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IMPROVED FUNCTIONALITY EXCIPIENTS FOR ORAL SOLID DOSAGE FORMS

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ABSTRACT: Over the years, significant advances in the manufacturing processes of oral solid dosage forms have occurred, including the transition from tablet preparation by wet granulation to direct compression. The development of various added functionality excipients (AFEs), which are used to achieve formulations with desired end-effects, is equally important. The majority of excipients used in the manufacture of solid oral dosage forms have existed for the past two to three decades, many of them continue to be used today for large-scale tablet and capsule manufacturing. Excipients also influence the safety and effectiveness of drugs depending on the route of administration. The qualitative and quantitative understanding of the excipient's composition is critically important to understand the bioavailability and bioequivalence of the dosage forms. In the case of orally administered dosage forms, excipients can affect safety and effectiveness outcomes by promoting or delaying gastrointestinal release.

INTRODUCTION: In earlier days, excipients were considered inactive ingredients. Over time, pharmaceutical scientists learned that excipients are not inactive and frequently have substantial impact on the manufacture and quality, safety, and efficacy of the drug substance(s) in a dosage form. Tablets and capsules are preferred drug delivery vehicles because they can be precisely dosed, easily manufactured and packaged on a large scale, and can contribute to good patient compliance.

Added functionality excipients facilitate the development of novel drug delivery methods and improve processing techniques.

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AFEs have helped solve formulation problems such as flowability, compressibility, hygroscopicity, palatability, dissolution, disintegration, sticking, and dust generation[1-2]. Global excipient markets are expected to grow rapidly with the emerging trends in the pharmaceutical industry. Textured, directly compressible Added functionality Mannitols Specially spray-dried, or granulated mannitol under defined manufacturing conditions gives them a highly porous and friable exterior structure upon compression, the structure crumbles into finer particles, which fill the interstitial spaces between larger porous particles.

In addition, the high friability of these tablets does not allow them to be packaged and dispensed in regular bottles. These challenges could be addressed by using a compression binder such as a cellulose derivative in addition to the mannitol powder. Another option is the development and optimization of coprocessed mannitols that exhibit a similar flowability and compressibility to the

directly compressible mannitols and impart low friabilities to the final dosage forms. Thus, the need for specialized packaging is eliminated. Co-processing mannitol with a small amount of other polyols is one way to create such an excipient. In the case of sorbitols, the presence of interlocking crystals that are generated using specific manufacturing conditions enable strong binding and result in a more robust tablet at low compression forces. In addition, the mannitol provides the required dispersibility. Added functionality partially pregelatinized starches are commercially available in fully pregelatinized and partially pregelatinized starch (PPS) grades depending on the degree of starch gelatinization.

PPSs are used as fillers in hard gelatin capsules (5–75%),binders in wet granulation tabletting (5–20%), disintegrants in tablet formulations (5–10%), and in direct compression tabletting Altering the composition of the starch and optimizing the gelatinization process can add functionality to PPSs and address some disadvantages of using existing PPSs The changes in the composition and particle-size distribution of PPS. Particles will ultimately influence the dissolution kinetics of the final oral dosage forms. Excipients (additives) are compounds other than the active ingredients that are intentionally incorporated into pharmaceutical dosage forms. They play specific functional roles in the formulation of dosage forms (**Table 1**).

The symbiotic relationship between the pharmaceutical and the excipient industries shows that both of them have the same fluctuations in the drug usage trend. Classification of excipients is based on their role in the pharmaceutical formulation, their interactions influencing drug delivery, or their chemical and physico-chemical properties. For example, methylcellulose is a coating material that is applied in the preparation of suspensions to increase viscosity or as a disintegrating agent or binder in tablets.

More than 800 excipients are currently used in the marketed pharmaceutical products. This number is expected to grow rapidly as new drug delivery technologies are developed to address the challenges of drug development such as poor solubility, permeability, and bioavilability.[3]

FUNCTIONAL USES OF EXCIPIENTS:

Excipients play a wide variety of functional roles in pharmaceutical dosage forms that include:

- Modulating solubility and bioavailability of active pharmaceutical ingredients.
- Increasing the stability of active ingredients in the dosage forms.
- Helping active ingredients to maintain preferred polymorphic forms.
- Maintaining the pH and/or osmolarity of liquid formulations.
- Acting as antioxidants, emulsifying agents, aerosol propellants, tablet binders, and disintegrants.
- Preventing aggregation or dissociation.
- Modulating immunogenic responses of active ingredients.

TABLE 1: DOSAGE FORM PARAMETERS AFFECTED BY EXCIPIENTS, AND THE MECHANISMS INVOLVED

Dosage form parameter	Effect of excipients
Stability	Residual moisture content—adsorbed moisture on excipients surface protects drug from hydrolytic degradation
Process ability	Surface area, surface free energy, crystal defects, and deformation potential affect compressibility and machine ability on high-speed tableting machines with reduced compression dwell times
	Particle size distribution and shape affect flow properties, efficiency of dry mixing process, and segregation potential
	Compressibility, flowability, and dilution potential affect the choice of direct compression as a manufacturing process
Performance	Cohesive and adhesive properties, surface free energy, and water uptake behavior affect disintegration and dissolution behavior

The spectrum of functionality modification can be substantially enlarged by the coprocessing or particle engineering of two or more existing excipients. Basic fundamental of co processing is based on particle engineering. Co-processing is another way that new excipients are coming to market without undergoing the rigorous safety testing of a completely new chemical [4]. Solid

substances are characterized by three levels of solid state- molecular, particle, and bulk level. These levels are closely linked to one another, with the changes in one level reflecting in another level. The molecular level comprises the arrangement of individual molecules in the crystal lattice and includes phenomena such as polymorphism, pseudo-polymorphism, and the amorphous state. Particle level comprises individual particle properties such as shape, size, surface area, and porosity. The bulk level comprises of large number of particles together and their properties such as flowability, compressibility, and dilution potential, which are critical factors in the performance of excipients.

Co -processing based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients. These solid state properties of particles such as particle size, shape, surface area, density influence the excipient properties such as flowability, compatctibilty, dilution potential. Hence creation of new excipient must begin with particle design. Co-processing involves interaction of two or more excipients at the sub particle level [5-6]

TABLE 2: EXAMPLES OF EXCIPIENT FUNCTION BY STAGE OR APPLICATION

Stage/application	Function	Example
Bulk Processing	Facilitate manufacture of bulk product	Solvent Co solvent Gelling agent pH adjuster Anti-foam
Dosage form processing	Facilitate manufacture of dosage form	Lubricant Glidant Binder Diluent Solvent Coating
Dosage form Packaging Processing		Capsules Stopper lubricant
Dosage form acceptability	Facilitate manufacture of finished product Patient tolerance Appearance Identification	Tonicity adjuster/pH adjuster Colour Flavour Fragrance Sweetner Colour Printing Ink
Dosage form activity/delivery	Aid Activity	Penetration enhancer Disintegrant Propellant Inhalation powder Carrier Polymeric coatings for API particles,tablets or patches
Control release of active	Retain Activity	Antioxidant Sequester Buffer
Product use	Prevent spoilage Ensure patient Receives dosage	Preservative Vial wetting agent Syringe lubricant

Co-processing of excipients provides products with superior properties in comparison to their parent excipients, alone or as a physical mixture. Co-processing is primarily aimed at addressing the issues of flowability, compressibility, and disintegration potential, and most importantly, the development of filler-binder combinations.

The combination of excipients for co-processing should complement each other to mask the undesirable properties of individual excipients while retaining or improving their desired properties. For instance, a substance used as filler-binder, with a low disintegration property, can be coprocessed with another excipient possessing good wetting properties and high porosity to enhance water uptake, which will aid and hasten the disintegration of the tablets.[7]

Material Characteristics and Compression:

Solid materials, by virtue of their response to applied mechanical force, can be classified under the following three heads [8]

Elastic: Any change in shape is completely reversible, and the material returns to its original shape upon release of applied stress.

Plastic: Permanent change in the shape of a material due to applied stress, e.g., MCC (Microcrystalline Cellulose), corn starch, and sodium chloride.

Brittle: Rapid propagation of a crack throughout the material on application of stress, e.g., sucrose, mannitol, sodium citrate, lactose, and dicalcium phosphate. The predisposition of a material to deform in a particular manner depends on its lattice structure, in particular whether weakly bonded lattice planes are inherently present.

In definite terms, most of the materials cannot be classified distinctly into individual categories. Pharmaceuticals exhibit all three characteristics, with one of them being the predominant response, thus making it difficult to clearly demarcate the property favorable for compressibility. Coprocessing offers an interesting tool for altering these physicomechanical properties of excipients. Coprocessing is generally conducted with a plastic and a brittle excipient. Cellactose is an appropriate example in this regard, which involves coprocessing of 75% lactose (a brittle material) with 25% cellulose (a plastic material) [9]. Usage of this particular combination prevents the storage of excessive elastic energy during compression, resulting in a small amount of stress relaxation and a reduced tendency for capping and lamination[10].

However, examples of the other extreme also exist, e.g., SMCC (Silicified Microcrystalline Cellulose), which has a large amount of MCC (a plastic material) and a small amount of CSD (Colloidal Silicon Dioxide) (a brittle material). These two cases exemplify the fact that coprocessing is generally performed with a combination of materials possessing plastic deformation and brittle fragmentation characteristics.

Material Characteristics and Flow Properties:

Powder flow is typically determined by particle size, particle size distribution, and particle shape [11]. Particle size and its distribution have a critical effect on the mixing of powders and the resulting content uniformity of the solid dosage form. Wide differences in particle size result in product segregation during manufacturing. Irregularly shaped particles also contribute to poor flow properties [12-13]. Particles having a more regular shape (nearly spherical) are easy to flow and pose minimal hurdles during dosage form production. Coprocessing overcomes all these limitations and provides excipients with predefined attributes.

Properties of Coprocessed Excipients:

The subject of co-processing of excipients is multifaceted, with the following characteristic properties. Absence of Chemical Change Co-processing of two excipients results in only a physical change without any chemical alteration. A comprehensive characterization of SMCC with X-ray diffraction, solid-state and C13 nuclear magnetic resonance imaging, and infra-red and Raman spectroscopy confirmed the absence of chemical changes, and indicated a similarity to the physicochemical properties of MCC [13]. This reduces the regulatory concerns and encourages the formulators to use co-processed excipients during the development phase.

Improved Physicomechanical Properties:

Co-processing provides a multitude of improvements in the product's functionality, the most notable of which are discussed below.

Improved Flow Properties:

Controlled optimal particle size and size distribution ensures superior flow properties of coprocessed excipients and reduced reliance on addition of glidants. The volumetric flow properties of SMCC were studied in comparison with those of the physical mixture of its parent excipients [14]. The particle size range of the two test samples was found to be similar, but the flow of coprocessed excipient was better than that of the physical mixture. A comparison of the flow properties of Cellactose with its parent excipients was also performed [15] by measuring the angle of repose and Hausner ratio, and Cellactose was found to have better flow characteristics than lactose or a physical mixture of cellulose and lactose.

The spray-dried coprocessed product had a spherical shape and even surfaces, which resulted in improved flow properties. On similar terms, mechanically coating the 2% CSD over microfine cellulose powder resulted in improving its flow properties.

The most common problem manifested due to poor flow property is the variation in fill weight. This problem is much more serious in the case of DC (Direct Compression) excipients,but coprocessed excipients are devoid of this effect, when compared with the physical mixture of their parent excipients.

This is because of the impregnation of one particle into the matrix of another, which reduces the rough particle surfaces and creates a near-optimal size distribution, causing better flow properties. Tablets prepared with M80K, a coprocessed cellulose

powder with CSD, showed lesser weight variation than those prepared with Avicel). Fill-weight variation tends to be more prominent with high-speed compression machines. This phenomenon was studied with various machine speeds for SMCC and MCC, and the former showed lesser fill-weight variation than the latter [16]

Improved Compressibility:

Co-processed excipients have been mainly used in DC tableting because of their better flow ability and compressibility, and the excipient formed is a filler-binder. The compressibility of several coprocessed excipients such as Cellactose1 [17] SMCC and Ludipress1 (BASF AG, Ludwigshafen, Germany) [18] have been reported to be superior to the physical mixtures of their constituent excipients. While comparing the compressibility profile of SMCC with MCC in the presence of high compression forces, the former was found to retain the compaction properties, yielding tablets of good hardness.

MCC, however, lost its compaction properties. A further utility of SMCC has been reported in the manufacturing of high-dose DC formulations, wherein it reduces the binder requirement by more than half, and results in overall reduction in excipient requirement [19] Co-processing of a-lactose monohydrate with cornstarch helped in improving its compressibility, and provided dual benefits of enhanced binding capacity and better disintegration potential, the attributes associated to starch [20]This effect was a result of binding of small starch particles together with a-lactose monohydrate crystals into compound particles.

Although DC seems to be the method of choice for tableting, wet granulation is still widely used in various product manufacturing. Excipients such as MCC lose compressibility upon addition of water, a phenomenon called ‘‘quasi-hornification’’[21]This property is improved, however, when it is coprocessed into SMCC.

Better Dilution Potential:

Dilution potential is the ability of the excipient to retain its functionality even after dilution with another material in a finite proportion. Most drug substances are poorly compressible, and require excipients to achieve better compressibility to retain good compaction even on dilution with them. Cellactose has been shown to possess a higher dilution potential than a physical mixture of its constituent excipients [22]

Reduced Lubricant Sensitivity: Co-processing endows lesser sensitivity of the product toward loss of their functionality in the presence of lubricants. Most coprocessed products consist of a relatively large amount of brittle material such as a-lactose monohydrate and a smaller amount of plastic material such as cellulose that is fixed between or on the particles of the brittle material. The plastic material provides good bonding properties by creating a continuous matrix with a large surface for bonding. The large amount of brittle material provides low lubricant sensitivity by preventing the formation of a coherent lubricant network by forming newly exposed surfaces upon compression, thus breaking up the lubricant network.

Multiple Advantages:

Various reports describe improved excipient functionality after coprocessing, with multiple advantages. Roller drying of a solution of anhydrous lactose (95%) and lactitol/sorbitol (5%) resulted in a DC excipient with good tablet strength[23]. A free-flowing, compressible powder was obtained by spraying a 4.5% aqueous solution of poly (vinyl pyrrolidone) (PVP) onto a fluid bed of starch and PVP admixture (48:1) [24]. Statistical optimization of a coprocessed product of lactose and MCC by various product evaluation parameters such as bulk density, Carr’s index, percentage friability, percentage fines, tensile strength, flow rate, and angle of repose resulted in a directly compressible product (with 9:1 composition) with satisfactory flow, compressibility and friability.

Coprocessing of lactose monohydrate, PVP (polyvinyl Pyrolidone), and croscarmellose sodium (79:15:6) by melt agglomeration resulted in a multifunctional DC adjuvant with satisfactory dilution potential, and superior flowability and compressibility than those of lactose monohydrate. [25] Spray drying of rice starch with jet-milled MCC (with volumetric mean diameter of 13.57 *m*m) in the proportion of 7:3 resulted in spherical

composites of a directly compressible excipient with high compressibility, good flowability, and self disintegration [26].

Other Benefits

- Coprocessed excipients offer the following additional advantages:
- Allow the development of tailor-made designer excipients with retention of functional and removal of undesirable properties, which can help in faster product development.
- Provide a single excipient with multiple functionalities, thereby reducing the inventory burden.
- Offer improvement in organoleptic properties, such as those in Avicel1 CE-15 (FMC BioPolymer, Newark, Delaware, U.S.A.), a coprocessed excipients of MCC and guar gum, designed for providing chewable tablets with reduced grittiness and tooth packing, minimal chalkiness, better mouth feel, and improved overall palatability.
- Provide more robust tablets at low compression force. Coprocessing of mannitol with sorbitol resulted in interlocked crystals with stronger binding capacity. [27] This eased the dispensing of orally dissolving tablet formulations in conventional bottles, eliminating the need for specialized packaging, and thus providing significant cost savings.
- Act as a constant source for development of value-added generic drug products.
- Reduce product cost due to improved functionality [28] and fewer test requirements compared with individual excipients [29].
- Provide intellectual benefits in terms of proprietary combinations, specific for in-house use.

TABLE 3: LITERATURE REVIEWS ON APPLICATION OF EXCIPIENTS [30]

Excipients	Drug	Approach used	Result
Ludiflash	Risperidone	Direct compression	Disintegration time 27 seconds
Pharmaburst	Famotidine	Taste masking microsphere for orally disintegrating tablets using Eudragit EPOand quick dissolving excipient pharmaburst by spray drying	Disintegration in 30 seconds with improved taste
FMELT	Acetaminophen	Direct Compression using 10% to 65%w/w	Good mouth feel and excellent oral disintegration time below 30 seconds
OROCELL 200&OROCELL 400	Ibuprofen	Direct Compressible	Disintegration time of 5 seconds
Pearlitol SD	Metformin	Wet Granulation	Disintegration time of 85 seconds,100%drug release in 10 min
Galen IQ 720 and 721	Placebo	Direct Compression	Even without superdisintegrants ,tablets containing both isomalt grades disintgrated quickly within 200-500 seconds
Polacrilin Potassium	Sumatriptan	Direct Compression	Disintegration time of 45 s.100%release in 10 minutes

CONCLUSION: All co-procesed and modified excipients are playing very important role in the development of easy dosage form which are resistant to atmosphere. Compared with existing excipients, the improved physical, mechanical, and chemical properties of such excipients have helped in solving formulation problems such as flowability, compressibility, hygroscopicity, palatability, dissolution, disintegration, sticking, and dust generation.

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