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FORMULATION AND DEVELOPMENT OF FAST DISSOLVING TABLET CONTAINING COPROCESSED EXIPIENT

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ABSTRACT
Excipients have been described in many ways, including as inert components used as motors and diluents for drugs. Excipients play an necessary function in formulating a dosage shape.Excipients play an essential function in formulating a dosage form Coprocessed excipients are a mixture of two or extra excipients designed to bodily mixing and besides great chemical change. These Coprocessed excipients have excessive functionalise in contrast to character excipients such as higher glide property, compressibility,decreased lubricant sensitivity. These excipients flow ability, compressibility, tablet manufacturing by spray drying, solvent evaporation, Crystallization, melt extrusion, granulation/agglomeration method.The following review gives brief information about multifunctional excipients and co-processed excipients.

KEYWORDS: Excipients, Multifunctional excipients, Co-processed excipient, Fast dissolving tablet.

INTRODUCTION

Definitions

Excipient:

An excipient is a substance formulated alongside the energetic ingredient of a medication,covered for the cause of long-term stabilization, bulking up strong formulations that comprise strong lively elements in small quantities (thus frequently referred to as "bulking agents", "fillers", or "diluents")Pharmaceutical excipients are substances other than the pharmacologically active drug or prodrug which are include in the manufacturing process or are contained in a finished pharmaceutical product dosage form.

The three U.S. Food and Drug administration (FDA) approval mechanisms are

- Determination by FDA that the substance is "generally recognized as safe" (GRAS) pursuant to Title 21, U.S. Code of federal regulation, parts 182, 184 or 186 (21 CFR182, 184 and 186) ;
- Approval of food additive petition as set forth in 21 CFR 171
- The excipient is referenced in, and part of, an approved new drug application (NDA) for a particular function in that specific drug product[1]

Multifunctional excipients

Multifunctional excipients are classification of excipients that consists of pre-processed and co-processed excipients that furnish delivered functionalities to the system (for example, Silicified Micro-Crystalline Cellulose, which is a processed aggregate of MCC and colloidal silicon dioxide). These functionalities encompass flowability, compressibility, particle measurement distribution, shape, porosity, etc. The time period multifunctional excipient is additionally prolonged to merchandise that serve more than one roles in the system (for example, Ludipress, which is co-processed product containing lactose, Kollidon and Kollidon-CL, serves the position of DC diluent with binder and disintegrant properties).

Multifunctional excipients can be acquired by means of growing a new excipient (such as cross-linked polymers) or by way of growing new grades of present excipients; amendment in the processing leads to adjustments in the particle size distribution, particle form and morphology and porosity. Traditionally, industry stays away from creating a new excipient altogether, due to the value involved and issues confronted in getting regulatory approvals. The exchange in the manufacturing procedure of an excipient alongside with addition of minor quantity of some other recognized excipient outcomes in a product that has improved bodily characteristics main to introduced functionality.[2]

Type of excipients:

1. Single entity excipients.

1. Mixtures/blends of multiple excipients.
2. Novel excipients or new chemical organization.
3. Co-processed excipients.

1. Single entity excipients:

It is described as excipients containing one aspect which is the primary aspect known as as single entity excipients[2]

2. Mixture/blends of multiple excipients:

Simple bodily combinations of two or compendial /non-compendial excipients with the aid of skill of low to medium shear procedure the place the character aspects are mixed collectively except large chemical changefor stable mixture/ blends the person excipient remain bodily separate at a particulate degree.[2]

3. Novel excipients or new chemical organization.

It is described as excipients which are chemically modified to structure new/novel excipients. These are generally no longer listed in FDA inactive ingredient database. The new excipient capability any inactive ingredient that are deliberately brought to therapeutic and diagnostic merchandise.[2]

4. Co-processed excipients

co-process excipients are mixture of two or greater compendia or non-compendia excipients designed to bodily alter their residences in a manner now not plausible by means of easy physical mixing and besides full-size chemical change.many distinctive co-processing techniques includes in pharmaceutical method improvement such as spray drying, solvent evaporation, crystallization, soften extrusion and granulation/agglomeration.[3,4,5]

The actual process of developing a coprocessed excipient involves the following steps:

- Identifying the team of excipients to be coprocessed through cautiously analyzing the fabric traits and performance requirements.
- Selecting the proportions of a range of excipients.
- Assessing the particle measurement required for coprocessing. This is in particular important when one of the aspects is processed in a dispersed phase.
- Post processing the particle dimension of the latter relies upon on its preliminary particle size.
- Selecting a appropriate procedure of drying such as spray or flash drying.
- Optimizing the method (because even this can make contributions to performance Variations.[6,7]

Need of co-process excipients

- The creating acceptance of the direct compression method and required for an perfect filler-binder that can alternative two or extra excipients.
- The functionality to modulate the solubility, permeability or stability.
- To tackle the issues of flowability, compressibility and disintegration potential.
- Effective use of present excipients: the developing recognition of the technique for best filler binder that can alternative two or greater excipients.
- Appreciation of new purposes for the economical excipients is a less expensive and much less time involving procedure as in contrast to an absolutely new development.
- The variety of real excipients which some of desirable homes gorgeous in some formulation.
- As new capsules are being development, their compatibility with the present excipients
- Hence co-process excipient will be fantastic to overcome these problems.[8]

Advantages of co-processed excipients

1. Improve compressibility ,dilution potential, fill weight variation, float property, lubricant sensitivity.
2. It can be additionally enhancing the tablet hardness and decrease disintegration time.[9,1]
3. Controlled optimal particle size and particle size distribution ensure superior flow properties or Coprocessed excipients without to add glidants.[11]

Example of coprocessed multifunctional excipients[11,12]

Exipients	Composition	Benefits	Manufacturer
Cellactose	Lactose, cellulose	High compressibility, Direct compression	Germany, Meggle GmbH
MicroceLac	MCC, lactose	High flowability, Direct compressible excipients for poorly compressible drug	Meggle GmbH, Germany
Prosolv	MCC,Silicon Dioxide	Low disintegratin time, High flowability, High Compression, direct compression, better tablet hardness	JRSpharma USA(Penewst USA)
Ludipress	Lactose, kolliodon30, kolliodonCL	Direct compression, tablet hardness, high flowability, disintegrstion functionality	BASF, Germany

Starlac	Lactose, Maize starch	Disintegrstion, high flowability, Direct compression	Meggle GmbH, Germany
StarCap 1500	Corn starch pregelatinized starch	Wet and dry granulation binder, enhance functionality of other binder, excellent flow chart	BPSI H ol ding,Inc
Eudragit	Acrylic polymers	Controlled release, very good flow property, high dissolution efficency	Evonik-Deguss a Germany
Captisol	Modified cyclodextrin Sulfobutylether cyclodexterin	Highly soluble in water, Improve API solubility	CyDex Pharmaceutical, Inc USA
Avicel CELS	MCC ,guar gum	Less constancy,creamier mouth feel	FMC,USA
Plasdone S-630	Vinyl acetate,vinyl pyrrolidone	Tablet binder, improve compressibility of other binder	International speciality products,USA
Compressol S	Polysol	Superiorcompatibility, high active loading, direct compression	SPI,USA
Ceolus^{TM} RC	MCC,NaCMC	Maximixe compatibility at high lubricant level,colloidal grade, suspension	Asahi kasel Amaerica
Ludipress LCE	Lactose, povidone (Kollidone 30)	Direct compression auxillary to use in chewable tablets, lozenges effervescent tablet	BASF, Germany
Pharmalactose DCL 40	Lactose,lactitol	High compatibility, co-processed, lubricant sensitivity	DMV, Germany
RanExplo^{TM}-S	MCC, silica, sodium starch glycoate	Super disintegrant, improve flowability	RarQ Pharmaceutical India

Starch

Starch, a white, granular, natural chemical that is produced through all inexperienced plants. Starch is a soft, white, tasteless powder that is insoluble in bloodless water, alcohol, or different solvents. The fundamental chemical method of the starch molecule is $(C_6H_{10}O_5)n$. Starch is a polysaccharide comprising glucose monomers joined in α 1,4 linkages. The easiest shape of starch is the linear polymer amylose; amylopectin is the branched form.

Microscopically, starch consists of colorless, especially refractive particles whose measurement and structure rely on a number elements most vital of which is the supply of the starch. A starch granule entails alternating areas of amorphous and crystalline lamellae considered as rings which are in fact the crystalline portion.

The starch molecule can be extracted and offered as such (native starch), however it can additionally endure various processing operations in order to enhance its proprieties and increase the vary of its uses.Native starch is the starch chain extracted from uncooked material, in its authentic form. It can both be dried (powder) or no longer (liquid starch). Unmodified starches have confined utilization due to their inherent weak spot of hydration, swelling and structural organization Official starches on hand encouraged by using British.

Pharmacopoeia for pharmaceutical functions include:

a. Maize starch received from caryopsis of Zea mays L.
b. Potato starch got from tuber of Solanumtuberosum L.
c. Rice starcstarchined from caryopsis of Oryza sativa L.
d. Tapioca starch obtained from the tuber of Manihotutilissima.
e. Wheat starch obtained from caryopsis of Triticumaestivum, L (T.vulgare)[15,16]

Lactose

In solid dosage forms, lactose is is probably the oldest but still one of the most important diluent in tabletting. However, the insufficient compactibility and poor flow property of α -lactose monohydrate powder limits the use of crystalline α -lactose monohydrate as a filler-binder for direct tabletting. Pharmaceutical grade lactose has a purity between 98.0 and 102.0 w/w %. Lactose is a naturally occurring simple carbohydrate, or sugar, found only in the milk of mammals. For this reason, it is also commonly referred to as “milk sugar.” All commercial lactose is obtained from the milk of cows as a by-product of the dairy industry. Chemically, lactose is the disaccharide of the simple sugars D-galactose and D-glucose.Lactose is mostly used as a filler and binderin tablets.

Geeneral properties of lactose:

1. Cost Effectiveness
2. Availability
3. Low Hygroscopicity
4. Water solubility

Chitosan

Chitosan is a multipurpose polymer with immense utility in pharmaceutical drug shipping systems. Low density,poor flowability and insufficient compression characteristics have litted its use as a tablet excipient. Chitosan occurs as odorless, white or creamy-white powder or flakes. Fiber formation is quite common during precipitation and the chitosan may look 'cottonlike'. Sparingly soluble in water, practically insoluble in ethanol (95%), other organic solvents, and neutral or alkali solutions at pH above approximately 6.5. Chitosan dissolves readily in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids.Chitin and its major derivative chitosan are non-toxic and approved by means of the FDA as a food additive and included in dietary supplements. The use of chitin as an excipient in tablet formulation is limited due to certain drawbacks such as poor flowability and low true density.

Microcrystalline cellulose (MCC)

MCC is a very important excipient for oral solid dosage forms, and was rated the most useful filler for direct compression tableting on account of low chemical reactivity combined with excellent compactibility at low pressures. Microcrystalline cellulose is the most many times used excipient in the pharmaceutical and nutraceutical industry. As a direct compression filler and binder, it points exceptional compactability and binding properties. It is consequently commonly critical to adapt the houses by means of including similarly substances for enhancing precise needs.[19]

Due to the reputation of microcrystalline cellulose, pharmaceutical formulators have deemed it applicable to encompass this excipient in a components which is moist granulated prior to tableting.Unfortunately, currently-available microcrystalline cellulose does now not maintain to the ordinary principle that the quantity of filler/binder wished in moist granulation is much less than that in direct compression. It is acknowledged that the publicity of the microcrystalline cellulose to moisture in the wet granulation procedure severely reduces the compressibility of this excipient.[20]

Microcrystalline cellulose is a accepted diluent, binder and disintegrant when used for pharmaceutical pill manufacturing, and in that subject its chief gain is that it can be without delay compressed into self-binding drugs that crumble hastily when positioned into water.[21,22]

Description

MCC is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle size grades. For example; the mean particle size of Avicel PH101 is 50µm and for Avicel PH200 is 180µm. Figure 1.2 shows Scanning Electron Microscopy (SEM) graphs of the different particle size grades of MCC.[23]

Limitations of MCC in formulation of solid dosage form

A number of limitations to the use of MCC have been detected, the most important of which were mentioned as following (El-Sakhawy and Hassan, 2007):-

- Low bulk density.
- The influence of moisture on the compression.
- Poor flow characteristics.
- High lubricant sensitivity characteristics.[23]

Silicon dioxide

Silicon dioxide is received by means of insolubilizing dissolved silica in sodium silicate solution. When received through the addition of sodium silicate to a mineral acid, the product is termed silica gel. When received by way of the destabilization of a answer of sodium silicate in such a manner as to yield very best particles, the product is termed precipitated silica. Silicon dioxide is insoluble in water. Prior to the existing invention, silicon dioxide, and in precise colloidal silicon dioxide, was once used broadly speaking as a glidant and anti-adherent in tabletting procedures and encapsulation, advertising the flowability of the granulation. The quantity of silicon dioxide blanketed in such drugs for these purposes is very limited, 0.1-0.5% by using weight.

This is due in phase to the truth that growing the quantity of silicon dioxide in the combination to be tabletted reasons the combination to float too well, inflicting a phenomena recognised to these expert in the tabletting artwork as "flooding". If the combination flows too well, a various pill weight with uneven content material uniformity can result.[24]

Description

Silicon dioxide, additionally recognised as sil-ica, is a ordinary and extensivelyused excipient. Its inert nature andhigh purity make it an best materialfor pharmaceutical formulations. Overthe years, silica producers haveperfected approaches that make ithighly useful and of consistentlyhigh quality.

For decades, silica functioned pri-marily as a glidant and widespread pro-cessing aid. As a glidant, it reducesthe inter-particulate friction of bulkpowders, permitting the particles toflow greater efficiently. This functionis vital due to the fact it improves thecontent.[25]

Method of coprocessing

1. Spray draying
2. Agglomeration
3. Melt Extrusion
4. Crystallization.

5. Solvent Evaporation
6. Wet granulation

1. Spray drying [26,27,28]

This spray drying method enable the conversion of feed from a fluid nation into dried particle. The feed can be a answer ,suspension, dispersion or emulsion .the dried product can be shape in the powders, granules or agglomerates and these are depending upon the bodily and chemical residences of feed and the dryer sketch last powder residences required. it is a non-stop particle processing drying operation. the spray drying method parameter like inlet air temperature ,atomization air pressure, feed rate, liquid viscosity, strong content material in feed, disc pace can be assist in format particle with want characteristics. as a result spray drying manner can bedesire as consisting of 4 steps

1. Atomization of the liquid into droplets.
2. Contact of the droplet with the heat drying gas.
3. Fast evaporation of the droplets to structure dry particles.
4. Recovery of the dry particles from the drying gas, the usage of a cyclone.

2. Agglomeration[29,30]

Agglomeration is the act or manner of forming or crystallizing into grains. Granules normally have a dimension vary between 0.2 to four mm relying on their subsequent use. Agglomeration of powders is broadly used to enhance bodily houses like: wettability, flowability, bulk density and product look (Blecher, 1993). Two types of granulation applied sciences are employed, namely, moist granulation and dry granulation. Wet granulation is the greater favored approach for coprocessing.

3. Melt extrusion[30]

Melt extrusion is a system of formation of small beads, pellets from the molten mass which is extruded via extruder. Extruders consist of 4distinct parts:

1. An opening although which fabric enters the barrel that can also have a hopper that is stuffed with the substances to be extruded.
2. A conveying part (process section), which comprises the barrel and the screws that transport, and the place applicable, combine the material.
3. An orifice (die) for shaping the cloth as it leaves the extruder.
4. Downstream auxiliary gear for cooling, cutting and/or gathering the completed product. Example: Compressol S [Mannitol, Sorbitol]

4. Crystallization[31]

Crystallization is the (natural or artificial) procedure of formation of stable crystals precipitating from a solution, soften or extra rarely deposited without delay from a gas. Crystallization is additionally a chemical solid–liquid separation technique, in which mass switch of a solute from the liquid answer to a pure stable crystalline section happens (Blecher, 1993). For crystallization to manifest from a answer it need to be supersaturated. This means that the answer has to include greater solute entities (molecules orisons) dissolved than it would include beneath the equilibrium (saturated solution). This can be carried out via a range of techniques such as: answer cooling, addition of a 2d solvent to limit the solubility of the solute (technique known as antisolvent or drown-out), chemical response and exchange in pH being the most frequent techniques used in industrial exercise

5. Solvent evaporation[32]

The method is carried out in liquid manufacturing vehicle. The coating excipient is dissolved in a volatile solvent, which is immiscible with liquid manufacturing automobile phase. A core excipient material to be microencapsulated is dissolved or dispersed in coating polymer answer with agitation. The core coating cloth combination is dispersed in liquid manufacturing car segment to obtain, the appropriate measurement microcapsule. The combination is then heated to evaporated the liquid automobile temperature is reduced to ambient temperature with persisted agitation.at this stage microcapsules can be used in suspension form, lined on to substrates or remoted.[33]

Development of Co-processed Excipients by Solvent Evaporation Method:

Procedure:

- The co-processed excipients were prepared by solvent evaporation method. A blend of excipient was added to 10 ml of ethanol.
- The contents of the beaker were mixed thoroughly and stirring was continued till most of ethanol evaporated.
- The wet coherent mass was granulated through # 44-mesh. The wet granules were dried in a hot air oven at 60º C for 20 minutes.
- The dried granules were sifted through # 44-mesh and stored in airtight container till further use.[34]

6. Wet granulation

Wet granulation technique is a system of dimension expansion in which pleasant powder particles are agglomerated or delivered collectively into larger, robust and notably everlasting shape referred to as granules the usage of a appropriate non-toxic granulating fluid such as water, isopropanol or ethanol (or combinations thereof). The granulating fluid can be used by myself or as a solvent containing binder or granulating agent. The desire of the granulating fluid relies upon noticeably on the homes of the substances to be granulated. Powder mixing, in conjunction with the cohesive homes of the granulating agent, allows the formation of granules. The traits and overall performance of the remaining product, radically relies upon on the extent to which the powder particles engage with every different to structure aggregates (granules).[34,41]

Formulation of tablet by wet granulation method

A granulation process comprising the steps of:

a) Adding binder to a powder in a mixer;
b) First mixing the powder and liquid binder to form intermediate granules;
c) Separating intermediate granules while wet that are larger than a predetermined diameter from smaller granules;
d) Crushing said intermediate granules to a size less than said predetermined diameter;
e) Second mixing said crushed granules with said smaller granules while still wet until granulation is complete.[38,39]

Fast dissolving tablet

Formulation of capsules into a presentable shape is the primary requirement and want of today. The dosage structure is a imply of drug transport system, used for the software of the drug to a residing body. Various kind of dosage varieties are handy such as tablets, syrups, suspensions, suppositories, injections, transdermal and patches having a one-of-a-kind kind of drug shipping mechanisms. These classical/ present day dosage types have some benefits and disadvantages.

Oral routes of drug administration have large acceptance up to 50-60% of complete dosage forms. Solid dosage varieties are famous due to the fact of ease of administration, correct dosage, self-medication, ache avoidance and most importantly the affected person compliance.[35] The most famous strong dosage types are being tablet and capsules; one essential disadvantage of this dosage types for some sufferers is the problem to swallow. Drinking water performs an essential function in the swallowing of oral dosage forms. Often instances human beings journey inconvenience in swallowing traditional dosage types such as tablet when water is now not available, in the case of the action health problem (kinetosis) and unexpected episodes of coughing at some stage in the frequent cold, allergic situation and bronchitis. For these reason, tablet that can hastily dissolve or crumble in the oral cavity have attracted a superb deal of interest.[36]

United States Food and Drug Administration (USFDA) described quick dissolving tablet (FDT) as "a stable dosage shape containing a medicinal substance or lively ingredient which crumble unexpectedly generally inside a count number of seconds when positioned upon the tongue"Fast dissolving drug shipping structures have been first developed in the late[37] Seventies as an alternative to traditional dosage types for the pediatric and geriatric patient. These tablets are designed to dissolve or collapse hastily in the saliva normally much less than 60 secondsTo fulfill these clinical needs, pharmaceutical technologists have developed a novel oral dosage varieties recognised as orally disintegrating (dispersible) capsules (ODTs) or Fast disintegrating (dissolving)tablets (FDTs) or mouth melting drugs (MMTs) or mouth dissolving tablets(MDTs), instantaneous launch drugs which fall apart swiftly in saliva, typically in a remember of seconds,without the want to take water.[38,39]

Requirements of fast dissolving tablets patient factors[40,49]

Fast dissolving dosage forms are suitable for those patients (particularly pediatric and geriatric patients) who are not able to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

- Patients who have situation in swallowing or chewing stable dosage forms.
- Patients in compliance due to worry of choking.
- Very aged sufferers of melancholy who may additionally no longer be capable to swallow the strong dosage forms
- An eight-year-old affected children with allergic reactions wishes a greater handy dosage structure than antihistamine syrup.
- A middle-aged affected person present process radiation remedy for breast most cancers might also be too nauseous to swallow her H2-blocker.
- A schizophrenic affected person who can also attempt to disguise a traditional pill beneath his or her tongue to avoid their day by day dose of an strange antipsychotic.
- A affected person with continual nausea, who can also be a journey, or has little or no get admission to to water.

Advantages of fast dissolving tablets[41,45]

- No want of water to swallow the tablet.
- FDTs can be without difficulty administered to pediatric, aged and mentally disabled patients.
- Accurate dosing as in contrast to liquids.
- Dissolution and absorption of the drug is fast, supplying fast onset of action.
- Bioavailability of tablets is increased as some tablets are absorbed from mouth, pharynx and esophagus via saliva passing down into the stomach.
- Advantageous over liquid medicine in phrases of administration as nicely as transportation.
- First skip metabolism is reduced, as a consequence presenting expanded bioavailability and for this reason decreased dose and facet effects.
- presenting accelerated safety.
- Suitable for sustained/controlled launch actives.
- Allows excessive drug loading.

Limitations of fast dissolving tablet[46,47,48,50]

- The predominant hazards of FDTs is associated to the mechanical strength of tablets.
- FDT are very porous and smooth molded metrics or compressed in a tablet with low compression, which makes pill friable and brittle which tough to handle.
- Bad tastes capsules are tough to formulate as FDT; exclusive precaution must have to be taken earlier than formulate such form of drug.
- Several FDT are hygroscopic can't keep bodily integrity under everyday situation from humidity which requires specialised package.

- Dryness of the mouth due to diminished saliva manufacturing may additionally no longer be exact candidates for these pill formulations.
- Rate of absorption from the saliva answer and common bioavailability.
- Drug and dosage shape stability.

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