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Review Article

CO-PROCESSING OF EXCIPIENTS: A REVIEW ON EXCIPIENT DEVELOPMENT FOR FAST DISSOLVING TABLET

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Abstract

The Co-processing is the most widely explored method for the preparation of directly compressible adjuvants because it is cost effective and can be prepared in-house based on the functionality required. This review article has been written with the aim of giving detailed information about the excipients, potential advantages of co-processed excipients, recent research on co-processed excipients for direct compression, various methods of preparing co-processed excipients for direct compression available in the market. Fast dissolving tablet have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms such as tablets, capsules, solutions and suspensions because of tremors of extremities and dysphasia. Recent development in fast dissolving technology mainly works to improve the disintegration quality of these delicate dosage forms without affecting their integrity. This article focuses on the patented technologies available Apart from the conventional methods of fabrication, this review also provides the concept of some unique technologies like freeze drying, direct compression, spray drying, tablet molding, sublimation and evaluation of Fast dissolving tablet.

Keywords: - Co-processing, Recent Research, Direct compression, Fast dissolving tablet.

Introduction

The International Pharmaceutical Excipients Council (IPEC) defines excipient as "substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system. For example, excipients can:

I.Aid in the processing of the drug delivery system during its manufacture,

II.Protect, support or enhance stability, bioavailability or patient acceptability,

III.Assist in product identification

IV.Enhance any other attribute of the overall safety, effectiveness or delivery of the drug during storage or use [1].

A co-processed excipient is a combination of two or more compendial or noncompendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing, and without significant chemical change. However in some instances, formation of necessary components may occur, such as in-situ salt formation. Many different co-processing methods may be used, including standard unit operations such as granulation, spray drying, melt extrusion, milling etc. The choice for a specific application will depend on the materials used, their form (e.g. whether dry powders or liquid) and the specific physical properties desired. Likewise the ratios of the components may vary depending on the desired performance[2].

There are many dosage forms in which coprocessed excipients are used mainly in solid dosage forms such as tablets, capsules, powders, etc., liquid dosage forms such as emulsions, suspensions, injections, etc. Semi-solid dosage forms such as creams, ointments, pastes, etc. As they have been used to enhance different properties of dosage forms so, it finds application preferred dosage form of pharmaceutical professionals because they can be accurately dosed and provide good patient compliance.

The development in the field of APIs, excipients and tablet machines during the past decades has made tablet manufacturing a science. This popularity of tablets coupled with an increased understanding of the physics of compression and of manufacturing process variables have matured the manufacture of tablets as a science in its own right [3].The oral fast-disintegrating tablets is also known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar. By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast dispersing dosage form. According to European Pharmacopoeia, the Oral Dissolving Tablets should disperse/disintegrate in less than three minutes. Difficulty in swallowing (dysphasia) is common among all age groups especially in elderly and is also seen in swallowing conventional tablets and capsules [4].

Most formulations (70–80%) contain excipients at a higher concentration than the active drug. Co-processed excipients are prepared by incorporating one excipients into the particle structure of other excipients using processes such as Co-drying. Co-processed excipients lead to the formation of excipients granules with superior properties compared with physical mixture of components or individual components. Co-processing these two kinds of material produce a synergistic effect in term of compressibility by selectively overcoming the disadvantage and can help improve functionalities such as compaction performance, flow properties, strain rate sensitivities, lubricant sensitivity or sensitivity to moisture. For example, Mannitol exhibits low moldability and a high dissolution rate and less sensitivity to humidity. Hard compact of microcrystalline cellulose disintegrant rapidly due to the rapid passage of water into the compact and the instantaneous rupture of hydrogen bond [5,6].

Advantages of Co-Processing: Co processing of Excipients offers many advantages in terms of formulation aspects of any dosage form. These advantages are discussed as follow

I.Improved Flow Properties: Controlled optimal particle size and particle- size distribution ensures superior flow properties of co-processed excipients without the need to add glidants.

II.Improved compressibility: Co-processed excipients have been used mainly in direct compression because in this process there is a net increase in the flow properties and compressibility profiles and the excipient formed is a filler–binder.

III.Fill weight variation: In general, materials for direct compression tend to show high fill weight variations as a 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. The primary reason for this phenomenon is 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. Fill weight variation tends to be more prominent with high-speed compression machines.

IV.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 acoherent lubricant network by forming newly exposed surfaces upon compression, thus breaking up the lubricant network [7].

V.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 [8].

Methods Of Preparing Directly Compressible Excipients: in Table no. 1, with advantage and Limitation.

METHODS OF PREPARING DIRECTLY COMPRESSIBLE EXCIPIENTS Table No. 1 [9,10]

Method	Advantages and Limitations	Examples
Chemical modification	Relatively expensive , Requires toxicological data, Time consuming	Ethyl cellulose, Methyl cellulose, Hydroxy propyl methyl cellulose, and carboxy methyl cellulose from cellulose , cyclodextrin from starch, lacitol
Physical modification Grinding and/or sieving	Relatively simple and economical , compressibility may alter	Dextrose or Compressible sugar , Sorbitol, α-Lactose monohydrate, Dibasic calcium phosphate
Crystallization	Impart flowability to excipients, Requires stringent control on possible polymorphic conversions and processing conditions	β-Lactose, Dipac
Spray drying	Spherical shape and uniform size, good flowability, poor reworkability	Spray-dried lactose, Emedex, Avicel pH, Karion Instant, TRI-CAFOS S, Advantose 100
Granulation/Agglomeration	Transformation of small, cohesive, poorly flowable powders into a flowable and directly compressible.	Granulated lactitol, Tablettose
Dehydration	Increased binding properties	Anhydrous α- Lactose

Recent Research on Co-processed Excipients for Direct Compression:-summarized in Table no.2.

S No	Co-processed Excipients investigated	Technology / Method used for Co-processing	Drugs studied (category)	Result/Purpose	Reference
1	Crospovidone-Croscamellose sodium {1:1, 1:2,1:3}	Solvent evaporation	Metoclopramide (antiemetic)	Superior in flow and compression characteristics	**11**
2	Crospovidone-Sodium starch glycolate {1:1, 1:2, 1:3}	Solvent evaporation	Metoclopramide (antiemetic)	Superior in flow and compression characteristics	**11**
3	Mannitol-Microcrystalline cellulose (Avicel pH-102) aerosil {70:29:1, 70:28;3,30:69:1, 30:68;2}	Solvent evaporation	Metoclopramide (antiemetic)	Superior in flow and compression characteristics	**11**
4	Chitosan and Aerosil(1:1)	Co-precipitation method	Metoclopramide (antiemetic)	Superior in flow and compression characteristics	**11**

5	Mannitol Microcrystalline Cellulose PH101(1:1,1.25:1,2:1,3:1,4:1,1:1.25,1:2, 1:3 and 1:4)	Spray drying	Glipizide(Antidiab-etic)	Improved performance of the fast dissolving tablets	**12**
6	Physically modified (nitric acid treated) wheat starch and Dicalcium phosphate		Acetaminophen (NSAID)	Improved flow and compressibility characteristics.	**13**
7.	Lactose and Mannitol (1:1, 1:2, 2:1, 1:3, 3:1, 90, 80 and 70%)	Melt granulation	Acetaminophen (NSAID) Paracetamol (antipyretic)	The tablets manufactured showed relatively better disintegration time and in-vitro drug release	**14**
8	Dicalcium phosphate and Starch (25:75)		Acetaminophen (NSAID)	Excipients showed optimum compressibility characteristics and tablets showed fast disintegration	**15**
9	Pre gelatinized starch-Microcrystalline Cellulose	Gelatinizing potato starch in presence of MCC	Sulphamethoxazole (Anti bacterial) Paracetamol (Antipyretic) Aceclofenac (NSAID)	PGS-MCC co-processed excipient developed in this study was found to be a promising directly compressible vehicle	**16**
10	Microcrystalline tapioca starch with Lactose monohydrate-‘microcrystarlac		Paracetamol (antipyretic) Ascorbic acid (anti scurvy)	Microcrystarlac shows improved functionality over direct physical mixture of the primary excipients	**16**
11	Mannitol:Cellulose (50:50, 60:40, 70:30)	Freeze thawing technique	Aceclofenac (NSAID) Nimesulide (NSAID) Metformin	Flowability, compactability, and dissolution rate were improved profoundly	**17**
12	PEG 4000, Gelucire 44/14, Gelucire 50/13, Crospovidone	Melt granulation agglomeration	Aceclofenac (NSAID	Melt granulation agglomeration may be adopted in preference to spray drying.	**18**

13	Cellulose- Ethyl cellulose	Kneading method	Pioglitazone (antidiabetic) Gliclazide (antidiabetic)	The tablets prepared gave rapid dissolution	**19**
14	Starch –PEG 1500	Gelatinizing potato starch in the presence of PEG 1500	Pioglitazone (antidiabetic) Gliclazide (antidiabetic)	The co-processed excipient was found to be a promising directly compressible vehicle	**20**
15	Microcrystalline cellulose, Silicon dioxide and Crospovidone	Spray drying	Diclofenac sodium (NSAID) Iron polymaltose (Treatment of iron deficiency anaemia) Amoxicillin trihydrate (antibiotic)	The co-processed materials have excellent flow properties, high compressibility, render low disintegration time to tablets and have better binding properties	**21**
16	Microcrystalline cellulose, Colloidal silicon dioxide and Sodium starch glycollate	Spray drying	Diclofenac sodium (NSAID) Iron polymaltose (Treatment of iron deficiency anaemia) Amoxicillin trihydrate (antibiotic)	The co-processed materials have excellent flow properties ,high compressibility, render low disintegration time to tablets and have better binding properties	**22**
17	Directly compressible co-processed sustained release multifunction agent (DCCSRA) comprising Povidone K 25 : Glyceryl behenate (1:1, 1:2, 1:3)	Hot melting	Tramadol Hcl (analgesic)	The DCCSRA exhibited good flow and compressibility and it served as a retardant, binder and lubricant in Tramadol Hcl sustain release tablets	**23**
18	Microcrystalline cellulose with SSL Hydroxypropyl cellulose (1:1, 1:2, 1:3)	Spray drying	Tizanidine Hydrochloride(Centrally acting muscle relaxant)	Formulation showed minimum disintegration time and higher amount of drug release in 1:3	**24**
19	Crospovidone: Croscarmellose (1:1, 1:2, 1:3)	Solvent evaporation	Chlorthalidone (Antihypertensive and antidiuretic)	The dissolution rate of chlorthalidone was enhanced.	**25**

20	Crospovidone: Sodium starch glycolate (3;1)	Solvent evaporation	Cefexime trihydrate (oral cephalosporin) Ibuprofen (NSAID)	Exhibited good flow and compression, improved dissolution.	**26**
21	Pregelatinized starch-Polyvinyl pyrrolidone	Gelatinizing potato starch in the presence of PVP	Ritonavir, Efavirenz, Stavudine(antir-eteroviral)	Exhibited excellent to good flow properties	**27**

Advantages of fast dissolving tablet

I.Improved compliance/added convenient new business opportunities product differentiation, line extension and lifecycle management, exclusivity of product promotion, and patent-life extension.

II.No water needed

III.No chewing needed

IV.Better taste

V.Improved stability

VI.Suitable for controlled/sustained release actives

VII.Ability to provide advantages of liquid medication in the form of solid preparation.

VIII.Adaptable and ameanable to existing processing and packaging machinery

IX.Cost- effective

X.Rapid drug therapy intervention

XI.Best for patent with oesophageal problems and have

XII.Difficulties of deglutition tablets.

XIII.High drug loading is possible.

XIV.Have acceptable taste and pleasant mouth feeling.

XV.Leave minimum residue [28,29].

Limitations to fast dissolving tablet

I.Drugs with relatively larger doses are difficult to formulate into MDT e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg of the drug.

II.Patients who concurrently take anticholinergic medications may not be the best candidates for MDT. Similarly patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations [30].

Technologies used to manufacture fast dissolving tablets:-

The technologies used to manufacture mouth dissolving tablets can be classified as Table3:

S.No	CONVENTIONAL TECHNOLOGIES	PATENTED TECHNOLOGIES
1	Freeze Drying.	Zydis Technology.
2	Tablet Molding.	Orasolv Technology.
3	Direct Compression.	Durasolv Technology.
4	Spray Drying.	Wowtab Technology.
5	Sublimation.	Flashdose Technology.

I.**Freeze drying:-** ZYDIS® (R.P. Scherer, Swindon, UK), using freeze drying processes, is one of the first generations of fast disintegrating dosage forms. There are approximately 12 marketed ZYDIS® products, including lorazepam, piroxicam, loperamide, loratidine, enalapril. A process in which water is sublimated from the product after freezing. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavilabity.

II.**Molding:-** In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-drying. Molded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution.

III.Spray drying:- The formulations contained hydrolyzed and unhydrolyzed gelatin as a supporting agent for the matrix,mannitol as a bulking agent and sodium starch glycolate/

croscaramellose as a disintegrant. Disintegration and dissolution were further enhanced by adding an acid (e.g.,citric acid) or an alkali (e.g., sodium bicarbonate). The suspension of above excipients was spray-dried to yield a porous powder which was compressed into tablets. Tablets manufactured by this method disintegrated in < 20 secs in an aqueous medium.

IV.**Sublimation:-** Sublimation has been used to produce FDTs with high porosity. A porous matrix is formed by compressing the volatile ingredients alongwith other excipients into tablets, which are finally subjected to a process of sublimation. Inert solid ingredients with high volatility (e.g.,ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, phthalic anhydride, urea and urethene) have been used for this purpose. Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix 31.

V.**Direct compression:-** It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production method.

Advantages of direct compression

•Requires fewer unit operations compared with wet granulation (shorter processing time and lower energy consumption)

•Fewer stability issues for actives that are sensitive to heat or moisture

•For certain compounds, faster dissolution rates may be generated from tablets prepared by direct compression compared with wet granulation; for example, norfloxacin

•Fewer excipients may be needed in a direct compression formula.

Disadvantages of direct compression

•Issues with segregation – these can be reduced by matching the particle size and density of the active drug substance with excipients

•In general, the drug content is limited to approximately 30% or approximately 50 mg

•May not be applicable for materials possessing a low bulk density because after compression the tablets produced may be too thin

•Not suited for poorly flowing drug compounds

•Static charges may develop on the drug particles or excipients during mixing, which may lead to agglomeration of particles producing poor mixing32.

Comparison of some patented technologies for mouth dissolving tablets in Table no. 4 [33]

S.No	Technology	Novelty	Handling/storage	Drug release/ bioavailability
1	Zydis (R.P. Scherer, Inc.)	First to market. Freeze Dried	Do not push tablet through foil. Do not use dosage form from damaged package. Sensitive to degradation at humidities >65%	Dissolves in 2 to 10 seconds. May allow for pre-gastric absorption leading to enhanced bioavailability
2	Orasolv (Cima Labs, Inc.)	Unique taste masking. Lightly compressed	Packaged in patented foil packs	Disintegrates in 5 to 45 seconds depending upon the size of the tablet. No significant change in drug bioavailability

3	Durasolv (Cima Labs, Inc.)	Similar to Orasolv, but with better mechanical strength	Packaged in foil or bottles. If packaged in bottles, avoid exposure to moisture or humidity exposure to moisture or humidity	Disintegrates in 5 to 45 seconds depending upon the size of the tablet. No significant change in drug bioavailability
4	Wowtab (Yamanouchi Pharma Technologies, Inc.)	Compressed dosage form. Proprietary taste masking. Smooth melt action gives superior mouth feel	Package in bottles. Avoid exposure to moisture or humidity	Disintegrates in 5 to 45 seconds depending upon the size of the tablet. No significant change in drug bioavailability

Evaluation of fast dissolving tablet :- Fast disintegrating tablets formulations have to be evaluated for the following evaluation test

I.**Size and Shape:-** The size and shape of the tablet can be dimensionally described, monitored and controlled.

II.**Tablet thickness:-** Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

III.**Uniformity of weight:-** United state pharmacopeia procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

Average weight of Tablets (mg)	Maximum percentage difference allowed
130 or less 10	10
130-324	7.5
More than 324	5

IV.**Tablet hardness:-** Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of the tablet of each formulation was determined using Monsanto Hardness tester [34].

V.**In-Vivo Disintegration test:-** The test was carried out on 6 tablets using the apparatus specified in I.P distilled water at 37°C ± 2°C was used as a disintegration media and the time in second is taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds [34].

VI.**Friability:-** Friability is a crucial parameter for evaluation of MDT. Attempts for decreasing the disintegration time increase the friability of MDTs than the conventional tablets. Dosage forms like Zydis are very fragile. Friability is a measure of mechanical strength of the tablet. If a tablet has more friability it may not remain intact during packaging, transport or handling. Roche friabilator is used to determine the friability by following procedure. Pre weighed tablets are placed in the friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets are rotated in the friabilator for at least 4 minutes. At the end of test tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as [35]:

% Friability = 1- (loss in weight / Initial weight) X 100

VII.**Wetting time:-** The initial process in the disintegration of a MDT involves water uptake and wetting of the tablet. So determination of wetting time is also important. It also helps in studying the effect of various excipients in the disintegration of the tablet. The method reported by yunixia et al., was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet as put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined [36].

VIII.**Dissolution test:-** The dissolution method for oral disintegrating tablets is the same as that of conventional tablets. USP 2 paddle apparatus is most suitable and common choice for dissolution test of oral disintegrating tablets, where the paddle speed is 50 rpm is used. The USP 1 (basket) apparatus may have certain application for such tablets but is used less frequently due to specific physical properties of tablets. Specifically tablet fragments or disintegrating tablet masses become trapped on the inside top of the basket spindle where little or no effective stirring occurs, yielding irreproducible results in dissolution profiles [37].

IX.**Stability study** (Temperature dependent):-The fast dissolving tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.40 ± 1 °C,50 ± 1°c,37 ±1 ° C and RH 75% ± 5%

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Vissual defects, Hardness, Friability, Disintegrations, and Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25 ° C.

Conclusion:- Coprocessed excipients are a result of this arduous innovation only, wherein two excipients are coprocessed to provide products with improved functionality by retaining their favorable an avoiding the unfavorable properties. The main obstacle in the success of coprocessed excipients is the non inclusion of their monographs in official pharmacopeias, which discourages their use by pharmaceutical manufacturers. With recommendations from IPEC and the continual efforts of excipient manufacturers, these products could find their way into official monographs, either as mixtures or as single-bodied excipients. Introduction of fast disintegrating dosage forms has solved some of the problems encountered in administration of drugs to the pediatric and elderly patient, which constitutes a large proportion of the world's population. Hence, patient demand and the availability of various technologies have increased the acceptance of Fast disintegrating tablets, which in turn prolongs the patent life of a drug. Keeping in view of the advantages of the delivery system, fast disintegrating dosage forms have been successfully commercialized, and these dosage forms very well accepted at doctors as well as patient level.

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