The New Era Of Functional Excipients - An Innovative Approach In Design Of Dosage Forms

Recently, the concept of *Quality by Design* has been applied to pharmaceutical development and production of drugs, contributing to more robust formulations, with less time and cost of development and where a single ingredient can be a solution for many features. A more efficient and less variable scale-up is chasing with a uniform regulatory criteria process for approval of its use. The potential of functional excipients have being revolutionizing the pharmaceutical industry.

In the industrial production of drugs, active substances rarely have the physical requirements needed for processing. An example is the compression of drugs in solid forms, where the addition of adjuvants in formulations becomes a requirement. In tablets, the API and excipients alone almost never have the physical and mechanical properties suitable for a compression technology. The excipients can also be found in variable amounts for active substances, contributing to functionality of formulations [(9)]. Success of pharmaceutical development is conditioned by a wide variety of factors. From an even traditional concept of "passive" and "inert" excipients we have gone to progressively more complex substances, functionally highly specific.

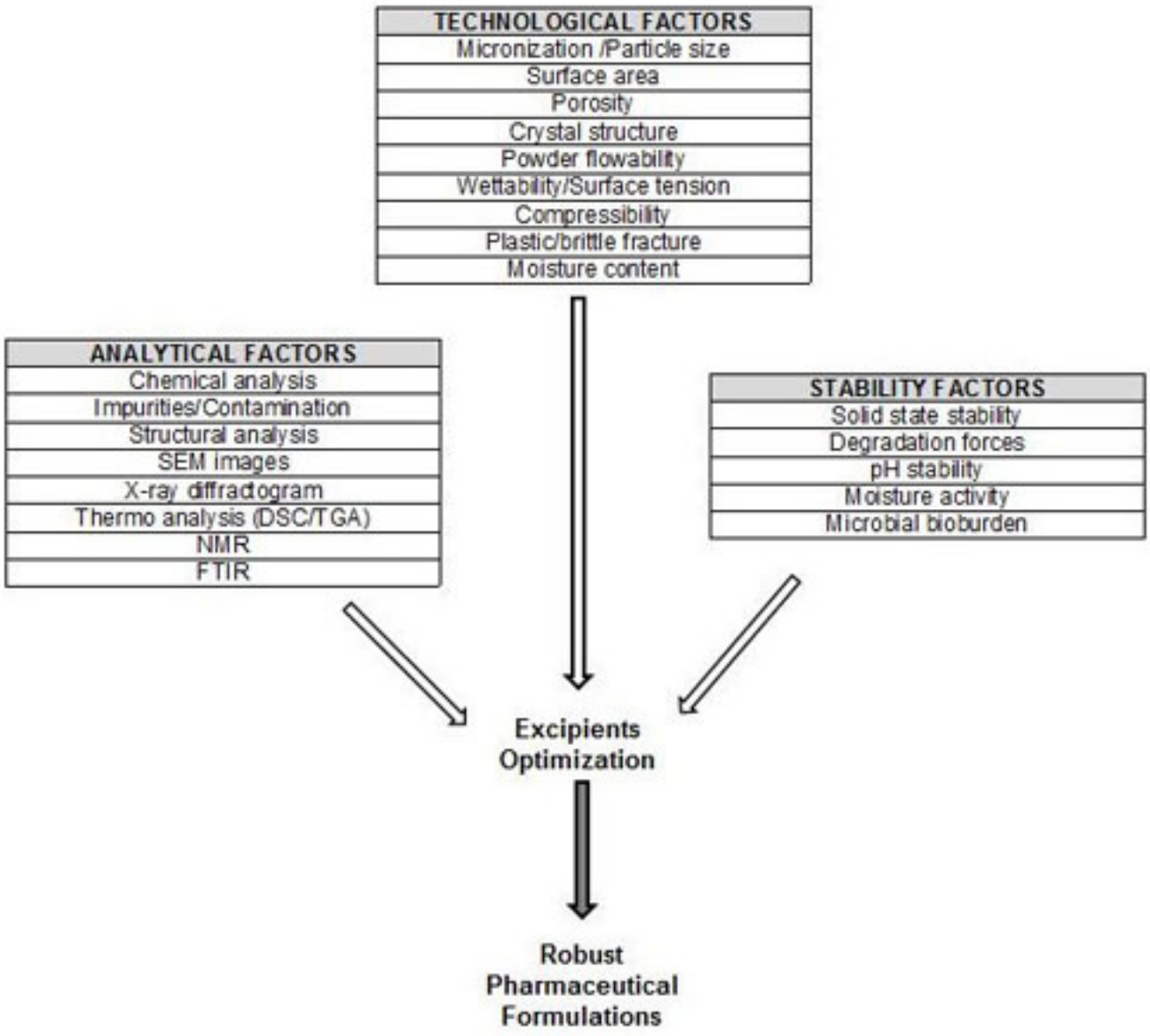

Figure 1 - Assessment for pharmaceutical formulation development, based on excipients properties.

Direct compression is regarded as an easy, economically and technologically flexible process today with novel interest in producing tablets. The high technological value excipients will enhance the flow characteristics of solid mixtures and their compaction, leading to the establishment of cohesion/adhesion forces between materials. Eliminating granulation, sometimes critical, the production is simplified and disintegration of tablets improved. Unlike classic ingredients, even at small quantities, the high functional performance is transmitted to entire formulation, facilitating production of large batches. The easy mixing, dilution with other components and the resulting density and compaction of powders reflects on the flow of mixture during compression, which is essential for tablets with uniformity of mass, even at high compression speeds.

These new ingredients are synergistic optimized combinations of fillers, binders, lubricants, disintegrants and glidants that reduces segregation by enhancing flowability. In finished products hygroscopicity may be changed, improving stability along time or minimized degradation reactions. The design of these particles becomes important to know its surface area, irregular shape, roughness and intrinsic porosity, polarity, wettability and its surface energy [(3)]. There are three ways to functionalize pharmaceutical excipients: physical changes, chemical modifications or by co-processing between those with drugs or excipientsOuvir

In the physical changes, materials less crystalline or even amorphous, allow the formulation to present a better dissolution and bioavailability, based on thermodynamic factors and molecular interactions, giving them the functional advantages compared to traditional[(3)]. The materials engineering introduces different degrees of functionality due to polymorphism and isomerism. The amorphous forms of lactose have better compaction behaviour. In general, the functionality of excipients is related to changes in particlesOuvir

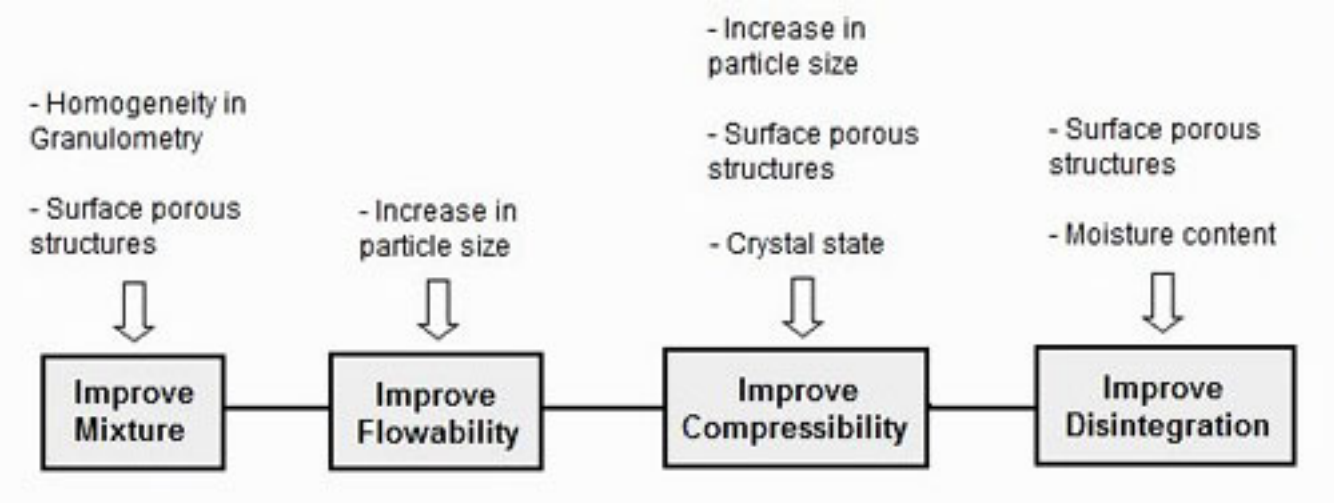

Figure 2 - Influence of changes in the excipients particles on the resulting functionality in a technological process.

The chemical modifications in cellulose derivatives improves the solubility, viscosity and different coating properties due to substitution reactions, polymerization, acid hydrolysis or alkaline oxidative degradation of vegetable fibers, resulting in various types of microcrystalline cellulose, with different residual moisture and apparent densities, good flow and standardized particle size distribution.

The co-processing allows the combination of two or more materials by processes such as fluid bed drying, resulting in highly functional and more stable materials [(3)]. Variables as the processing temperature, presence of inhibitors or catalysts, pressures, mixture systems or activation by solvents atomized, allows the control of diameter, size and shape of resulting particles. Products with better properties are obtained compared with a simple mixture of individual components [(10)]. A big advantage of co-processing is that it induces mostly physical changes rather than altering the chemical structure or the stability of excipients. However, bonds breaking, reorientation, stereochemical environment and the intermolecular forces

established are responsible for the new shapes that determine the formation of a new material [1]. Several interactions result from the combination of particles: hydrogen bonding, van der Waals forces, polar and ionic interactions, covalent links or even chemisorption complexes by absorbing carriers. The greater the number of ingredients involved the more complex are these interactions, which must be controlled and monitored. Also the moisture in those excipients is of particular importance, influencing the balance of water adsorption [1] and disintegration in solid dosage forms.

The co-processing can occur among or between excipients and active substances, improving the dissolution profiles of the latest. The optimum ratio for the components results from experimental studies and compatibilities, targeting the development to products with less variability between batches [10]. The co-processing usually occurs by a combination of ingredients that create plastic deformation with those with brittle behaviour, a symbiosis required for the best compression performance [9].

The official pharmacopoeias define quality tests for the analytical characterization of the individual excipients but regarding determination of their functionality, methods are mostly omitted. In such combinations, the biggest challenge is the gap of a unique official monograph analysis. To approve the use of these functional adjuvants there is no uniform global strategy. The harmonization has high importance to the general acceptance of these new ingredients [6]. Compared to their classical relatives, the analytical techniques focus on the characterization of particle size distribution, SEM images, the specific surface area and X-ray diffractogram obtained for these materials[8]. Also the techniques of HPLC, DSC, NMR and FTIR are used in order to aid and control their structural properties [3]. For a new excipient to be accepted by regulatory authorities, it is required to demonstrate studies on chronic and acute toxicity, pharmacokinetics, toxicology and reproductive effects, as considered a new entity. The co-processed excipients may be GRAS granted if the excipients from which it gets are also certified by regulatory authorities[9], with well-documented toxicological studies.

According to the European Medicines Agency [4] for pharmaceutical development, the use of an excipient should be well reasoned, explaining its role and justification for inclusion in the amount used. Studies of compatibility and safety must be observed, especially if using a new route of administration or a higher amount than previously described. Despite this some regulatory issues still exist, and their widespread use could be accepted based on a document type (EMF, *Excipient Master File*) that relates the properties of the product, supported on its physicochemical characterization and in the safe use basis.

In Europe this process has been very restrictive as opposed to other countries like the U.S.A. The safety profile must be obtained medicine by medicine, not being all the results accepted for a given innovative excipient to another pharmaceutical product. Due to high development costs, many pharmaceutical companies will eventually continue to prefer the traditional ingredients listed on the international database of non-active ingredients. The U.S.A. has been more flexible, working with an opinion on ICH safety guidelines requirements of a technical committee of

qualified persons (IPEC, International Pharmaceutical Excipients Council), on request of companies that intend to launch into a market[5]. This Council is a tripartite organization with representatives from America, Europe and Japan, working for the harmonization of regulatory requirements for those materials [9]. After a favourable pronunciation, FDA may already accept some of these ingredients as "approvable", encouraging the benefits of new drugs and innovative therapeutic methods [5]. Such approval is not based on individual evaluations on the excipient but on drug products where it has already been used, along with other safety information and data on the EMF described.

In parallel with the companies developing these new products, a committee of experts in toxicology pronounces on the knowledge of the new excipient considering the route of administration and prepares an impartial report on the substance, based on all existing knowledge related. It prepares CTD format documentation on safety of the excipient and data allows the FDA to shorten and simplify the regulatory approval. Also due the nature of changes made on the classic excipient and based on its use in food or cosmetics industry or even in other countries, may be excessive and unnecessary to perform some of the extensive range of tests required by FDA safety standards[5]. The co-processed excipients presented with minor molecular changes causes undoubtedly the best regulatory acceptance with the medicines authorities.

Some major world-known companies have been dedicated to innovation in these functional excipients obtained in accordance with the latest technologies, quality standards and cGMP requirements. Also combinations of ingredients mixed with certain drugs of common use have also emerged on the market, in the form of premixes, allowing in many cases a simple technological step to obtain the final product. Be aware that these products require a long period of time from conception to commercialization, a continuous investment in developing these materials is required, along with new challenges for drug delivery. The development of these excipients is a new area, particularly in oral dispersible tablets, in formulations for controlled release or also inhaler devices. It is estimated that in the future, nanotechnology and biotechnology can bring changes to this field.

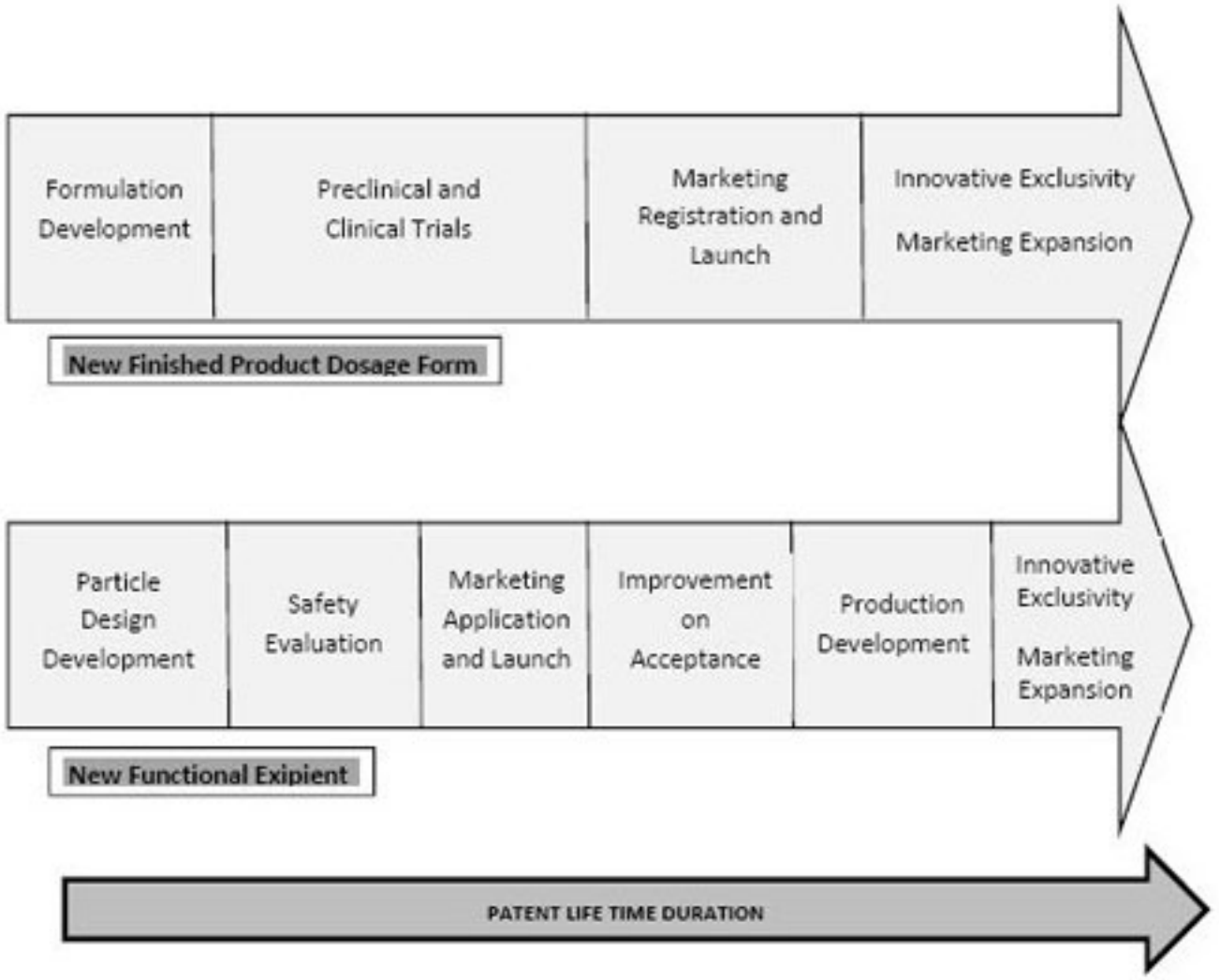

Figure 3 – Comparative development timelines for a finished pharmaceutical product and a new functional excipient.

The most common combination of co-processed excipients consists of mixtures of microcrystalline cellulose, lactose monohydrate, cornstarch, crospovidone, colloidal anhydrous silica and lubricants such as magnesium stearate, stearic acid or sodium stearylfumarate. Economically, these premixes may have a higher cost compared to traditional excipients but are offset by lower production times [(9)].

The combination of corn starch with lactose allows matching the smooth flow and deformation of spray-dried lactose with the elastic deformation and the rapid disintegration of starch[(8)]. Combinations of cellulose and lactose with similar purposes are available too. Enhanced features have also been made with materials such as sorbitol and mannitol, converting them into materials with better rheological characteristics, better suited for direct compression.

During processing, testing of compressive strength, hardness, disintegration time

and dissolution profiles are most often used to make comparisons with the procedures using the traditional ingredients.

One of the newest application areas of these excipients has been in orodispersible products, where the technology requirements of the previously mentioned features are added to the high solubilization capacity of oral mucosa, the pleasant taste and texture resulting from the disintegration. Those are important factors in the choice of excipients to incorporate [2] [9], with several studies published comparing the properties of several commercial alternatives for rapidly dissolving oral formulations. The alternatives marketed differ in the time of disintegration with slight differences, distinguishing between mixtures of co-processed excipients, mannitol and modified derivatives of the modified sugars, which are all competing for the same effect on immediate release, but with different specificities also depending on the target public to whom they are intended.

In future one will continue to assist the new approaches and concepts of functionality. Property rights and patents of several of these associations can bring economic benefits to companies, who bet on their development and use. The particular characteristics of functional excipients, along with their physical and chemical properties weight son the choice between conventional excipients and the co-processed ones. Some people with specific needs such as diabetics, hypertensive or intolerant to lactose or orbital are also significant arguments for the development of co-processed excipients. The use of drugs with the necessary requirements of quality, safety and efficacy meet economy and simplicity of production processes [7], resulting in reduced costs of finished drug forms and in easier and more efficient administration.

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Links:
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