Front. Chem. Sci. Eng. 2014, 8(2): 225–232
DOI 10.1007/s11705-014-1429-7

REVIEW ARTICLE

Semi-solid materials for controlled release drug formulation: current status and future prospects

Michelle TRAN, Chun WANG (✉)

Department of Biomedical Engineering, University of Minnesota, 7-105 Hasselmo Hall, 312 Church Street S.E., Minneapolis, MN 55455, USA

Abstract Semi-solid materials represent an important category of inactive ingredients (excipients) of pharmaceutical products. Here we review several common semi-solid polymers currently used in the controlled release formulations of many drugs. These polymers are selected based on their importance and broad scope of application in FDA-approved drug products and include several polysaccharides (cellulose, starch, chitosan, alginate) and carbomers, a group of mucoadhesive synthetic polymers. Glyceride-based polymers used in self-emulsifying drug delivery systems (SEDDS) will also be discussed for its importance in formulating poorly water-soluble drugs. Unique features and advantages of each type of semi-solid materials are discussed and examples of their use in oral delivery of drugs are provided. Finally, future prospects of developing new and better semi-solid excipients are discussed with the objective of facilitating clinical translation.

Keywords semi-solids, polymer, excipient, controlled release, drug delivery

1 Introduction

The use of polymers in drug formulation and delivery has enabled great advancement in drug therapy [1]. The use of engineered polymeric biomaterials can help preserve and improve specific functions of drugs through targeted local or systemic delivery, modulated release, and sustained release to deliver desired dosages over appropriate periods of time. The objective of designing the most ideal drug delivery systems is to transport the desired amount of drug to the right body location at the right time. It begins with pre-formulation studies to understand solubility and compatibility properties of drug molecules. These parameters affect the development of the final drug product formulation, and dictate the choice of the most appropriate combinations of active pharmaceutical ingredient (API) and excipients (many of which are polymers). Through subsequent drug formulation studies, one must find solutions to potential problems such as drug instability, excipient/drug or excipient/excipient incompatibility [2].

The purpose of using excipients is to enhance the bioavailability, biocompatibility, pharmacological activity, solubility, toxicity profile, stability, cosmetic acceptability, and time duration [2]. Many natural and synthetic polymers have been used as excipients and incorporated into delivery systems of drug products approved by the Food and Drug Administration (FDA). These drugs are given to patients through different routes. The most common one is the oral route. The physico-chemical properties of excipients must be understood so that the appropriate materials or combinations of materials can be selected to suit particular drugs.

Semi-solid materials are a major category of drug excipients [3]. The term "semi-solids" has a broad definition that refers to a large variety of materials that share a similar physical form of between pure liquid and pure solid at ambient temperature and pressure, and in particular, with relevance to medicine, physiological environment. It may include viscous fluids, gels, ointments, slurries, creams, emulsions, dispersions, etc. Apparently, a large number of specific materials including polymeric materials may fall into this category. Here we will review some of the most common semi-solid materials used in FDA-approved drug products. In choosing these particular materials, we consider primarily their popular use in approved products. Experimental materials in developmental, preclinical stages that are not yet used in drug products on the market are excluded from our discussion. To further focus our discussion, we do not include hydrogels, microparticles, nanoparticles, and liposomes. Excellent reviews on these subjects can be found elsewhere [4–7].

Received January 22, 2014; accepted February 22, 2014

E-mail: wangx504@umn.edu

We will begin with a briefly discussion on the importance of controlled release formulations of drugs and the roles that excipients play in achieving optimal efficiency of drug delivery. What follows is a detailed discussion on the selected semi-solid materials, highlighting their specific properties that make them excellent drug excipients. We will focus on selected polysaccharides including cellulose, starch, chitosan, alginate, and a family of synthetic polymer called carbomers. Cellulose esters are the most useful, acting as hydrophilic matrices aiding delivery of poorly water-soluble drugs [8]. Some of the most popular cellulose derivatives used are hydroxypropyl methylcellulose and ethylcellulose. Starch, such as Contramid, is another material of the polysaccharide family. Its kinetics of swelling and hydrophilicity allow for a faster drug delivery [9]. Another versatile polysaccharide is chitosan, utilizing encapsulation systems to remain in the intestine and deliver the drug [10]. Similar to chitosan, alginates were found to be useful for swelling and gelling of an encapsulation system which delivered the drug by controlling dissolution [11]. Carbomers act as mucoadhesive polymers, prolonging the gastric residence time similar to chitosan [12]. In light of the enormous challenge of delivering poorly water-soluble drugs, we will further discuss self-emulsifying drug delivery systems exemplified by Gelucire, which are mixtures of glycerol, glycerides, polyethylene glycol (PEG), and PEG modified glycerides, for the improvement of bioavailability of lipophilic drugs by forming emulsion droplets [13]. All the excipients above will be reviewed mainly in the context of oral delivery route, probably the most common and important route of drug delivery. Finally, some of the future trends in developing excipients that are superior in property, novel in structure, and readily translatable to clinical application, will be analyzed.

2 Semi-solid excipients for controlled drug delivery

In order to achieve desired drug delivery profiles, rate-controlled mechanisms involving excipients must be understood and utilized. Many delivery systems have been designed to improve drug release, both systemic and locally, where the permeability, or transport, of particular drugs must be accomplished [14]. These systems provide advantages through ease of administration, reduced dosing frequency and concentration, improved bioavailability, and lowering overall costs.

The loading capacity of a drug formulation is limited by the ratio between the drug and the rest of the inactive ingredients, or excipients. Excipients typically constitute the majority of a drug formulation. The ideal drug delivery system controls the stability and release of the drug through modulating its excipient/drug interactions, so that the optimal therapeutic efficacy is reached. Traditionally, excipients have been used as fillers or binders such as in tablets and are responsible for holding together drug particles and to assist disintegration and dissolution of the tablets. Because of this, a binder's solubility and associated properties affect binder and drug interactions [15], and by choosing or modifying the properties of the binder, one can improve the bioavailability of the drug through enhanced stability and optimized release. In the case of oral drug delivery, absorption in the intestines is required before the drug reaches the circulation [16]. Drug absorption depends on the solubility properties of the drug through the gastrointestinal wall, yet it was found that 40% of new drugs displayed low water solubility [17], thus greatly hinders drug absorption. Many drugs also tend to crystallize during transportation and storage. For these reasons, they do not always fully reach the bloodstream, and excipients must be used to enhance the effectiveness of the drug by reducing crystallization, often because extended chain conformations in polymeric structures can block furthering crystal growth [18]. This has led to systems using solid and semi-solid excipients in order to improve bioavailability and solubility of these hydrophobic and unstable drugs, particularly in supersaturated dosage forms.

Semi-solid materials may take on different physical forms. For a material soluble in a solvent, including water or organic solvents, a viscous solution can be prepared, which may be categorized as a semi-solid. To attain sufficiently high viscosity, several conditions must be met to create intermolecular contact between solutes and solute/solvent molecules. This can be achieved by preparing the solution at high solute concentration, using polymeric materials to maximize intermolecular interactions and chain entanglement, or selecting certain solutes and solvents capable of intermolecular attractive bonding (such as hydrogen-bonding). As intermolecular linkages render the material insoluble, gels are formed. Instead of dissolution, gels swell in good solvents such as water in the case of hydrogels. Some hydrogels exhibit a dynamic thermo-responsive behavior allowing it to switch physical states from liquid to gel reversibly as temperature varies from room temperature to physiological temperature [19]. Micelles and liposomes are self-assembled structures consisting of large numbers of repeating molecular building blocks such as amphiphilic block copolymers or lipids. Dispersions and emulsions are often metastable suspensions of hydrophobic particles of micrometer or nanometer scale that are stabilized by surfactants at the particle/water interface and less regularly structured than micelles or liposomes.

Over the last several decades, great advancement has been made in polymeric biomaterials as controlled drug delivery systems [1]. A large variety of novel synthetic and natural polymers as well as micro and nano-particulate systems have been investigated and tested in various preclinical and clinical settings. The function of these

biomaterials in drug delivery is to act as excipients. However, relatively few novel biomaterials have emerged from years of research to gain the status of FDA approval as acceptable excipients for human use. In addition to superior performance in enhancing drug delivery, polymeric biomaterials must demonstrate excellent biocompatibility, where the interactions of the excipient and drug neither interferes with homeostasis nor triggers adverse immune response. In other words, the toxicology of biomaterials has to be thoroughly studied and deemed as safe [15]. Nonetheless, a few common polymeric biomaterials systems have been widely adapted as excipients in FDA-approved products. They have proven record of safety as well as effectiveness in enhancing drug delivery with a wide range of drug administration routes, dosages and formulations.

3 Polysaccharides and lipid-based systems

Many polysaccharides are excellent semi-solid excipients because they are often chemically or biologically degradable through hydrolysis or enzymolysis, giving them excellent biocompatibility [20]. Some of them have good solubility in water and can be used as viscous solutions in drug formulation. These natural polymers such as cellulose derivatives, chitosan, alginate and gelatin can also be crosslinked into hydrogels due to their affinity toward water. Hydrophilic and amphiphilic synthetic polymers such as carbomers and PEG-type block copolymers including Pluronics are widely used in soluble and gel formulations.

Many polysaccharides are uniquely suited for controlled drug delivery. Normally, the binding of a drug to a polysaccharide polymer improves its physico-chemical and biological properties, making it biocompatible, biodegradable, and nontoxic. Polysaccharides are ideal drug carriers because these materials contain large quantities of reactive groups for drug fixation, such as OH, NH_2, and COOH. The two main purposes of using polysaccharides as excipients are (1) to control the timing of drug release to achieve the right drug concentration, and (2) to deliver to the right location, or control the distribution of drugs *in vivo*. A high loading capacity is normally desired so it is ideal to have high drug-to-excipient ratios in all formulations. Likewise, surface energies of excipient materials affect the behaviors of the dosage form and the drug's tendency to aggregate around the excipient carrier [15]. Due to the high capacity of drug binding and solubilization, polysaccharides can be used in relatively small quantities and still be effective excipients in formulations. For site-specific delivery, selectivity is executed by targeting moieties attached to the drug carrier. Specific cell surface receptors found at the target tissue site may be recognized by the targeted drug carriers, resulting in greatly enhanced drug retention at the desired anatomical locations. In this regard, polysaccharides are superior candidates for targeted drug delivery, because multiple functional chemical groups are available not only for drug binding, but also for attachment to targeting ligands. Polysaccharides can be used for both systemic and local drug release, providing high molecular mass, negative charges and appropriate hydrophilicity/hydrophobicity balance, to ensure efficacy and biocompatibility [21].

Lipid-based excipients are used to modulate drug absorption activity. Lipids are collections of fats and similar substances such as fatty acids, glycolipids, and phospholipids [16]. They can take on different forms including micelles and liposomes, which allow for improved drug delivery through easy conjugation, high drug loading capacity, and rapid cellular uptake [22]. Lipid systems of triglycerides, lipophilic surfactants, and cosolvents are common in pharmaceutics and particularly useful as better solvents for poorly water-soluble drugs, which, given orally, tend to precipitate in the lumen of the gastrointestinal tract. For example, three types of lipid-based formulations are developed to mitigate the problem of oral drug precipitation in the gut [22]. According to the lipid formulation classification system, Type 1 formulations are oils which can be digested. They are simple, compatible with capsules, but have poor solvent capacities. Type 2 formulations are water-insoluble, self-emulsifying drugs. Those are unlikely to lose solvent capacity but contain turbid oil and water dispersions. Type 3 formulations are both self-emulsifying drugs and water-soluble. They are clear and absorb without digestion, but can lose solvent capacity [23]. It is therefore imperative to choose the appropriate lipids, cosolvents, and surfactants in designing a formulation so as to achieve good drug/excipient compatibility. For instance, if there is inadequate drug solubility in physiological medium and poor compatibility with the excipient, drugs can be easily released but target doses will not be achieved due to poor absorption by the tissues. On the other hand, when the drug is highly soluble in lipids-based excipients, it may limit delivery too, due to poor drug release from the excipients. Therefore, compatibility between the drugs and lipid-based excipients based on physical, chemical, and physiological interactions must be considered during formulation development [2].

4 Cellulose derivatives

One of the most popular renewable, natural polymers is cellulose, which are water permeable but not soluble. Cellulose and a large number of its chemical derivatives are used to control the rate of drug release and prevent crystallization, and thus, they represent an important category of excipients. Cellulose acetate has been used successful in three different HIV drugs, a pain reliever, two

antibiotics, and five flavonoids, just name a few. Not only is it the most abundant natural polymer, cellulose passes through the body safely and some of the derivatives can be broken down into natural metabolites in the gastrointestinal tract [24]. A cellulose derivative that has proven to be useful in oral drug delivery is hydroxypropyl methylcellulose (HPMC). Due to its bioadhesive properties, it is often used as a binder in granulation. Unlike unmodified cellulose, HPMC is soluble in water. It is able to increase contact with the intestinal epithelium membrane for poorly water-soluble drugs such as cyclosporin. It's well-established that oral drug formulations containing HPMC prolong the residence time in the small intestine, allowing increased drug transportation across the intestinal wall to enter the circulation [21].

While hydroxyalkyl- and carboxyalkyl-cellulose such as HPMC and carboxymethyl cellulose (CMC) are water-soluble, most alkyl modified cellulose esters are not. Even soluble cellulose derivatives can be crosslinked chemically to form hydrophilic matrices. Such hydrophilic matrix-based drug delivery systems release drugs from the polymer dosage forms when matrices (or tablets) are in contact with the gastrointestinal fluid. The surface of the tablet hydrates into a vicious mucilage in order to release the drug. Once the drug is released directly from the surface, it diffuses through the hydrated layer which can then be eroded. This mechanism of action for hydrophilic matrices enables poorly water-soluble drugs to be better delivered via diffusion through the hydrophilic matrix systems. The rate of drug release depends on many factors including the coating membrane porosity for diffusion of the drug. The polymer molecular weight is usually directly related to drug release, but other factors such as hydration rate and viscosity of the material need to be taken into account. Surface area of the tablet also affects drug release. Convex base drug tablets have the highest increase in matrix surface area from swelling, whereas concave shaped tablets are the lowest. A flat surface tablet is intermediate. When two matrices were formulated together, the system then contains double the amount of the drug for delivery but with a lower surface area-to-volume ratio [25]. However, using two different grades of the same polymer often does not significantly improve the formulation but adds to its complexity. Therefore, simple formulations including a single cellulose derivative polymer are more desirable [15]. One of the most influential factors is the polymer-to-drug ratio in the formulation. From examining dissolution curves of aminophylline and propranolol hydrochloride for HPMC, as the polymer-to-drug ratio increased, the dissolution of the drug decreased. Therefore, for formulations containing HPMC, a minimum of 20% of the polymer to drug ratio should be used if possible [15].

Another important cellulose-like polysaccharide commonly used in oral capsules is xanthan gum [26]. This linear polysaccharide can be produced by the *Xanthomonas campestris* bacterium through viscous fermentation. Xanthan gum, being completely water-soluble, can also be used in a hydrophilic matrix delivery system. Compared to other hydrophilic matrix polymers, its properties make its formulation more unique. Due to its wide viscoelastic range, the hydrated polymer erodes at a very slow rate resulting in a slow drug release rate. However, xanthan gum swells extensively from hydration, also due to its viscoelasticity. This allows for a large amount of drug dosage formulated into smaller sized tablets [15].

A unique type of diffusion-based drug delivery system with cellulose esters that has been utilized is osmotic-controlled oral delivery system (trademarked as OROS by Alza). Here, the dissolved drug is delivered through osmotic pressure from a capsule or tablet in a controlled manner. The permeation rate through the membrane of the tablet made of cellulose ester again depends on solubility, molecular weight, and solute concentration of the materials. Excipients often incorporated into the system include hypromellose, or HPMC and cellulose acetate as the semipermeable membrane. The concept can be applied to capsules for controlled oral delivery over an extended period of time. The osmotic-controlled release has been used for many drugs such as oxybutynin, isradipine, and verapamil [25].

5 Starch and amylose

Similarly to cellulose derivatives, starch has been used for controlled drug delivery as a natural, soluble or crosslinked polymer. An often used starch excipient is contramid, a hydroxypropyl high-amylose starch [9]. Contramid and other starches are often used for oral controlled release formulations. They work by controlling drug release through its kinetics of swelling. Starch's increased swelling capacity governed by its own self-assembly process called starch retrogradation, which entails realignment of molecular chains to form crystalline regions, results in a faster drug delivery. Once delivered orally, it provides a slow release of the medication in the gastrointestinal tract in order to reach an efficient drug concentration in the blood. Because the drug-blood level variations decrease, dosing frequency, side effects, and costs all decrease as well. With high-amylose starch, a gel membrane can form at the water-tablet interface, increasing sustained release. An increase in temperature and hydration leads to faster swelling of a highly porous material structure, which controls the water uptake and drug diffusion, which is why it is such an effective sustained release system. Moreover, specific cross-linked starch form ionic or neutral networks leading to higher drug loading capacity. These starch matrices are also able to control and accelerate drug release by enzymatic activity, such as the addition of alpha-amylase to the formulation to accelerate matrix decomposition [21].

Amylose and amylopectin, two building blocks of starch, can be modified and denatured further through carboxymethylation, aminoethylation, and acetylation, using activated hydroxyl groups on the polysaccharides. The preparation of starch tablets involves heating slurries. To improve the hardness and stability, a phosphorous oxychloride crosslinking agent can be added. Spray-drying is also employed to heat and gelatinize the excipient. Introduction of starch into a formulation of common drugs, such as acetaminophen, results in better sustained release for over 24 h (with 60% starch excipient) whereas conventional dosing only provides a few hours of drug release [21].

6 Chitosan

Chitosan, a versatile and biocompatible linear cationic polysaccharide, is essentially a poly(D-glucosamine) [10]. It has limited solubility in aqueous media, but it's often used for drug encapsulation and its bioadhesive properties enable its use in promoting site-specific drug release in the gastrointestinal tract. Depending on the degree of deacetylation of chitin, precursor of chitosan, it is possible to tune the water solubility of the materials using pH, for example, having a soluble material only at acidic pH but turn to insoluble at neutral pH, which serves as the basis of dosage retention in the small intestines [15]. Besides extension of the drug carrier residence time at the absorption site due to mucoadhesion of the polymer, chitosan may help open up tight junctions of the intestinal epithelium to assist in drug absorption. Chitosan can be further modified to prepare microspheres, films, and gels to be used in depot systems, and has been used in formulations of anti-inflammatory drugs [21].

7 Alginate

Similarly to chitosan, alginate is a natural polysaccharide [11], but is oppositely charged than chitosan. Consisting of copolymerized guluronic acid and mannuronic acid, alginate comes with various monomer compositions with slightly different physical properties. For example, molecular chains of alginate with higher mannuronic acid content tend to be more rigid and mechanically stronger. It's numerous anionic charges and hydrogen-bonding potential with waters give rise to the excellent water solubility of alginate. While uncrosslinked alginate is useful, alginate is more commonly used as ionically crosslinked hydrogels (such as crosslinked by Ca^{2+}). Crosslinked alginate hydrogels swell significantly in water, and when loaded with drugs, the concentration gradient of drugs between the surrounding environment and the alginate gel itself controls release of the drugs in a often Fickian process, assuming minimal interaction exist between drugs and matrix, uniformity of the matrix, and maximal stability of the crosslinked network during the diffusion process. On the other hand, when the crosslinking Ca^{2+} is not uniformly distributed throughout the alginate matrix but is more concentrated to the outer layer, then more capsule-like beads or tablets with dense shells can be prepared with drug release rate potentially more precisely determined by the diffusivity through the shells, and can be used to achieve sustained drug release. Tablets coated with alginate can also be protected from destrution in the acidic stomach environment due to alginate swelling posing as barrier for diffusion. Besides oral drug formulations, alginate is also a popular material in cell encapsulation, where swollen hydrophilic alginate matrix protects transplanted cells from attack and rejection by the immune system of the host, the classic concept of immunoisolation since the 1960s [15].

8 Carbomers

Carbomers, or polyacrylic acid, are synthetic, hydrophilic cross-linked polymers that have been proved to be useful as high-molecular-weight excipients [12]. They can act as mucoadhesion polymers similarly to chitosan, allowing for prolonged gastric residency due to adhesion to gastric mucosa. They are produced by polymerizing acrylic acid followed by chemical crosslinking of carboxylic acid groups with no more than 2% of various crosslinking agents. Tablets containing carbomers can be prepared by direct compression or wet granulation. The quantity of carbomers used in the formulation controls the rate of release of the active drug. Carbomers are commonly used in aqueous solvent-based systems such as topical, oral, or mucosal gels. It allows for decreased dosing, lowered side effects, and a more constant drug level. As high-viscosity and high-swelling hydrogels, they allow the active drug to be suspended in the interstitial spaces of the gel or dissolved in the polymer itself. The acid groups present in carbomers bind to and equilibrate with basic active drugs. The active drug can then be absorbed through the gastrointestinal tract due to the acidity of the stomach where the active drug is displaced from the hydrogel. Studies have shown that carbomers utilize a site-of-action delivery by a semi-enteric or complete enteric controlled drug delivery, which means it can achieve a slow dissolution in the stomach and a fast dissolution in the intestine (similar to another type of enteric polymer Eudragit, which are copolymers of acrylic and methacrylic acid esters) [27]. This bioadhesive polymer allows for a desired localized delivery, where the drug can be applied at low, steady rates slowly absorbing into the bloodstream. Drugs that have used carbomers as the release controlling excipient include aspirin, atenolol, furosemide, isoniazid, theophylline, and verapamil [15].

9 Formulating poorly water-soluble hydrophobic drugs

A large number of small-molecule drugs are either poorly soluble or insoluble in water. Around 40% of all new drug candidates are insoluble in water. Poor water solubility results in low bioavailability, which is a significant challenge facing the pharmaceutical industry. Semi-solid excipients have unique advantages for oral delivery of poorly water-soluble drugs. Hydrophobic drugs can be formulated in semi-solid excipients and loaded into hydrophilic soft, elastic gelatin capsules. These soft gels release hydrophobic drugs in gastric fluid, which are quickly absorbed, resulting in improved bioavailability [28]. For example, the bioavailability of 5-mg glipizide Scherersol® softgel is improved compared to the same drug in tablet form [15]. Other poorly soluble drugs successfully formulated in softgels include nifedipine, cyclosporin, and temazepam. Common semi-solid materials used to fill softgels are PEG-400, glycerin, and propylene carbonate [15], because they are compatible with the gelatin capsule.

Self-emulsifying drug delivery systems (SEDDS) have been used to improve the oral bioavailability of poorly water-soluble and lipophilic drugs [29,30]. The isotropic mixtures of drug and oil/lipid surfactants in the system form emulsion droplets which remain in the gut. These lipids can improve the oral bioavailability of drugs by increasing the effective drug solubility in the gastrointestinal tract and increase the gastric retention time [16]. These systems improve drug delivery by avoiding the drug dissolution step that limits the absorption rate of poorly water-soluble drugs in their crystalline state. Therefore, the efficiency of SEDDS is determined by the rate of emulsification and their droplet size. To fill capsules with SEDDS using semi-solid formulations, the semi-solid mixture is first heated above its melting point. Then, the incorporation of the active substances is introduced by stirring, and the capsule is filled with the heated mixture. The capsule filling is completed once cooled to room temperature [17]. SEDDS can be incorporated into soft gelatin capsules, too, such as cyclosporin, ritonavir, and saquinavir [16].

Hydrophobic semi-solid excipients are well established as controlled releasing materials for drug delivery systems. Glycerides, a group of insoluble excipients, are often used as controlled releasing matrices, as solvents, suppository bases, or the oil phase in emulsion products. Glycerides are produced by direct esterification of glycerol with fatty acids with saturated or unsaturated hydrocarbon moieties. Unfortunately, obtaining its derivation naturally can be chemically complex and may exist in a number of unstable forms. It is a low cost pharmaceutical product and can be studied to understand its behavior but is still limited in its application [15].

One of the most well known glyceride-based semi-solid excipients used in SEDDS is Gelucire [13]. These materials are mixtures of glycerol, glycerides, PEG, and PEG modified glycerides. Manufactured by Gattefossé, this material is prepared by polyglycolysis with PEG. In general, increasing the amount of PEG esters compared to glyceride creates a more hydrophilic base. Properties of Gelucire in terms of melting, crystallization, and hydrophobicity can vary, making it a versatile and desirable excipient in many drug formulation applications. Gelucire is used in many drug products and is digested and metabolized safely. Furthermore, it was found that the most active lipases hydrolyzing Gelucire started in the stomach. Due to this gastric lipase, gastric digestion step is the most important in drug delivery using Gelucire [31]. Unfortunately, due to the complex nature of glycerides (being a mixture) and possible altered profile and instability during storage, Gelucire could be particularly difficult to formulate [15].

10 Future prospects

There is a well-established panel of semi-solid materials with well-documented history of successful use in FDA-approved drug products. Some of the common semi-solid excipients, as we have reviewed above, provide a variety of properties and functions for many common pharmaceuticals, as solvents, stabilizers, sustained release agents, site-specific release agents, and absorption enhancers. As new drug candidates arise, this panel of FDA-approved materials is the source of excipients, from which new formulations are realized [32].

Despite tremendous success on the market, significant challenges in drug formulation and drug delivery still exist. One challenge is solubilizing poorly water-soluble drugs, which constitute roughly 40% of all new drug compounds. Rapid emergence of biologics including peptides, proteins, and nucleic acid therapeutics has posed unique challenges [33]. Large molecules are more difficult to be absorbed by the body, more fragile, prone to denaturation and degradation, prone to aggregation during storage, with low bioavailability and high cost. With the exception of antibodies, whose glycosylation provides protection and stability, many biologics have *in vivo* half-life too short for lasting effect. While existing excipients could always be repurposed for new applications, it is becoming apparent that these problems are not likely overcome by using existing excipients. However, developing new excipient is no easy task. In addition to scientific challenges, it must face significant regulatory hurdles [34], because no drug maker would use or invest in a new excipient unless it's already used in an approved product, and regulatory agencies would not approve a drug product unless all its excipients involved are either already approved or with extensive safety record, which requires tremendous investment from the drug maker to acquire, hence, a

classic "catch-22". New excipients of the future must promise to solve significant costly problems of the pharmaceutical industry to warrant significant investment from the industry.

Existing semi-solid excipients have many drawbacks. Many of them, such as Gelucire, are mixtures with multiple molecular components. Quality control and understanding of the interactions involving each and every ingredient can be difficult. Because of molecular heterogeneity, the degradation and metabolism of each ingredient may be different and the impact of that on drug delivery can be uncertain. Many existing excipients are natural products, which is largely why they are molecularly heterogeneous, and their metabolism and degradation *in vivo* can be influenced by fluctuations of enzyme concentration at different anatomical sites and therefore, the release of drugs can be difficult to control. As natural products, many excipients may trigger allergic reactions, such as in the case of Cremophor EL, which is essentially PEGylated castor oil. As an effective excipient and solvent for poorly water-soluble drugs such as Taxol, Cremophor EL causes much adverse effect on human patients, and much effort has been paid to find replacements for Cremophor EL with little success. Furthermore, many excipients are rather "single-minded", that is, they are often capable of only limited function, such as dissolving a drug, whereas drug release is simply diffusion of a matrix system as a result of swelling or erosion with little control and sophistication. Drug release in these systems is of low precision; it is only possible to achieve organ-specific drug release but not possible to selectively target specific cells.

To develop semi-solid excipients of the future, one may need to focus on solving these problems facing the existing excipients. A shift from natural materials to semi-synthetic or totally synthetic materials is already being noted. Carbomers are good examples of chemically simple materials that provide support in oral drug delivery, although the polymer structure and composition is still not well defined. More sophisticated yet scalable synthetic techniques should be explored to produce better-defined polymer excipients with tunable degradation and metabolism and drug release profile. Completely synthetic hydrophobic semi-solid polymers [35] with controlled degradation and sustained drug release are expected to gradually replace natural polymers in the formulation of poorly water-soluble drugs and may be particularly suited for sustained release of biologics such as protein drugs [36,37].

A previously tested, effective approach in the development of new excipients is through combination of existing materials but in ways that confer new and better properties. Examples of this approach include Gelucire (through conjugation of PEG with glyceride) and polysorbates (through conjugation of PEG with sorbitan), both of which are extremely useful semi-solid excipients. This strategy can be further expanded to produce excipients with more variety to even include thermo-sensitivity to allow *in situ* gelation [38] and delivery and targeting ligands to deliver drugs only to specific cells and subcellular compartments [39,40]. Such "super-excipients" must also be extensively tested for biocompatibility and processes of synthesis and purification must be optimized for industrialization.

References

1. Langer R, Tirrell D A. Designing materials for biology and medicine. Nature, 2004, 428(6982): 487–492
2. Benson H, Watkinson A. Topical and Transdermal Drug Delivery: Principles and Practice. Hoboken, NJ: John Wiley & Sons, 2012, 1–407
3. Niazi S. Handbook of Pharmaceutical Manufacturing Formulations, Semisolid Products, Volume 4. Florida: CRC Press, 2004
4. Vashist A, Vashist A, Gupta Y K, Ahmad S. Recent advances in hydrogel based drug delivery systems for the human body. Journal of Material Chemistry B, 2013, 2(2): 147–166
5. Varde N K, Pack D W. Microspheres for controlled release drug delivery. Expert Opinion on Biological Therapy, 2004, 4(1): 35–51
6. Bao G, Mitragotri S, Tong S. Multifunctional nanoparticles for drug delivery and molecular imaging. Annual Review of Biomedical Engineering, 2013, 15(1): 253–282
7. Allen T M, Cullis P R. Liposomal drug delivery systems: from concept to clinical applications. Advanced Drug Delivery Reviews, 2013, 65(1): 36–48
8. Edgar K J. Cellulose esters in drug delivery. Cellulose, 2006, 14(1): 49–64
9. Ravenelle F, Rahmouni M. High-Amylose Starch for Controlled Drug Delivery. Polysaccharides for Drug Delivery and Pharmaceutical Applications. ACS Symposium Series 934, American Chemical Society, 2006, Chapter 4, 79–104
10. Bernkop-Schnürch A, Dünnhaupt S. Chitosan-based drug delivery systems. European Journal of Pharmaceutics and Biopharmaceutics, 2012, 81(3): 463–469
11. Tønnesen H H, Karlsen J. Alginate in drug delivery systems. Drug Development and Industrial Pharmacy, 2002, 28(6): 621–630
12. Singla A K, Chawla M, Singh A. Potential applications of carbomer in oral mucoadhesive controlled drug delivery system: a review. Drug Development and Industrial Pharmacy, 2000, 26(9): 913–924
13. da Fonseca Antunes A B, De Geest B G, Vervaet C, Remon J P. Gelucire 44/14 based immediate release formulations for poorly water-soluble drugs. Drug Development and Industrial Pharmacy, 2013, 39(5): 791–798
14. Hashida M, Takakura Y. Pharmacokinetics in design of polymeric drug delivery systems. Journal of Controlled Release, 1994, 31(2): 163–171
15. Karsa D, Stephenson R. Excipients and Delivery Systems for Pharmaceutical Formulations. Cambridge: Royal Society of Chemistry, 1995, 36–189
16. Wasan K. Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery. Hoboken, NJ: John Wiley & Sons, 2007, 1–196
17. Tang B, Cheng G, Gu J C, Xu C H. Development of solid self-

emulsifying drug delivery systems: preparation techniques and dosage forms. Drug Discovery Today, 2008, 13(13–14): 606–612
18. Liu H, Ilevbare G A, Cherniawski B P, Ritchie E T, Taylor L S, Edgar K J. Synthesis and structure-property evaluation of cellulose ω-carboxyesters for amorphous solid dispersions. Carbohydrate Polymers, 2014, 100: 116–125
19. Cui L, Jia J, Guo Y, Liu Y, Zhu P. Preparation and characterization of IPN hydrogels composed of chitosan and gelatin cross-linked by genipin. Carbohydrate Polymers, 2014, 99(2): 31–38
20. Liechty W B, Kryscio D R, Slaughter B V, Peppas N A. Polymers for drug delivery systems. Annual Review of Chemical and Biomolecular Engineering, 2010, 1(1): 149–173
21. Marchessault R, Ravenelle F, Zhu X. Polysaccharides for Drug Delivery and Pharmaceutical Applications. Washington, DC: American Chemical Society, 2006, 19–339
22. Pouton C W. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. European Journal of Pharmaceutical Sciences, 2006, 29(3–4): 278–287
23. Pouton C W, Porter C J. Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. Advanced Drug Delivery Reviews, 2008, 60(6): 625–637
24. Ilevbare G A, Liu H, Edgar K J, Taylor L S. Impact of polymers on crystal growth rate of structurally diverse compounds from aqueous solution. Molecular Pharmaceutics, 2013, 10(6): 2381–2393
25. Wilson C, Crowley P. Controlled Release in Oral Drug Delivery. New York: Springer, 2011, 1–412
26. Badwaik H R, Giri T K, Nakhate K T, Kashyap P, Tripathi D K. Xanthan gum and its derivatives as a potential bio-polymeric carrier for drug delivery system. Current Drug Delivery, 2013, 10(5): 587–600
27. Wen H, Park K. Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice. John Wiley & Sons, 2010, Chapter 5
28. Li Z, Kozlowski B M, Chang E P. Analysis of aldehydes in excipients used in liquid/semi-solid formulations by gas chromatography-negative chemical ionization mass spectrometry. Journal of Chromatography A, 2007, 1160(1–2): 299–305
29. Gursoy R N, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomedicine and Pharmacotherapy, 2004, 58(3): 173–182
30. Patel P V, Patel H K, Mehta T A, Panchal S S. Self micro-emulsifying drug delivery system of tacrolimus: Formulation, *in vitro* evaluation and stability studies. International Journal of Pharmaceutical Investigation, 2013, 3(2): 95–104
31. Fernandez S, Rodier J, Ritter N, Mahler B, Demarne F, Carrière F, Jannin V. Lipolysis of the semi-solid self-emulsifying excipient gelucire® 44/14 by digestive lipases. Molecular and Cell Biology of Lipids, 2008, 1781(8): 367–375
32. Inactive ingredient search for approved drug products. Inactive ingredients in FDA approved drugs. US Department of Health & Human Services. 21 Sept. 2013, http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm
33. Burgess B E. Optimizing drug delivery for modern biologics. BioPharm International, 2012, 25(5): 30–32
34. Koo O M Y, Varia S A. Case studies with new excipients: development, implementation and regulatory approval. Therapeutic Delivery, 2011, 2(7): 949–956
35. Amsden B G. Liquid, injectable, hydrophobic and biodegradable polymers as drug delivery vehicles. Macromolecular Bioscience, 2010, 10(8): 825–835
36. Rigo M V, Allemandi D A, Manzo R H. Swellable drug–polyelectrolyte matrices (SDPM) of alginic acid characterization and delivery properties. International Journal of Pharmaceutics, 2006, 322(1–2): 36–43
37. Wan J. Microfluidic-based synthesis of hydrogel particles for cell microencapsulation and cell based-drug delivery. Polymers, 2012, 4 (4): 1084–1108
38. Heller J. Patient-friendly bioerodible drug delivery systems. Journal of Controlled Release, 2009, 133(2): 88–89
39. Nicolas J, Mura S, Brambilla D, Mackiewicz N, Couvreur P. Design, functionalization strategies and biomedical applications of targeted biodegradable/biocompatible polymer-based nanocarriers for drug delivery. Chemical Society Reviews, 2013, 42(3): 1147–1235
40. Salamat-Miller N, Chittchang M, Johnston T P. The use of mucoadhesive polymers in buccal drug delivery. Advanced Drug Delivery Reviews, 2005, 57(11): 1666–1691