Expert Opinion

Excipients with specialized functions for effective drug delivery

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Introduction: There is a growing need for the development of pharmaceutical excipients that could improve product performance and overcome the shortcomings of new drug moieties, such as their poor solubility and membrane permeability, as well as to aid with modern manufacturing processes.

Areas covered: Different types of functional excipients are discussed in this paper, in terms of their roles in modern dosage forms to optimize drug delivery and manufacturability. Functions of specialized excipients that are covered in this article include the enhancement of drug membrane permeability, the improvement of drug solubility and stability, the regulation of drug release in response to feedback mechanisms and assistance with the production of dosage forms.

Expert opinion: Modern drug delivery systems rely on sophisticated excipients with multiple functions to improve overall product performance. The excipient market is expected to grow substantially with emerging trends in the development of these advanced drug delivery systems.

Keywords: absorption enhancer, biopharmaceutics classification system, controlled release, multifunctional, pharmaceutical excipient

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1. Introduction

A drug is usually not administered alone in its pure form, but is combined with additives or excipients to facilitate the preparation of an effective drug delivery system [1]. The term 'excipient' originated from the Latin word *excipiens* derived from the verb *excipere*, which literally means 'to mix.' Pharmaceutical excipients have originally been included in dosage forms to serve as vehicles and to provide the correct consistency, shape or mass. Excipients were conventionally not considered to be pharmacologically active or expected to participate in the pharmacological activity of the active pharmaceutical ingredient in any way. For this reason, the importance of pharmaceutical excipients in drug delivery has for a long time been largely underestimated [2-4]. Traditionally, the following typical pharmaceutical excipients have been incorporated in dosage forms [3]:

- fillers/bulking agents to make up volume,
- binders to assist in tablet formation during compaction,
- disintegrants to improve tablet breakup,
- lubricants to prevent sticking to punches,
- propellants to assist in delivery of inhalants from pressurized cans,
- emulsifying/solubilizing agents to assist in the formation of acceptable liquid dosage forms,
- colorants or flavorants to improve organoleptic properties of dosage forms, and
- coating agents to delay drug release or improve stability.

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Article highlights.

- Excipients are not only used to formulate active pharmaceutical ingredients into administrable dosage forms, but also needed to improve product performance.
- A single multifunctional excipient could reduce cost by reducing the total number of excipients needed to effectively deliver the drug and simultaneously simplify the production process.
- Modern excipients fulfill specialized functions in advanced drug delivery systems such as enhancing membrane permeability, improving solubility, preventing degradation, controlling drug release according to the need of the patient and streamlining the manufacturing process.
- Novel excipients can be produced by chemical or physical modification of current excipients or by combining excipients in physical mixtures or through coprocessing techniques.

This box summarizes key points contained in the article.

Nowadays, a combination of excipients that fulfill different functions or a single multifunctional excipient is necessary to meet the needs of modern formulation scientists to produce pharmaceutical products with improved performance. Furthermore, a single multifunctional excipient reduces the final product cost by reducing the total number of ingredients needed in a formulation and simplifying the preparation method. It also reduces the chances of excipient–drug or excipient–excipient interactions [5,6].

The International Pharmaceutical Excipient Council has defined a pharmaceutical excipient as follows: 'Substances, other than the active drug substance or finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture, protect, support, enhance stability, bioavailability, or patient acceptability, assist in product identification, or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use' [7]. The modern tendency is to develop pharmaceutical products with excipients that have specific functionality-related characteristics. The term 'functionality' in this context can be described as a material with a specific property that improves the manufacture, quality or performance of the drug product [8]. Excipients have been categorized into three classes based on their functions in dosage forms namely those that influence stability, those that influence drug release and absorption and those that influence manufacturability [9]. High-functionality or multifunctional excipients are defined as those excipients that are able to contribute to at least two functions in a formulation through a single ingredient. These functions include improved processability of active pharmaceutical ingredients into dosage forms, better tablet binding and disintegration, higher drug stability, increased drug solubility and enhanced drug bioavailability [10,11]. The schematic illustration in **Figure 1** compares the components and characteristics of a conventional pharmaceutical product containing multiple excipients and an improved pharmaceutical product containing a single multifunctional excipient.

The type of excipient required in a dosage form to optimize drug delivery is determined by the type of constraint preventing the drug from reaching the optimum therapeutic plasma level. It is, however, important to realize that multiple factors are usually simultaneously responsible for drug delivery problems [12]. This strengthens the view that a single multifunctional excipient or multiple excipients each with a specific function are needed to address multiple factors contributing to the poor performance of certain conventional dosage forms and/or to address the unfavorable physicochemical properties of some of the new drug moieties in order to optimize drug delivery.

2. Excipients enhancing membrane permeability

Limited permeability across biological membranes is arguably one of the most significant obstacles that prevent the achievement of therapeutic blood levels of macromolecular and hydrophilic drugs administered by enteral routes of administration. Although several strategies have been proposed to overcome low membrane permeability, coadministration of chemical permeation enhancers has been identified as a promising solution. Unfortunately, the use of chemical permeation enhancers as functional excipients in dosage forms has been restricted by indications of toxicity associated with their ability to enhance drug absorption. For example, although the drug absorption-enhancing effects of bile salts are reversible, they can still cause damage to the intestinal mucosa due to the removal of phospholipids and proteins from the cell membranes. Surfactants such as polyoxyethylene ethers as well as the acylcarnitine, palmitoyl-DL-carnitine chloride, not only showed high potential as absorption enhancers but also decreased cell viability in several *in vitro* and *in vivo* tests. It was shown, however, that certain compounds provide effective drug absorption enhancement without causing significant toxicity and thereby keeping the possibility alive of finding a commercially viable absorption-enhancing agent [12,13].

Many excipients included in formulations that are assumed not to influence drug absorption may have an unwanted effect on the active pharmaceutical ingredient's pharmacokinetics, which can affect its efficacy or lead to side effects [14]. On the other hand, permeation-enhancing excipients can be intentionally included in formulations to modulate drug absorption in a controlled manner by different mechanisms and thereby optimize systemic drug delivery [15]. The simplicity with which absorption-enhancing excipients can be incorporated into

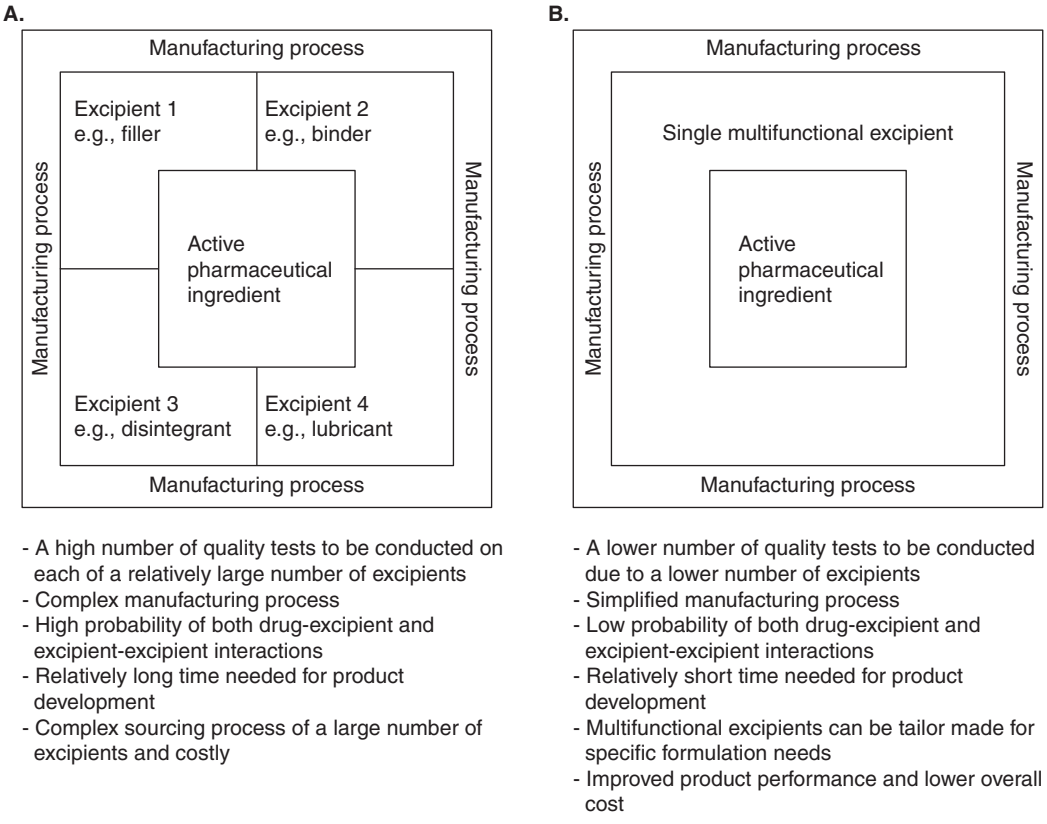

Figure 1. Comparison of the components and characteristics of **A)** conventional pharmaceutical product containing multiple excipients and **B)** improved pharmaceutical product containing a single multifunctional excipient.

dosage forms renders them more financially feasible than the development of sophisticated parenteral dosage forms [16].

Different permeation-enhancing agents with diverse chemical structures have been investigated for their ability to overcome the physical barriers of the cell layers lining the different enteral routes of drug administration [17]. They improve drug absorption by means of several different mechanisms such as disrupting cell membranes to increase transcellular passive diffusion [18], loosening of tight junctions to allow paracellular transport [19], serving as substrates for transport carriers [20], serving as vectors to carry cargo molecules across the membrane [21] or inhibiting active efflux transporters [22].

A large number of chemical permeation enhancers have been investigated for their drug absorption-enhancing effects by means of different mechanisms of action. Selected examples of these permeation-enhancing agents for the intestinal route of administration are given in **Table 1**.

Some of these absorption-enhancing agents have also been investigated for their drug permeation-enhancing effects across mucosa of other routes of administration. The cationic polysaccharide, chitosan and its derivatives have, for example, been found to enhance drug absorption not only across the intestinal epithelium [23], but also across the nasal [24], buccal [25] and pulmonary mucosa [26] as well as transdermally [27].

The profile of the intended pharmaceutical product needs to be considered for effective permeation-enhancing agents to be developed rationally. Important factors include stability of the permeation enhancer at the storage conditions of the product (e.g., room temperature vs cold chain), stability in the type of formulation (e.g., solution vs solid dosage form) and cost of the final product if the permeation enhancer is included as an excipient, which is also linked to its potency or the amount that needs to be included [19].

3. Excipients enhancing drug solubility

Membrane permeability and the solubility behavior of a drug can be considered as key determinants of oral bioavailability. Classical examples of drugs for which solubility has presented as a challenge in oral dosage forms include griseofulvin, digoxin and chloramphenicol [28]. Based on the ability of a drug to permeate a biological membrane and the solubility, drugs can be classified into four groups (**Table 2**).

An astonishing 40% of all new active pharmaceutical ingredient candidates possess poor aqueous solubility [29]. The aqueous solubility of a compound can be considered as a major indicator for the solubility in the intestinal fluids and consequently contributes to bioavailability issues [30]. The contribution of solubility to bioavailability problems can be attributed to the fact that

Table 1. Examples of potential permeation-enhancing excipients categorized according to their mechanisms of action for the intestinal route of administration.

Examples of permeation-enhancing excipients according to mechanism of action				
Membrane disrupting agents/modulators of membrane fluidity	**Modulators of tight junctions/intercellular joints**	**Substrates of uptake transporters**	**Vectors/carriers across membranes**	**Inhibitors of efflux transporters**
Hydroxypropyl beta cyclodextrin, dimethyl beta cyclodextrin [85] Medium-chain fatty acids, cyclodextrins, bile salts [86,87] *N*-acetylcysteine, *p*-*t*-octyl phenol polyoxyethylene-9.5 [88] *N*-[8-(2-hydroxybenzoyl) amino] caprylate [89]	Zonula occludens toxin, delta G [90] Dodecylmaltoside [91] Cyclodextrin, chitosan and sodium lauryl sulfate [92] Poly(methacrylic acid) grafted with poly(ethylene glycol) [93] Sodium caprate and melittin [94] *Aloe vera* gel and whole leaf material [95] Sinomenine [96]	Vitamin B12 [97] Pro-drugs targeting hPepT1 transporters [98]	Sodium *N*-[8-(2-hydroxybenzoyl) amino] caprylate [99] Penetratin [100] Oligoarginine, Penetratin [101]	Verapamil, cyclosporine [22] Surfactants such as polysorbate [102] Thiolated poly(ethylene glycol)-polyethylenimine copolymer [103]

Table 2. The biopharmaceutics classification system (BCS) [104].

Class	Solubility	Permeability
1	High	High
2	Low	High
3	High	Low
4	Low	Low

dissolution is often the rate-limiting step in the absorption of moderate to poor water-soluble compounds [31]. The influence of the solubility of a drug on the dissolution rate is evident from the Noyes–Whitney equation [32]:

$$\frac{dC}{dt} = k(C_5 - C_t),$$

where $\frac{dC}{dt}$ is the dissolution rate of the drug; k is a constant; C_s is the solubility of the drug and C_t is the concentration of the drug in the dissolution medium, for example, gastrointestinal fluids.

Typically, compounds that are classified as BCS class II or class IV drugs dissolve slowly, poorly and irregularly and as a consequence can pose serious systemic delivery challenges. These challenges include incomplete release from the dosage form, poor bioavailability as well as high inter-patient variability [33]. To improve the solubility of poorly soluble compounds, various techniques and excipients are available. Since this article focuses on excipients, those that are used to improve drug solubility will be discussed in the following sections in more detail, while the techniques fall outside the scope and will not be covered except where it directly relates to excipients. Excipients that have an effect on the solubility of drugs can be classified into the following groups [34]:

- Surfactants,
- water-soluble organic solvents,
- water-insoluble lipids (oils),
- organic liquids/semisolids,
- phospholipids,
- cyclodextrins and
- buffers.

3.1 Surfactants

Surfactants can play a functional role in pharmaceutical dosage forms such as modulating solubility and, therefore, the bioavailability of compounds. Nonionic surfactants and polymers are widely used for this purpose and their popularity stems from both their high surface activity and low toxicity [35]. Surfactants can increase the solubility of substances by either a direct co-solvency effect or uptake into micelles [34]. In **Table 3**, examples of commonly used surfactants used in pharmaceutical formulations are listed.

Some examples of drug products commercially available that contain surfactants are Neoral® (active ingredient: cyclosporin A; surfactant: Cremophor RH 40), Kaletra® (active ingredients: lopinavir and ritonavir; surfactant: Cremophor EL) and Rapamune® (active ingredient: sirolimus; surfactant: polysorbate 80) [34].

3.2 Water-soluble organic solvents

The solubility of a drug can be higher in a mixture of solvents than in one solvent such as water alone. This phenomenon is called co-solvency [36]. By adding a co-solvent, the polarity of the solvent system is altered to increase the solubility of poorly soluble compounds. Water-soluble co-solvents disrupt water's self-association and reduce the ability of water to squeeze out nonpolar hydrophobic compounds, thereby increasing solubility [37].

Table 3. Examples of surfactants commonly used in pharmaceutical formulations [34,105].

Chemical group	Chemical name	Commercial name	Application and dosage form
Sorbitan esters	Sorbitan laurate	Span 20	Employed as water-in-oil emulsifiers and as wetting agents
	Sorbitan palmitate	Span 40	
	Sorbitan stearate	Span 60	
	Sorbitan tristearate	Span 65	
	Sorbitan oleate	Span 80	
	Sorbitan trioleate	Span 85	
Polysorbates	Polyoxyethylene (20) sorbitan laurate	Tween 20	Employed as emulsifiers in oil-in-water emulsions
	Polyoxyethylene (20) sorbitan palmitate	Tween 40	
	Polyoxyethylene (20) sorbitan stearate	Tween 60	
	Polyoxyethylene (20) sorbitan tristearate	Tween 65	
	Polyoxyethylene (20) sorbitan oleate	Tween 80	
	Polyoxyethylene (20) sorbitan trioleate	Tween 85	
Macrogol ethers	Cetomacrogol 1000		Emulsifier in oil-in-water emulsions Cremophors are quite effective solubilizers of hydrophobic drugs
	Polyoxyethylene (4) lauryl ether	Brij 30	
	Polyoxyethylene (2) stearyl ether	Brij 72	
	Polyoxyethylene (10) oleyl ether	Brij 97	
	Polyoxyl 35 castor oil	Cremophor EL	
	Polyoxyl 40 hydrogenated castor oil	Cremophor RH 40	
Polyglycolyzed glycerides	Polyoxyethylated oleic glycerides	Labrafil M-1944CS	To formulate water-insoluble drugs in lipid-based formulations
	Polyoxyethylated linoleic glycerides	Labrafil M-2125CS	
	Polyoxyethylated caprylic glycerides	Labrasol	

Various water-soluble organic solvents (co-solvents) are employed as solubilizers. Commonly employed organic solvents in oral and injectable formulations include ethanol, glycerol, propylene glycol and polyethylene glycol 400. The common use of these co-solvents can be attributed to their low toxicity [34,38,39].

Some examples of drug products commercially available that contain water-soluble organic solvents are Lanoxin® soft gelatin capsules (active ingredient: digoxin; co-solvents: ethanol and propylene glycol), Claritin® syrup (active ingredient: loratadine; co-solvent: propylene glycol) and Donnatal® elixir (active ingredient: phenobarbital; co-solvent: ethanol) [34].

3.3 Water-insoluble lipids (oils), organic liquids/semi-solids and phospholipids

This group includes a broad range of excipients, which are generally incorporated into 'lipid' formulations for drug delivery. Lipid-based formulations can range from simple solutions to complex mixtures of oils, surfactants, co-surfactants and co-solvents. These more complex systems are often referred to as self-emulsifying drug delivery systems or self-microemulsifying drug delivery systems [40,41].

Lipid-based formulations can enhance the bioavailability of poorly soluble substances by keeping it in solution. The simplest lipid-based formulations are prepared by dissolving the drug in a digestible oil, usually a vegetable oil or medium-chain triglyceride (e.g., fractionated coconut oil). Long-chain triglycerides such as peanut oil, corn oil, sesame oil, olive oil and peppermint oil are also included in this group. These do not present a toxicological risk and are safe food substances. Most of the oily oral formulations are filled into soft gelatin capsules but some are formulated as oral solutions [34,42].

With regard to the more complex lipid-based systems, several classes of excipients such as surfactants and co-solvents are included simultaneously with the lipid excipient. The most widely used surfactants are the nonionic surfactants especially those with a high hydrophilic–lipophilic balance. The most common examples include various solid or liquid ethoxylated polyglycolyzed glycerides and polyoxyethylene 20 oleate (Tween 80). Co-solvents are included as they can dissolve the drug or a hydrophilic surfactant. Besides this function, co-solvents can also act as co-surfactants [43].

Some examples of drug products commercially available that contain water-insoluble lipids are Prometrium® soft gelatin capsules (active ingredient: progesterone; lipid: peanut oil), Marinol® soft gelatin capsules (active ingredient: dronabinol; lipid: sesame oil) and Sandimmune® oral solution (active ingredient: cyclosporin A; lipid: olive oil) [34].

3.4 Cyclodextrins

Cyclodextrins are cyclic oligosaccharides. The most important structural feature of these compounds is their toroidal or doughnut shape. The cavity of this structure exhibits a hydrophobic character and the outside of the structure is hydrophilic [44]. Only α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin as well as some of their derivatives have advanced to the market. The two most important cyclodextrin derivatives for pharmaceutical applications are hydroxypropyl-β-cyclodextrin (HPβCD) and sulfobutylether-β-cyclodextrin (SBEβCD) [45].

Cyclodextrins solubilize drugs by forming inclusion complexes by taking up a lipophilic drug or a lipophilic part of the drug into the hydrophobic cavity of the cyclodextrin molecule. During complexation, no covalent bonds are formed and the drug molecules in complex are in rapid equilibrium with those in solution. In terms of stoichiometry, the most common type of cyclodextrin complexes is 1:1 complexes. Cyclodextrins improve the apparent solubility and thereby the dissolution rate of poorly soluble drugs by means of inclusion complexation [46].

An example of a drug product commercially available that contains cyclodextrin is Sporanox® solution (active ingredient: itraconazole; cyclodextrin: HPβCD) [34].

3.5 Buffers

Drugs that are ionizable such as weak acids or bases exhibit pH-dependent solubility. The extent of ionization of weak acidic and basic drugs depends on the dissociation constant of the drug and the pH of the dissolution medium [47]. The unionized form of a drug is less soluble than the ionized form, and it follows that by manipulating pH, solubility can be enhanced. Often, an ionizable drug can be solubilized by pH adjustment if the drug's pK_a value is sufficiently apart from the pH of the formulation (liquid formulations) [34]. Adjustment of the pH is achieved by employing pharmaceutical buffers. Examples of pharmaceutical buffers include boric acid/sodium borate and sodium acid phosphate/disodium hydrogen phosphate.

Some examples of drug products commercially available that contain buffers are Agenerase® (active ingredient: amprenavir; buffer: citric acid/sodium citrate) and Kaletra® oral solution (active ingredient: lopinavir and ritonavir; buffer: citric acid/sodium citrate) [34].

4. Excipients protecting drugs against degradation

The stability of drugs is an important aspect in the development of drug formulations. Excipients are rather known for their ability to promote drug degradation than to promote drug stability. This can be related to the fact that excipients sometimes possess functional groups that can interact with labile active ingredients [48]. However, excipients that can protect the active ingredient from degradation can fulfill an important function in pharmaceutical formulations [49,50]. In terms of promoting drug stability, excipients can be classified as follows [51]:

- Antioxidants,
- chelating agents,
- preservatives,
- stabilizers and
- buffers.

Drug degradation by means of oxidation is second only to hydrolysis as the major mechanism of drug breakdown. Therefore, antioxidants are frequently employed as stabilizing agents in pharmaceutical products [48,52]. Examples of commonly used antioxidants include tocopherol, butylated hydroxyanisole and butylated hydroxytoluene [53]. Cyclodextrins have also been shown to protect drugs not only against oxidation, but also against hydrolysis and photodecomposition [54]. The stabilization effect is due to the complexation of the labile drug molecule with the cyclodextrin molecule. Sulfobutylether-β-cyclodextrin exhibited a greater stability enhancement than the other cyclodextrins [55].

Certain degradation reactions such as oxidation and photolytic degradation can be catalyzed by certain factors such as the presence of heavy metals. For this reason, chelating agents such as ethylenediaminetetraacetic acid can be incorporated into pharmaceutical formulations to improve drug stability [56].

Drug degradation can be pH dependent; the photodegradation of ciprofloxacin is, for example, more prominent at a slightly basic pH. Stability of this drug could be considerably improved by lowering the pH to between 3 and 4, where the drug exhibits maximum stability. Examples of buffers used in pharmaceutical products include citrate, acetate and phosphate buffers [57]. Besides buffer systems, other excipients such as citric acid, monobasic sodium phosphate and dibasic sodium phosphate and sodium hydroxide are also used alone to adjust the pH of formulations and thereby increase the stability or even the solubility of a drug [50,52].

5. Excipients improving the manufacture of dosage forms

Modern high-speed rotary tablet presses have reduced time for pressure application to the powder mixture during the formation of a compact while producing tablets, which places increased demands on the flow and compression properties of excipients. Differences in properties may occur in tablets produced by these high-speed machines compared with those produced by single-punch presses during the dosage form development process and, therefore, emphasizes the need to

find more versatile excipients that can withstand these changes during upscaling from laboratory to production batch sizes [58]. By chemical and physical modifications of hydrogenated isomaltulose, which is a disaccharide (6-*O*-α-D-glucopyranosyl-fructose) derived from sucrose, a range of multifunctional excipient materials (GalenIQ™) have been developed to assist in the tablet production process [59]. Another example of chemical modifications to a well-known excipient is the formation of starch acetates with different degrees of substitution to improve the poor flow properties and sensitivity of native starches to the effects of lubricants in the formulation of direct compressible tablets with modified release properties [60].

In addition to chemical modifications, the properties of existing excipients can be modified to improve their performance in formulation design by changing their manufacturing processes. For example, the flow properties of starch are improved by preparing pregelatinized starch containing powder particles that are chemically and physically different in nature compared with starch as produced by means of a mechanical and/or chemical process such as heating starch in a solution [61]. Partially pregelatinized starch is obtained by mixing fully pregelatinized starch with unmodified starch, amylose and amylopectin to produce a multifunctional excipient that not only is an effective binder but also serves as a disintegrant, flow aid and lubricant. Starch 1500® is an example of a very effective disintegrant and consists of partially pregelatinized starch that is prepared by a process that breaks the bonds between amylose and amylopectin molecules, which are normally bound together in a spherical crystal structure [6].

Coprocessing is yet another way to modify excipient performance and has the advantage of having a lower risk of failing regulatory approval when it is prepared from excipients already generally regarded as safe [62]. Coprocessing involves combination of excipients by appropriate processes such as crystallization, spray-drying and granulation that provides a product that has superior properties compared with that of a simple physical mixture of the individual excipients [63,64]. An example of a coprocessed excipient used as a multifunction sustained-release agent in direct-compressed matrix-type tablets is that of glyceryl behenate and povidone produced by a hot-melt process [65].

Several coprocessed cellulose excipients exist such as a product that consists of microcrystalline cellulose and colloidal silicon dioxide with enhanced flow and compaction properties (Prosolv® SMCC). Another coprocessed excipient consisting of microcrystalline cellulose, sodium starch glycolate and sodium stearyl fumarate (Prosolv® Easy Tab) facilitates rapid tablet manufacturing [66]. Magnesium silicate coprocessed with starch by means of a co-precipitation technique resulted in a multifunctional excipient that produced compacts with higher mechanical strength, short disintegration time and less lubricant sensitivity [67]. A universal granular excipient based on microcrystalline cellulose, hydroxypropyl methyl cellulose and crospovidone (PanExea MCC333G) provides particles with a unique shape, porosity and surface activity to improve flowability, compressibility and mixing ability. A comprehensive list of commercially available multifunctional excipients produced by coprocessing that are used to improve manufacturability is available elsewhere [9].

6. Excipients modifying drug release

Direct-compressible monolithic matrix-type tablets are considered as one of the most popular controlled-release drug delivery systems due to relative ease and low cost of manufacture [68]. Polymers have been successfully employed as matrix-forming excipients in controlled-release oral dosage forms. Several natural and synthetic polymers, which are either biodegradable or nondegradable, have been investigated for this purpose [69]. Hydroxypropyl methyl cellulose is one of the most commonly used hydrophilic polymers as excipient in matrix-type tablets [70], but several other polymers have been investigated for modifying drug release from matrix systems such as xanthan gum [71], alginate [72], guar gum [73], high-amylose carboxymethyl starch [74], carbomer [75] and pectin [76]. Different combinations of polymers as well as interpolymeric complexes have also been employed as excipients in matrix-type dosage forms [77-79].

The conventional aim of modified-release drug delivery systems is to achieve zero-order drug release so that blood plasma levels remain constant at an optimum level of therapeutic effectiveness over an extended period of time. For some drugs the challenge is, however, to find tailor-made excipients with the ability to release drug based on predetermined responses to supply drug according to the needs of the patient. In certain conditions, the programmability of the drug release is of primary concern to treat imbalances of biological homeostasis. The conventional concept of therapeutic window should, therefore, be extended to include a specific time of reaching the therapeutic levels. For example, the use of advanced or so-called smart polymers in innovative dosage forms would be able to deliver a drug like insulin in response to a rise in blood glucose levels [80,81].

Recent advancements in synthesis of biocompatible polymers has led to the development of drug delivery systems, where the rate of drug release is determined by feedback information from environmental changes such as temperature, pH, enzyme–substrate reactions, competitive binding, antibody interactions and concentration of certain molecules or by external triggers such as ultrasound, magnetic field, electric stimulation, light, chemicals or biochemical agents to provide pulsatile drug release [82]. Stimuli-sensitive polymers have been classified into groups that include interpolymeric complexes, graft copolymers and hydrogels [83], and examples of polymers from these groups that are sensitive to different stimuli for inclusion in novel drug delivery systems have been summarized before [84].

7. Conclusion

Functional excipients are essential components of pharmaceutical products that are included in the formulation to play specific roles such as to assist in the manufacturing process of the dosage form or to improve drug delivery. The emerging trend is to incorporate a lower number of multifunctional excipients in advanced drug delivery systems. These multifunctional excipients can each fulfill different functions in a dosage form; for example, an excipient can be used not only to improve compressibility of a tablet but also to ensure fast disintegration. Specialized functions that excipients need to fulfill in modern drug delivery systems include enhancement of drug membrane permeability, increased drug solubility, improved drug stability, modification of drug release and facilitation of the drug manufacturing processes. New excipients with tailor-made properties can be prepared by synthesis of new compounds, by chemical and physical modifications of existing excipients or by using techniques such as coprocessing. These newly designed multifunctional excipients have the potential to increase pharmaceutical product performance and decrease the overall cost.

8. Expert opinion

The awareness that even the so-called inert excipients were performing necessary functions in dosage forms have stimulated further interest in finding new compounds that can play specific roles such as facilitating dosage form manufacture and improving the therapeutic outcomes of active pharmaceutical ingredients by improving their bioavailability. This is becoming even more important with new drug moieties that are complex and that face challenges such as low solubility and low membrane permeability. The concept of 'multifunctional excipients' is not new but needs to be redefined because novel excipients are now developed that can perform specialized functions in addition to the conventional roles. These functions include enhancement of drug absorption, controlled modulation of drug stability, improved drug solubility and stimuli-responsive drug release in addition to the usual functions of providing sufficient mass to highly potent, low-dose drugs or compressibility or binding with good disintegration for tablets.

It is important to mention that the need for new multifunctional excipients implies a need for standardization of functionality tests to identify potential candidates for further development. These screening tests should be accurate and meaningful to facilitate excipient selection according to the needs of the formulator for a specific drug delivery system. Properties such as the functionality, safety, compatibility, availability and cost of the new excipient are important aspects that should be made available to formulators.

Although the process to gain regulatory approval for new excipients is probably too costly to justify continuous development efforts for innovative excipient materials that could potentially bring about relatively modest cost savings, realistic and affordable techniques exist to get better performance out of existing excipients. These methods that include chemical and physical modifications as well as coprocessing techniques to provide excipients with improved functionality in dosage form design will be increasingly exploited by role players in the pharmaceutical industry. Through these techniques, excipients can be tailor made to provide a competitive edge in modern pharmaceutical products. There are indications that these excipients will revive interest in the field of excipient development to establish an economically viable environment for investments in research to provide novel excipients. Multifunctional excipients are essential to develop a new generation of advanced drug delivery systems and hold the key to improve the therapeutic value of conventional and new drug moieties. With the current emergence of novel drug delivery system platforms, it is expected that the global excipient market will grow substantially in the near future.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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