unit doses together to form a single tablet. This can work with existing tablets, but would be more suitable if the products are reformulated or reshaped to allow easy combining of the units. A template system could be provided to multiple originator or generic drug companies providing a potential universal system.

Advances in oral dissolving tablets accompanied by more universal taste masking technology could open the door for companies to reformulate drugs into more age appropriate formulations for both paediatric and geriatric use. Many current taste-masking systems rely on waxy coatings which can effect the dissolution of drugs and also provide a bulky, hard to compress, excipient load. New excipients and technologies in this area could potentially add great value.

4. Compliance and the patient

Producing medicines is one challenge, ensuring the patient takes them in the correct and prescribed manner is a second, far more complex, challenge. Estimates from the World Health Organization indicate that only about 50% of patients with chronic diseases, living in developed countries, follow treatment recommendations [15]. This is bourne out by many studies in specific therapeutic areas where poor compliance to chronic prophylactic regimes, where direct benefit is not obvious to the patient, are a source of continual adverse therapeutic events in what should be controllable diseases. It is claimed that patients missing dosages costs the US healthcare system approximately $290 billion each year.

Advances in electronic sensing and monitoring, data capture and data transfer, are beginning to provide tools for both physicians and pharmacists to both monitor a patients compliance to a drug plan, but also actively remind or encourage a patient to take the dosage form. Use of feedback loops from the data monitoring systems to the prescriber and back to the patient show considerable increase in adherence [16]. The use of technologies can be extended by including sensory systems built into the packaging, or even into the dosage form itself.

A current example of this is the Proteus Digital Health™ Feedback System [17] which utilizes an ingestible silicon sensor which can be attached to tablets. This is activated by stomach acids to produce an electronic signal that can be captured by a local monitoring device. This can subsequently be transferred, either by computer or smart phone, to a central monitoring facility providing real time feedback on patients compliance to drug therapy. This system is currently added externally to the tablet but, as costs fall, one can foresee a time when units of this type can be built into the formulation at time of manufacture. At this time, cost would restrict usage in all medications. However, for vital anti-infective, diabetic, HIV, cardiovascular or oncology compounds this could have real therapeutic benefit.

For topical products such as cream and ointments, this would be far harder to achieve in the dosage form, although smart packaging systems could be utilized. Electronically registering transdermal patches, activated once backing strips are peeled away and skin contact made are not, however, beyond current sensing and reporting technology.

5. Unmet therapeutic need: targetted therapies

For several therapeutic areas, notably the treatment of excess inflammation, there is a move to try to repurpose current systemically delivered oral dosage forms to more targeted local therapies. This change is driven by the premise of increasing local efficacy for reduced systemic side-effects. Topical treatments to treat skin, lung, mouth and eye diseases are well precedented. The treatment of gut inflammatory diseases such as inflammatory bowel disease and ulcerative colitis are now being targeted by orally delivered topical treatment rather than systemic approaches. A lot of this approach will rely on suitable molecular properties of the API. However,

the formulation technology to deliver drug to the site of action in the colon will be required. Coating systems to bypass the small intestine have been well established for many years, however, the challenge in deriving a formulation that can spread over the colon surface and reach the distal colon to deliver the drug is not insignificant. Examples of current approaches to this include the reformulation of cyclosporine for topical colon delivery [18] an approach which is producing encouraging clinical results.

A whole range of molecules are under investigation for topical delivery to the skin for acute dermatitis, puritis and acute eczema. For many of these prospective treatments, the molecular constraints of drug delivery through the stratum corneum are a limiting factor. Despite extensive research over the past 30 years, the panacea of effective and acceptable permeation enhancement to enable the delivery of molecules outside of the normal transdermal spectrum (low molecular weight moderately lipophilic log P), is still beyond the current formulators' grasp. In recent years the language of topical delivery has evolved from that of a non-invasive therapy to minimally invasive treatments, targeted at delivery of both therapeutics and high value cosmetic treatments, such as Botox. The development of micro-needle systems [19], through the creation of both materials and new manufacturing processes, have moved the goal posts for potential transdermal and intradermal molecules. The formulations to compliment these new 'devices' either already exist or will require some development to take advantage of the microchannels within the systems. Whilst microneedle systems are not an answer to all skin problems, especially those conditions that cover a wide area of the skin surface, they are a step forward towards local and systemic delivery via the skin which is set to be exploited over the next decade.

6. Stratified medicine - tailored individual therapies

As described above with respect to medicine for older adults, there is potentially large variation in the parameters which produce an effective safe dose of a medicine for patients. Currently, therapies are based on giving a dosing regime that has been worked out on a population basis, where the effective dose is suitable for an 'average' patient. This means that many patients are effectively under or overdosed or may be prescribed a medication which will not be efficacious due to variations in their genetic or phenotypic make up. There is now a push from regulators and a pull from physicians to develop treatments which are tailored to an individual's needs. This is the basis of personalized or stratified medicine.

For many treatments, companion diagnostic units are already a mandatory accompaniment. This is the case for all new cancer treatments which tend to be very specific for cancer types. This is now extending to other treatment areas where specific diagnostics will accompany treatments. Simple at point of care diagnostics or use in physicians surgeries could drastically improve dosing. Tests for renal clearance, enzymatic profiling and body fat levels could greatly increase the specifics of oral systemic dosing. Hydration meters are already in use to prescribe the optimum cream type to help hydrate dry skin. The problem comes with being

able to vary the dose at point of care or from within pharmacies in order to dispense bespoke dosage levels. The GSK system described previously could enable this with several dose strengths that could be added together e.g. placebo, 1mg and 3mg dose units could be added together in pairs to give dose ranges across 1-4mg +6 mg. Other technologies in development such as Sticky Web from GSK and 42 Technology [20] and printing drugs onto placebo tablets offer far more flexibility. The advent of 3D printer technology brings into focus the ability to produce bespoke devices and dosage forms at the point of dispensing, post simple diagnostic tests. The main barriers to entry of this type of product for general use will be the cost and the regulatory compliance, where validation of the system and application of cGMP may prove very difficult. It may be far easier to develop this type of system for hospitals and primary care units, some of which still have formulating pharmacies.

The future is hard to predict, but the role of the pharmaceutical scientist in delivering novel and innovative medicines to meet the market and patient needs is a key part of any therapeutic strategy.

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