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Review Article

A REVIEW ON DEVELOPMENT OF MULTIFUNCTIONAL CO-PROCESSED EXCIPIENT

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ABSTRACT

The demand for directly compressible co-processed excipients has increased mainly due to the availability of high-speed tableting machines, time-saving in filing abbreviated new drug applications (ANDA), simplified validation and stability of active pharmaceutical ingredient (API). The cost of new excipient development is very high as it demands toxicity study also. Hence, industry has focused on co-processing of approved materials. The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality/price. The risk to product quality is reduced, and productivity is improved due to the use of multifunctional co-processed excipients. In the present era, the Quality by Design (QbD) concept is useful for the development of multifunctional co-processed excipients. Co-processing is not restricted to diluents. It can be extended to other ingredients such as binders and disintegrants of tablets and capsules. There is also scope for obtaining patents by working upon newer avenues of developing multifunctional co-processed excipient for lozenges (e. g. iso-melt of sugar) or for herbal excipients. The present review focuses on formulation and evaluation techniques of multifunctional co-processed excipients. The characteristics of currently available multifunctional co-processed materials are enlisted in the review to facilitate further research by research scholars and R & D scientists.

Keywords: Co-processed**,** Excipients, Oral drug delivery

INTRODUCTION

As oral drug delivery is simple, most convenient, safest, noninvasive and most economical, it continues to be the preferential route of administration and researchers are seeking ways to incorporate various technologies in oral formulations. Even small improvements in drug delivery technology can make significant differences in enhancing patient compliance and drug bioavailability [1].

The tablet is a preferred dosage form by industrial pharmacists because of their ease of manufacturing, convenience to administration, accurate dosing, and improved stability compare to liquid and semisolid dosage forms. Direct compression is widely used in tableting because it requires fewer processing steps, simplified validation, elimination of heat and moisture, economy, and improved drug stability compared with wet granulation. Most drugs do not possess direct compression characteristic. Hence, the addition of directly compressible adjuvants becomes mandatory in such cases. The most important requirements for directly compressible filler-binders are good flow ability and compatibility of the powder [2, 3].

No single excipient possesses all the desired physicomechanical properties for the development of a robust drug delivery system. Hence, there is a need to have excipients with multifunctionality such as better flow, low/no moisture sensitivity, superior compressibility and rapid disintegration ability [4]. The functionality of excipients can be improved by either developing new excipient or co-processing of existing excipient. The relatively high cost involved in discovery and development of new excipients favors co-processing of existing excipients [5].

Co-processed excipients can be defined as combining two or more established excipients by adopting an appropriate manufacturing process. They offer substantial benefits of the incorporated excipients and minimize their drawbacks. The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality/price [6, 7]. Co-processed excipient is a combination of permissible pharmaceutical excipients, and it must demonstrate one or more different properties from a physically modified mixture of those excipients [8]. It is worthwhile to note that co-processing will not bring chemical changes in excipients. Goyanes A. *et al.,* prepared co-processed MCC-Eudragit E excipient and compared IR spectra of co-processed excipient with its individual excipient, MCC and Eudragit E. The peaks of individual excipient were retained in spectra of co-processed MCC-Eudragit E which indicated the absence of chemical reaction. X-ray powder diffractograms revealed that the co-processing did not alter the crystallinity characteristics of MCC [9]. Detailed studies of silicified microcrystalline cellulose by X-ray diffraction analysis, nuclear magnetic resonance (NMR) spectroscopy, infrared (IR) spectroscopy, Raman spectroscopy, detected no chemical changes and indicated a similarity to the physicochemical properties of MCC [7]. The breaking of bonds, reorientation, stereochemical environment and established intermolecular forces are responsible for new shapes that determine the formation of co-processed material. Several interactions may result from hydrogen bonding, Van der Waals forces, polar and ionic interactions, covalent links or even chemisorption complexes by absorbing carriers. These reactions are more complex when greater numbers of ingredients are involved hence they must be carefully monitored and controlled [10]. Co-processed excipients can alter in particle size, particle shape, bulk density, tap density, true density, porosity and surface roughness of existing excipients. Patel S. *et al.,* observed SEM photograph of cellulose, mannitol, and co-crystallised agglomerates. Untreated cellulose and the mannitol showed no evidence of porosity, whereas the crystallized agglomerated particles indicated evidence of porosity. Untreated cellulose and mannitol particle were slightly fibrous and plate like in appearance, respectively, whereas co-crystallized agglomerates were random in size and nearly spherical in shape (fig. 1) [11].

Co-processing improves adherence of drug particles to excipients to decrease the possibility of segregation. Michoel A. *et al.,* prepared co-processed Microlec 100 by spray drying method and produced tablets of folic acid with it. In the prepared blend, stronger adherence of folic acid to the porous surface of the Microlec 100 was observed [12]. The co-processing improves compression behavior of excipient as it is generally performed with a combination of materials that have plastic deformation and brittle fragmentation characteristics [10, 13]. Many times humidity can also change the physicomechanical properties of co-processed excipients. Haware RV. *et al.* checked the effect of relative humidity (RH) and

hydroxypropyl methylcellulose (HPMC) on the physicomechanical properties of coprocessed MacroceLac® 100 using 'DM³' approach. They found that Significant MicroceLac®100 changes occurred with % RH exposure affecting performance attributes. HPMC physical addition did not prevent molecular or macroscopic matrix changes [14].

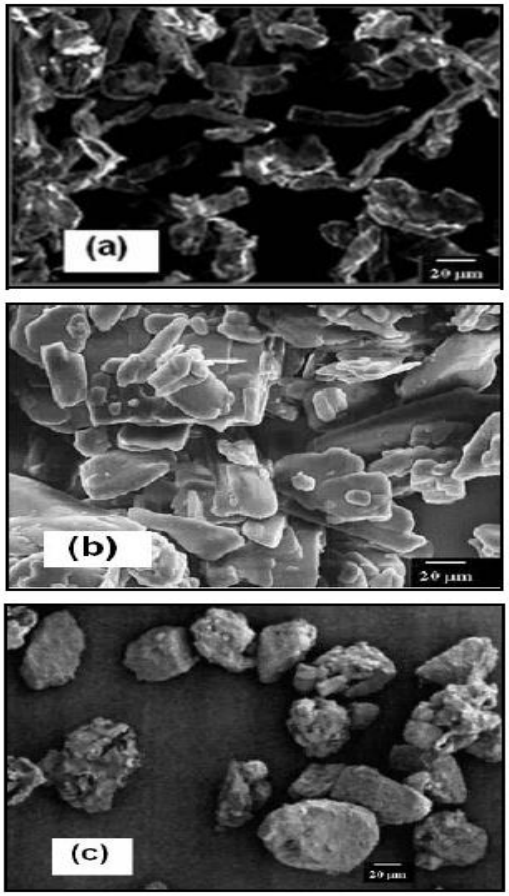

Fig. 1: SEM photograph of cellulose (a), mannitol (b) and Co-crystallized agglomerates

Functionality of co-processed excipients

Influence of changes in the excipient particles on the resulting functionality is reported in fig. 2.

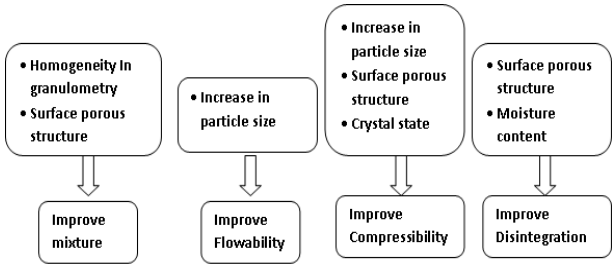

Fig. 2: Influence of changes in the excipient particles on the resulting functionality in a technological process

Following are the examples of multifunctional co-processed excipients

i. Microcrystalline cellulose is used as an efficient dry binder in direct compression technology because of its excellent compaction property. It is, however, not a good tablet disintegrant. Dry starch is one of the most commonly used disintegrant having poor flow and compaction. It produces friable tablets which limited its use. The demand for robust tablets with high mechanical strength and faster dissolution properties was satisfied with formulating co-processed MCC and starch [15].

ii. Co-processed super disintegrants consisted of crospovidone, and croscarmellose sodium exhibited good flow and compression characteristics. It exhibited quick disintegration and improved drug dissolution compare to a physical mixture of crospovidone and croscarmellose sodium used in granisetron hydrochloride fast dissolving tablets [16].

iii. Clerch A. V. *et al.,* proved the effectiveness of the combination of calcium phosphate dihydrate (brittle material) and microcrystalline cellulose (plastic material). Calcium phosphate exhibits good flow characteristics, high porosity, and hydrophilic behavior, enabling fast disintegration; however the tablets exhibit low breaking force and high friability in the final formulation. Owing to this brittle behavior, the combination using microcrystalline cellulose was prepared since this has good compatibility properties which compensate the inadequate compression properties of calcium phosphate [17].

iv. Amorphous silicon dioxide (SiO_2) has been widely used as a flow enhancer in powder formulations. It can be used as a companion excipient for co-processing with chitin, starch, MCC I and MCC II [18].

v. Co-processed maize starch and spray dried lactose, StarLac, exhibits good flowability depending on the spray-drying process, an acceptable crushing force due to its lactose content, rapid disintegration and faster drug release depending on the starch content in co-processed excipient [19].

vi. Gohel M. C. *et al.,* prepared multifunction co-processed excipient containing microcrystalline cellulose, lactose and dibasic calcium phosphate dehydrate (DCP) to overcome disadvantages of individual excipient [2].

vii. Bowe KE *et al.,* prepared co-processed sugar consisted of 95% sucrose and 5% sorbitol which was free flowing and compressible. Tablets made with this new excipient were stronger and disintegrated faster than tablets made with some of the commercially available compressible sugars (sucrose and dextrose). Co-processed sucrose has a porous, open crystalline structure and a pleasant taste, which can be helpful with masking the bitter taste of pharmaceutical actives [20].

viii. The co-processed excipient can also be used to produce direct compressible sustained release tablets. Patel *et al.* developed co-processed glyceryl monostearate-dicalcium phosphate dihydrate, to improve flowability and compressibility of the blend and to provide sustained release of the highly water soluble drug, tramadol hydrochloride [21]. Co-processing of sucrose and microcrystalline cellulose (MCC) can also provide sustained release of the drug [22].

ix. Co-processing of acacia-calcium carbonate is the example of binder-filler co-processing in which calcium $CaCO_3$ also acted as alkalizer to improve the dissolution rate of pH dependent soluble drugs like atorvastatin [23].

Preparation of multifunctional co-processed excipients

- Selection of parent excipients based on the physical characteristics and functionalities desired in the final product. This is analogue to define stage of six sigma components (DMAIC) and element of quality target product profile (QTPP) of QbD.
- Selection of the level and proportion of component excipients based on the functionalities required in the final product [17].
- Processing of the excipients using one of the suitable methods mentioned below. The process understanding and process control are important considerations in QbD [24]

Methods to prepare multifunctional co-processed excipient

a. Dry granulation by roller compaction

Dry granulation process is a particle-bonding process [7]. Fig. 3 shows flow diagram of roller compaction process [25]. Daraghmeh N

et al. developed co-processed chitin and mannitol (Cop–CM) by roll compaction method to use it in orodispersible tablets (ODT) [26].

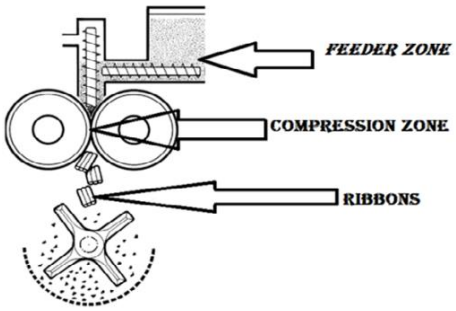

Fig. 3: Flow diagram of roller compaction process

b. Wet granulation method

Wet granulation process can be performed either in fluid bed granulators or high shear mixers [7]. Gohel M. C. *et al.* prepared a novel co-processed excipient containing MCC, lactose and DCP by wet granulation method using starch paste as a binder [2].

Micro granule preparation

Muhammad A. *et al.,* prepared co-processed granules of lactose monohydrate, microcrystalline cellulose and corn starch by wet granulation method. The wet mass was passed through oscillating granulator to obtain micro granules. An optimized batch of tablets had excellent flow properties, high compressibility, better binding properties and low disintegration time [27].

Melt granulation technique

Melt granulation technique involves mixing of co-processed excipients with the meltable binder on a water bath, cooling of agglomerates to solidify the mass and subsequently passing through a sieve. It can be adopted in conventional equipment. It is solvent-free technique and requires a short processing time. The concentration of binder and diluent to binder ratio are critical variables in the process. Gohel M. C. *et al.,* proved that melt granulation technique can be effectively used to prepared co-processed excipient. They have prepared and evaluated lactose and microcrystalline cellulose based, directly compressible adjuvant in which effect of percentage of polymer blend (PVP K 30 and PEG 4000; 5, 10, or 15%) and the polymer blend ratio (9:1, 1:1, or 1:9) were studied [28]. Kothiya M. *et al.* developed co-processed excipients for fast dissolving tablets of Irbesartan by melt agglomeration technique. Lactose monohydrate and mannitol was selected as a diluent and Polyethylene glycol 4000 was used as a binder. To improve the functionality of co-processed excipients 8 % crospovidone was incorporated [29].

c. Hot-melt extrusion (HME)

This process is widely used in transferring and melting of polymer inside a barrel by a rotating screw. The polymer melt is then pressurized through the die and solidify into a variety of shapes. Extrusion can be further processed into tablets or granules [7]. Schematic diagram of hot melt extrusion process is shown in fig. 4.

d. 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. 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 and the dryer design. Construction of spray drier is shown in fig. 5 [25].

e. Freeze-thawing

It is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flow ability and compatibility of the excipients. Patel S. *et al.,* combined mannitol with cellulose by the freeze-thawing process [11].

f. solvent evaporation technique

Goyanes A. *et al.,* prepared co-processed MCC-Eudragit E excipient where acetone and isopropanol were used as solvents for Eudragit E. The wet mass was subsequently dried till organic solvents were evaporated [9]. Residual solvent has to be checked in the co-processed product as per the current ICH guidelines. Uppuluri P *et al.* prepared co-processed excipient having corn starch and Sodium lauryl sulphate by two methods: solvent evaporation method and co-grinding method. He concluded that the solvent evaporation method with water as a solvent was the best suited for the preparation of co-processed excipients [30].

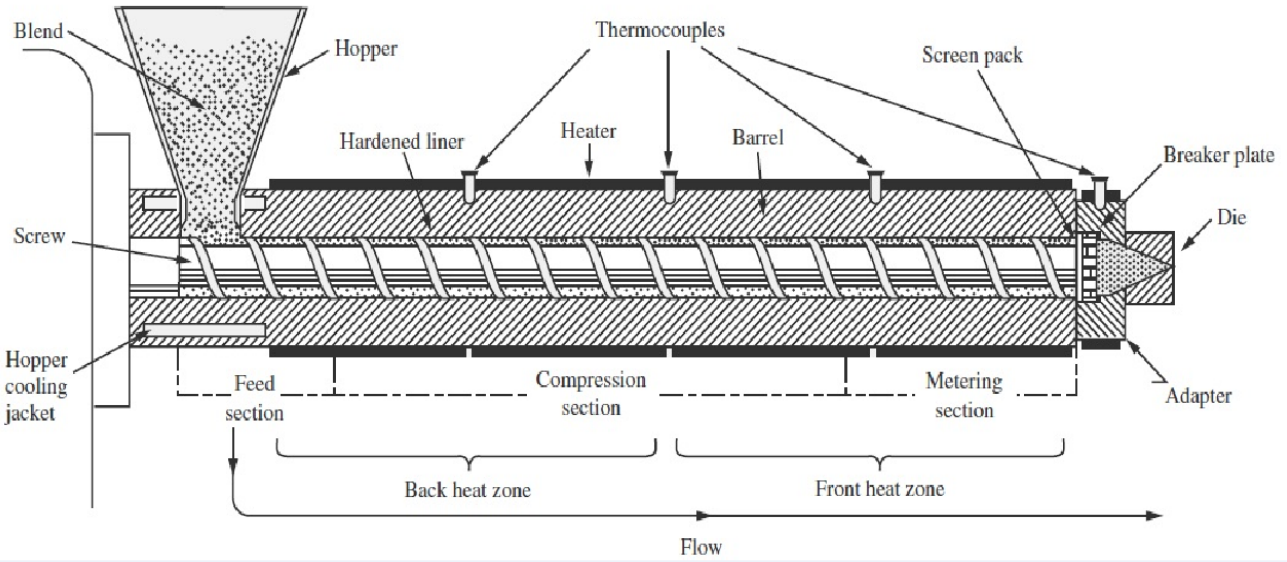

Fig. 4: Schematic diagram of hot melt extrusion process

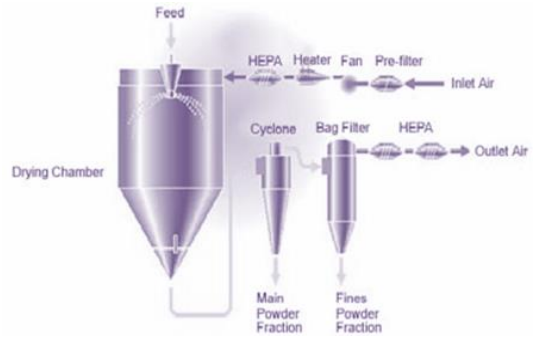

Fig. 5: Schematic diagram of spray drier

Evaluation of multifunctional co-processed excipients

I. Evaluation parameters of co-processed excipient

A. Bulk density, Tapped density, True density, Hausner's ratio, Carr's index and angle of repose

These parameters can be determined by USP method [31].

B. Porosity

Total intra-particle porosity, pore area, and pore size distribution are determined using a mercury porosimeter [32].

C. Particle sizes analysis

Mean particle size of co-processed excipient is analyzed by sieve analysis method [33].

D. Percentage fines

The percentage fine is defined as the percentage of the sample passed through a 200 mesh (74 mm) sieve. The sample is agitated on a sieve shaker on a 200 mesh for 5 min for finding percentage fines [33].

E. Morphology study

Scanning electron microscopy is used to study morphology (Shapes, surface, etc) of co-processed excipients. SEM technology helps to understand adsorption or deposition of one excipient on second [9].

F. Equilibrium moisture sorption (EMS)

The moisture sorption isotherm is determined by the gravimetric method [34].

G. Loss on drying (LOD)

A sample of co-processed excipient is spread in a Petri dish, and the dish is placed in hot air oven at 100 °C for 3 hr. The percentage decrease in weight is noted to calculate loss on drying as per equation 8 [2].

$$\%\ LOD = \frac{\text{Initial weight of sample} - \text{final weight of sample}}{\text{Initial weight of sample}}\ x\ 100 \quad (8)$$

H. Compatibility of co-processed excipient

The sample is compressed in a hydraulic press at compression forces of 0.5, 1.0, 1.5, 2.0 and 3.0 tons, using flat face punches. The hardness of each compact is measured using a hardness tester [15].

I. Heckel's plot

The directly compressible adjuvant should exhibit good pressure-volume profile. The sample is compressed in a hydraulic press using and matching die at pressures of 1, 2, 3, 4, 5 and 6 tons for 1 min. The compacts are stored over silica gel for 24 hr to allow elastic recovery, hardening and prevent falsely yield low values before evaluations. Weight, diameter, and thickness of the compacts are determined, and data are processed using Heckel equation 9.

$$\ln [1/(1-D)] = kP+A \quad (9)$$

Where k and A are constant, D and P are the packing fraction and pressure respectively. Equation (9) is fitted to the linear part of the Heckel plot to calculate numerical values to the constants A (intercept) and K (Slope). Reciprocal of k is known as yield value (Py) which reflects the deforming ability of the material. The soft, ductile powders have lower yield value. The agglomerates with low yield value could be plastically deformed as a result of smaller primary crystals. The low value of Py (Steep slope) reflects low resistance to pressure, good densification and easy compression. A Large value of slope indicates the onset of plastic deformation at relatively low pressure [11, 35]. From the value of A (the intercept), the total relative density "Da" (Da =1-exp-A) or powder solid fraction due to die filling and particle rearrangement can be calculated [36]. The reciprocal of *b* gives a pressure term PK which is the pressure required to reduce the powder bed by 50% [37].

J. Kawakita's and kuno's equation

The packability is evaluated by tapping the agglomerates in a measuring cylinder. The data are analyzed by using Kawakita's and Kuno's Equation 10 and 11, respectively.

$$\frac{n}{C} = \frac{1}{ab} + \frac{n}{a} \quad (10)$$

a and C can be calculated as follows:

$$a = \frac{v0 - Vinf}{V0} \text{ and } C = \frac{v0 - vn}{v0}$$

Where "a" and "b" are the constant, n is the tap number, Vo, Vn, and Vinf are the powder bed volumes at initial, after *n*th tapping and at equilibrium state, respectively.

$$pf - pn = (pf - p0)e^{(-kn)} \quad (11)$$

Where, po, pn, and pf, are the apparent densities at the initial state, after *n*th tapping (5, 10, 15, 20, 25, 50, 75, 100, 200, 300, and 400) and equilibrium (500th tap) respectively, and k is a constant.

Kawakits's constant 'a' represents the proportion of consolidation at closest packing, and the 'b' represents the packing velocity. The smaller the value for a for the granules indicate good packing even without tapping. The large value of 'b' for the granules indicate rapid packing velocity. Smaller the value of Kuno's parameter 'k' indicates the slower packing velocity of the powder or agglomerates. The slow packing velocity corresponds with a proportion of the consolidation of the powder bed per tap [38,39].

K. Compact elastic relaxation

The sample is compressed in a hydraulic press using and matching die at pressures of 1, 2, 3, 4, 5 and 6 tons for 1 min. Compact height is measured with an electronic digital caliper after immediate ejection of compact from the die and stored in a desiccator. After five days, compact height is measured again, and elastic relaxation (ER) is expressed in percentage as per equation 12.

$$\%\ ER = 100^* (H_b - H_a)/H_a \quad (12)$$

Where, ER is elastic recovery, H_b and H_a are the compact height after five days of storage and immediately after ejection, respectively [36].

L. Evaluation of physical and chemical changes in co-processed excipients

Results of X-ray diffraction analysis, solid-state nuclear magnetic resonance (NMR), IR spectroscopy, Raman spectroscopy, [13]C NMR spectroscopy and differential scanning calorimetry study of co-processed excipients are compared with an individual excipient to observe physical and chemical changes due to co-processing [39,40].

M. Granular friability index

Friability index is obtained by the ratio of the mean particle size of pulverized granules (FR) to the mean particle size of the unpulverized granules (UFR). If no erosion occurs during the test, no reduction in the particles is seen, and FI equals 1.0, which is the ideal state. In practice, however, abrasion occurs to some extent in the particles and FI becomes smaller than 1.0. According to the FI value, whether it is near to or distant from 1.0, it is concluded whether the mechanical strength of the granule is sufficient or not. FI is a parameter that defines a single point. However, the friability event in the granules shows continuity, changing as a function of time during the mixing period at the industrial manufacturing stage. Therefore, indicating the friability of granules as "friability rate constant" (FRC) is a more

realistic approach than the one-point identification. The higher the value of FRC, the more friable is the granule. The granular friability is determined using the friability test with a Roche Friabilator. Granules are placed in a Roche Friabilator together with rubber balls. The apparatus is rotated for 5, 10, 15, 20, 30, 60 and 90 min at 25 rpm. All the material is then transferred to the nest of sieves, and the mean particle size was determined after abrasion in the friabilator as before. FI is calculated as the ratio of the mean particle size of friabilator-treated granules (FR) to the mean particle size of the non-friabilator-treated granules (UFR). The logarithm of FI of granules is plotted against time. The slope of the FI line is called the friability rate constant (FRC) [41, 42].

II. Evaluation parameters of tablets which depends on nature of co-processed excipients

N. Tensile strength

The dimensions of tablets are measured by using a micrometer. The crushing strength is determined after 24 hr (time for stress relaxation) of compression, by using a Monsanto hardness tester. From the values of diameter (D, cm), thickness (L, cm), and crushing strength (P, Kg), the tensile strength (T) (MPa) of the tablets is calculated by using Equation 13.

$$T = \frac{0.0624\,XP}{DXL} \_\_\_\_\_ (13)$$

O. Composite index

On completion of the individual experiment, a weighted composite index is used to designate a single score utilizing two responses, For example, Carr's index (%), and crushing strength. As the relative contribution of each individual constraint to the "true" composite score is unknown, a decision was made to assign an arbitrary value of one-half to each of the two response variables. In one variable (For example, Carr's index) lowest value is assigned as a score equal to 50, and the highest value is assigned zero scores in all batches as lower Carr's index is required for better flow. Second variable (For example, crushing strength) highest value is assigned a score equal to 50 and the lowest value is assigned zero scores [11, 28].

Composite Index = Transformed value of Carr's Index+Transformed value of crushing strength

P. Reworkability

It is the ability to reprocess the defective batch. The reworkability is influenced by the deformability of the directly compressible adjuvant on the first compression. Co-processed excipients prepared by spray drying method has the poor reworkability capacity [6].

Q. Lubricant sensitivity ratio

Co-processed excipient and magnesium stearate are mixed and compressed into tablets. The lubricant sensitivity ratio (LSR) is calculated as per equation 14.

$$LSR = \frac{H0 - Hlub}{H0} \_\_\_\_\_ (14)$$

Where, H_0 and H_{lub} are the crushing strengths of tablets prepared without and with lubricant, respectively [3].

R. Dilution potential study

Dilution potential is the amount of poorly compressible drug that can be satisfactorily compressed into a tablet with a directly compressible excipient. The drug is added in increasing order (10%, 20%, etc) into tablets with a co-processed excipient and maximum concentration at which satisfactory tablets are produced can be concluded. High dilution potential helps to produce tablets with less weight.

S. Adhesion tendency

The co-processed excipient is mixed with drug and sieved for 10 min. To promote the separation of drug particles from carrier excipient particles, different negative pressures were used during sieving. The oversize fraction is analyzed, and the amount of drug adhering to this oversize fraction is calculated as a percent of the initial concentration and expressed as % adhesion.

T. Demixing potential

The sample is split into different sieve fractions using a vibrating sieve apparatus. To avoid segregation during sieving, only a short period of 2 min and a low vibrational energy input must be used. Each sieve fraction is analyzed in terms of drug content, allowing the calculation of demixing potential as per equation 15.

$$\%\,DP = \left(\frac{100}{B}\right)[\sum f(x-b)^2]^{1/2} \_\_\_\_\_ (15)$$

Where, b = $\sum fx/\sum f$, x is the drug concentration in each sieve fraction(mg/g), f is the sieve fraction (% weight/100) and B is the theoritical drug content in the total powder mixture(mg/g)[12].

U. Friability, disintegration time and drug release study

These parameter has to be performed as per compendial requirements.

V. Stability study as per ICH guideline

Optimized co-processed excipients and final dosage forms like tablets, pellets, etc. are stored at room temperature as well as accelerated conditions (40 °C/75%RH) and observed for changes [43].

3. Examples of multifunctional co-processed excipients

Few commercial and patented multifunctional excipients are listed in table 1 and 2. [13, 40, 44-49].

Regulatory perspective of co-processed excipients

Co-processed adjuvant lacks the official acceptance in Pharmacopoeia, which is one of the major obstacles to their success in the marketplace [6]. Although spray crystallized dextrose–maltose (EMDEX) and compressible sugars are co-processed, they are commonly considered as a single component and are listed as such in the *USP–NF*.

The third edition of the *Handbook of Pharmaceutical Excipients* has listed SMCC as a separate excipient [40]. In 2009, the USP Excipient Monographs 2 Expert Committee published a stimuli article on co-processed excipients to solicit public input. The article summarized the Expert Committee's thoughts regarding co-processed excipients and presented some suggested criteria for acceptance of such monograph proposals into NF [50, 51].

Table 1: Examples of co-processed excipients with their trade name, manufacturer and added advantage(s)

Co-processed excipients	Trade name	Manufacturer	added advantage(s)
Lactose, 3.2% Kollidon 30, Kollidon CL	Ludipress	BASF AG, Ludwigshafen, Germany	Low degree of hygroscopicity, good flowability, tablet hardness independent of machine speed
Lactose, 25 % cellulose	Cellactose	Meggle GmbH & Co. KG, Germany	Highly compressible, good mouthfeel, better tableting at low cost
MCC, silicon dioxide	Prosolv	Penwest Pharmaceuticals Company	Better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability
MCC, guar gum	Avicel CE-15	FMC Corporation	Less grittiness, reduced tooth packing, minimal chalkiness, creamier mouth-feel, improved overall palatability
Calcium cabinate sorbitol	ForMaxx	Merck	Controlled particle-size distribution
MCC, Lactose	Microcelac	Meggle	Capable of formulating high dose, small tablets with poorly flowable active
85 % a lactose MH+15 %	StarLac	Roquette	Good flow

native corn starch

Table 2: Patent review on co-processed excipients

Patent no.	Co-processed excipient	Process	Advantages
United States patent 4744987	Microcrystalline cellulose-calcium carbonate	• Most preferable ratio of MCC: calcium carbonate is 65:35 to 50:50 • Spray drying of aqueous slurry of excipients	Economical directly compressible excipient blend with good flowability and compressibility, low lubricant sensitivity
United States patent 5686107	Microcrystalline cellulose-galactomannan gum	• The most preferred galactomannan gum is guar gum • High shear stirring of an aqueous slurry of excipients and spray drying.	In chewable tablets: Provide compressibility, improves mouthfeel, eliminate tooth packing and improves patient acceptability
WO 95/17831	Galactomannan-glucomannan	• The most preferred galactomannan is locust bean gum, and glucomannan is konjac • Prepared by co-precipitation technique with IPA	• Dry powder which is soluble in water • Used as thickeners, viscosifier or gelling agent in food industry
WO 2003/051338	Mannitol-sorbitol	• Spray drying of aqueous slurry of excipients	Rapidly compressible and rapidly dissolved or disintegrated within 60 sec so used for Orally disintegrating tablets.
(WO 2010/132431 A1)	Silicified MCC-a polyol and sugar with or without disintegrant	• Preferable ratio of MCC: Polyol is 1:1	Rapidly disintegration, acceptable mouth feel, low friability, high dilution potential
WO 2014/165246A1	Vinyl lactam derived polymer and deagglomerated co-processing agent	• Vinyl lactam derived polymer is selected from the group consisting of N-Vinyl-2-pyrolidone,poly(vinyl pyrollidone), N-Vinyl-2-caprolactam, etc. • The co-processing agent is silica comprised of fused silica, colloidal silica, silicon dioxide, calcium silicate and/or combinations thereof. • Prepared by passing excipient blend through blender and universal mill	Suitable blend for direct compression, dry granulation or hot melt extrusion processing.

Susanne Keitel**,** director the European Directorate for the Quality of Medicines and Healthcare (EDQM) gave an update on development at the European Pharmacopoeia (Ph. Eur.), with a close look at the activities in recent years on multifunctional excipients to assure consistent quality and performance of the medicinal products. IPEC Europe Secretary Hubertus Folttmann has strongly recommended that the user of co-processed excipients must enter into a supply agreement with the excipient manufacturer to ensure supply [52]. The global pharmaceutical excipients market is estimated to grow at a CAGR of 6.7% from 2014 to 2019.

Growing demand of functional excipients, patent cliffs, increasing the demand of generics, and the emergence of new excipients in the market are the major factors driving the growth of the pharmaceutical excipients market.

However, declining investments in R&D by pharmaceutical excipients producers and increasing regulatory requirements leading to scarcity of U. S. FDA-approved manufacturing sites are some of the major factors that could weaken the growth of this market to a certain extent [53].

CONCLUSION

Formulation of multifunctional excipient by co-processing of two or more existing excipients is a practical approach. With the absence of chemical changes during processing, co-processed excipients can generally be considered regarded as safe (GRAS) if the parent excipients are also GRAS certified by the regulatory agencies. Hence, these excipients do not require additional toxicological studies. Co-processed adjuvant lacks the official acceptance in Pharmacopoeia, which is one of the major obstacles to their success in the marketplace.

CONFLICT OF INTERESTS

Authors report no declaration of interest

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