Review Article

Coprocessed Excipients for Orally Disintegrating Dosage Form

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ABSTRACT

Orally disintegrating tablets are an emerging trend in novel drug delivery system and have received ever increasing demand during the last few decades. Orally disintegrating tablets ODTs are the dosage form which will disintegrate in mouth within seconds without need of water. This type of property in dosage form can be attained by addition of different varieties of excipients. But the number of fillers/binders/disintegrant which can be used for ODT formulations is limited because these bulk excipients have to fulfill special requirements, such as being soluble in water, pleasant taste, mouth feel, sweetness, and rapid dispersibility. In recent years drug formulation scientists have recognized that single component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. New combinations of existing excipients are an interesting option for improving excipient functionality now a day. In excipients mannitol is used as diluents but now a day's modified mannitol is available which give extensive flow, compression and rapid dispersibility to the tablet e.g. like Orocell, Mannogem EZ, and Pearlitol SD 200. The current review article is prepared to have a look over the recent development in excipient technology and the approaches involved in development of such excipients. It emphasizes on the different examples of functional excipients also called as co processed excipient available in market such as Ludiflash, Pharmburst, and F- MELT.

Keywords: Coprocessing, excipients, mannitol, orally disintegrating dosage form

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INTRODUCTION

Over the past three decades, ODTs have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance. ODTs are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds, when placed on the tongue. This type of property in dosage form can be attained by addition of different varieties of excipients. Excipients in brief can be defined as "The components of a formulation other than the active ingredient". As compounds become more challenging to formulate, new excipients are needed to enable the delivery, manufacture and development of these compounds. Conventional excipients have been replaced with sophisticated compounds that fulfil multifunctional roles in modern pharmaceutical dosage forms such as improvement of the stability and bioavailability of the active ingredient, enhancement of patient acceptability, Compared with existing excipients, the improved physical, mechanical properties of such excipients have helped in solving formulation problems such as flowability, compressibility, hygroscopicity, palatability, dissolution, disintegration, sticking, and dust generation.

An ideal bulk excipient for orally disintegrating dosage forms should have the following properties:-

1) Disperses and dissolves in the mouth within a few seconds without leaving any residue.
2) Masks the drug's offensive taste and offers a pleasant mouth feel.
3) Remains relatively unaffected by changes in humidity or temperature.

Principle of coprocessing [6]

Basic fundamental of coprocessing is based on particle engineering. 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 is comprises of large no. of particles together and their properties such as flowability, compressibility, and dilution potential, which are critical factors in the performance of excipients. Coprocessing 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.

METHODS OF COPROCESSING [7]

1) Spray Drying
2) Solvent Evaporation
3) Crystallization
4) Melt Extrusion
5) Granulation/Agglomeration.

1) Spray Drying

This technique enables the transformation of feed from a fluid state into dried particulate form by spraying the feed into a hot drying medium. It is a continuous particle processing drying operation. The feed can be a solution, suspension, dispersion or emulsion. The dried product can be in the form of powders, granules or agglomerates depending upon the physical and chemical properties of the feed, the dryer design and final powder properties desired. Hence the spray drying process can be described as consisting of four events:

1. Atomization of the liquid into droplets
2. Contact of the droplets with the warm drying gas
3. Rapid evaporation of the droplets to form dry particles
4. Recovery of the dry particles from the drying gas, using a cyclone/filter.

   Example: Emdex [Dextrose, Maltose, Maltodextrin]

2) Solvent Evaporation

The processes are carried out in a liquid manufacturing vehicle. The coating excipient is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core excipient material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated to evaporate the solvent. Once all the solvent is evaporated, the liquid vehicle temperature is reduced to ambient temperature with continued agitation. At this stage, the microcapsules can be used in suspension form, coated on to substrates or isolated as powders. The core materials may be either water soluble or water insoluble materials. A variety of film forming polymers can be used as coatings.

Example: Eudragit RS100 [Copolymer of ethyl acrylate, methyl acrylate]

3) Crystallization

Crystallization is the (natural or artificial) process of formation of solid crystals precipitating from a solution, melts or more rarely deposited directly from a gas. For crystallization to occur from a solution it must be supersaturated. This means that the solution has to contain more solute entities (molecules or ions) dissolved than it would contain under the equilibrium (saturated solution). This can be achieved by various methods, with (1) solution cooling, (2) addition of a second solvent to reduce the solubility of the solute (technique known as antisolvent or drown-out), (3) chemical reaction and (4) change in pH being the most common methods used in industrial practice.

Example: Sugar Tab [Sucrose, Invert sugar].

4) Melt Extrusion

Melt extrusion is a process of formation of small beads, pellets from the molten mass which is extruded through extruder. Hot melt extrusion is carried out using an extruder – a barrel containing one or two rotating screws that transport material down the barrel. Extruders consist of four distinct parts:

1. An opening though which material enters the barrel that may have a hopper that is filled with the materials to be extruded.
2. A conveying section (process section), which comprises the barrel and the screws that transport, and where applicable, mix the material.
3. An orifice (die) for shaping the material as it leaves the extruder.
4. Downstream auxiliary equipment for cooling, cutting and/or collecting the finished product.

Example: Compressol S [Mannitol, Sorbitol]

5) Granulation/Agglomeration

Granulation is the act or process of forming or crystallizing into grains. Granules typically have a size range between 0.2 to 4.0 mm depending on their subsequent use. Synonym "Agglomeration": Agglomeration of powders is widely used to improve physical properties like: wettability, flowability, bulk density and product appearance. In pharmaceutical industry, two types of granulation technologies are employed, namely, Wet Granulation and Dry Granulation. Wet granulation is the more preferred method for coprocessing.

Example: Xylitab100 [Xylitol, polydextrose]

ADVANTAGES OF COPROCESSING [7]

- **Improved Flow Properties**

  Controlled optimal particle size and particle size distribution ensures superior flow properties of coprocessed excipients without the need to add glidants. The volumetric flow properties of silicified microcrystalline cellulose were studied in comparison with microcrystalline cellulose. The particle size range of these excipients was found to be similar to those of the parent excipients, but the flow of coprocessed excipients was better than the flow of simple physical mixtures.

- **Improved Compressibility**

  Coprocessed excipients have been used mainly in direct compression because in this process there is a net increase in the flow properties, which results in improved compressibility. The pressure hardness relation of coprocessed excipients, when plotted and compared with simple physical mixtures, showed a marked improvement in the compressibility profile.

- **Better dilution potential**

  Dilution potential is the ability of the excipient to retain its compressibility even when diluted with another material. Most active drug substances are poorly compressible, and as a result, excipients must have better compressibility properties to retain good compaction even when diluted with a poorly compressible agent.

- **Fill weight variation**

  In general, materials for direct compression tend to show high fill weight variations as result of poor flow properties, but co processed excipients, when compared with simple mixtures or parent materials, have been shown to have fewer fill weight variation problems.

- **Reduced lubricant sensitivity**

  Most co processed products consist of a relatively large amount of brittle material such as 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 because it creates a continuous matrix with a large surface for bonding. The large amount of brittle material provides low lubricant sensitivity because it prevents the formation of a coherent lubricant network by forming newly exposed surfaces upon compression, thus breaking up the lubricant network.

LIMITATION [7]

1. Major limitation of co-processed excipient mixture is that the ratio of the excipients in a mixture is fixed and in developing a new formulation, a fixed ratio of the excipients may not be an optimum choice

for the API and the dose per tablet under development.

2. Coprocessed adjuvant lacks the official acceptance in pharmacopoeia. For this reason, a combination filler binder will not be accepted by the pharmaceutical industry until it exhibits significant advantages in the tablet compaction when compared to the physical mixtures of the excipients.

Table 1: Composition and characteristics of excipients

EXCIPIENT	COMPOSITION AND CHARCTERISTICS
Pharmburst	Coprocessed blends of Mannitol, Starch, Crosspovidone, Cross Carmellose Sodium, Collidal Silica and Silica
Ludiflash	Coprocessed blends of 90% Mannitol, 5% Kollidon CL-SF (Crosspovidone), 5% Kollicoat SR 30D (Polyvinyl Acetate)
F-MELT	Coprocessed blends of Mannitol, Xylitol, Calcium Sulphate, Crosspovidone, and MangesiumAluminometasillicate.
Modified chitosan with silicon dioxide	Coprecipitation of Chitosan and Silica.
Orocell 200 &	Orocell 200 with 90% Mannitol (<315µm)
Orocell 400	Orocell 400 with 90% Mannitol (<500µm).
Advantose	Spray dried disaccharide carbohydrate maltose powder
Polacrilin Potassium	Potassium salt of a cross linked polymer derived from methacrylic acid and divinyl benzene.

EXAMPLES OF COPROCESSED EXCIPI-ENTS:

1) Coprocessed blends of excipients

It involves the mixture blend of more than two excipients to satisfy the required quality using different technique like spray drying and freeze drying etc.

- **Pharmaburst [8,9]**

Pharmaburst is a Quick Dissolving delivery system in which there is addition of active drug in a dry blend with Pharmaburst excipients and compress by tablet machine. Pharmaburst was found to be significantly more compactable, less friable, and more rapidly disintegrating. Pharmaburst is a coprocessed excipient system with specific excipients, which allows rapid disintegration and low adhesion to punches. Pharmaburst is smooth and creamy and helps to mask taste and grittiness of the actives. Main advantages Pharmaburst is highly compatible, rapid disintegration and cost effective

- **Ludiflash [10]**

Ludiflash is a formulation for fast disintegrating dosage forms. It is designed to disintegrate readily within a few seconds in oral cavity with pleasant mouth feel. It is specially designed for direct compression on standard high speed tablet machine. It gives extremely fast release rate. It has neutral to mildly sweet, pleasant taste and sugar free composition.

- **F-MELT [11]**

F-MELT is designed not only for manufacturing ODTs, but also suitable for soft chewable tablets. It is suitable for direct compression manufacturing of ODTs by simple blending with active pharmaceutical ingredients (APIs) and lubricants. F-MELT exhibits excellent tabletting properties and it has advantages of disintegration time within 30 seconds. It is cost effective, less sticking or capping and has pleasant mouth feel.

2) Modified chitosan with silicon dioxide [12]

This is the new excipients based on co precipitation of chitosan and silica. The physical interaction between chitosan and silica create an insoluble, hydrophilic highly absorbent material. It has water wicking and swelling properties. It is Superdisintegrant with improved flow and compaction properties. It acts as Superdisintegrant and filler both.

3) Modified Mannitol

Generally in orally disintegrating dosage forms mannitol is used as sweeteners. It will also give good mouth feel. Now a day mannitols are highly modified so that they can perform more than one function of excipients.

- **Orocell [13]**

Orocell is a spheronised mannitol with different particle size. It acts as a filler binder with high dilution potential and good disintegrating property useful for orally disintegrating tablets.

- **Pearlitol 200 SD [14]**

It is white, odourless, slightly sweet tasting and crystalline powder. It has a unique blend of exceptional physical and chemical stability, with great organoleptic, sugar free properties. It can be used in different processes like dry granulation, direct compression, and compaction. Pearlitol SD dissolves very rapidly because of its porous crystalline particles.

4) Modified sugars

- **Advantose 100 [15]**

Advantose 100 is spray dried particles which are spherical in shape and is made up of fine and coarse particles of sugars which provide superior flow properties. The safety and mouth feel qualities of maltose are well known. By spray drying, the flow and tabletting properties are greatly improved.

- **GalenIQ [16]**

It is a novel multifunctional sugar free excipient. GalenIQ is white, odourless, water soluble, crystalline substance derived from sucrose. It has very low hygroscopic nature, excellent chemical stability. The direct compressible grades of GalenIQ have high tabletting properties due to their excellent compactability. The main properties of direct compressible GalenIQ in tabletting are excellent flow; unique morphology of GalenIQ ensures homogeneity of the mixture and content uniformity.

- **Glucidex IT [17]**

It is developed by Roquette. Glucidex IT is obtained by moderate hydrolysis of starch. It is micro granulated form enables almost instantaneous dispersal and dissolution in water. Different range of Glucidex IT products is available. It has properties like free flowing due to fewer fine particles and it mainly used as diluent for tablet, capsule.

5) Modified resins

- **Polacrilin Potassium [18]**

Polacrilin Potassium is weakly acidic cation exchange resin. Upon hydration it gives tablet disintegration by swelling of resin and it also having taste masking application. Tablet disintegration property is due to its extremely large swelling capacity in aqueous solutions. This resin adsorbs water rapidly due to its hydrophilic nature.

CONCLUSION

All coprocessed and modified excipients are playing very important role in the development of easy dosage form. Excipients are no more considered as inert ingredients of a formulation, but have a well defined functional role. Coprocessing could hold the key to a successful future for synthetic excipients.

FUTURE PROSPECTIVE [19]

The obvious advantages of solid dosage forms and changing technological requirements will keep alive the search for newer excipients. They are playing a vital role in the development of easy dosage forms which are resistant to atmosphere. The newer excipients are required to be compatible not only with the latest technologies and production machineries, but also with the innovative active principles such as those originating from biotechnology. The improved physical, chemical and mechanical properties of such excipients as compared to existing excipients, have helped in solving formulation problems such as flowability, compressibility, hygroscopicity, palatability, dissolution, disintegration, sticking, and dust generation. The advantages of these excipients are numerous, but further scientific exploration is required to understand the mechanisms underlying their performance. With development a number of new chemical entities rising day by day, there is a huge scope for further development of and use of these excipients in future.

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