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A Systematic Review on Co-Processed Formulation and Development

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ABSTRACT

The objective of this article is to review co-processed formulation and their development in pharmaceuticals. In formulation and development ofa specific dosage form, there is no single component that will fulfill all the requisites of formulation, this gave rise to the novel concept of co-processing. Co-processing is a combination of two or more excipients having specific quality and advantages. Nowadays co-processed excipients have received higher attention in the formulation and development of dosage form mainly in solid dosage form e.g. tablet manufacturing by direct compression. Advantage of co-processing excipients is that it will help both pharmaceutical industry and academicians to develop newer and novel dosage forms with better bioavailability and intended release profile. Furthermore, co-processing provides the opportunity for advancement to multifunctional excipients rather than multiple types of excipients in one formulation. The productivity, quality, and drug release profile of the formulation will be enhanced by co-processing. Many review articles are available on the co-processed formulation but those review articles are missing out on some of the other important aspects of co-processed formulation so, we are trying to cover all the aspects of co-processed formulation and their development also. We cover commercial status also so you will get all the information regarding co-processed formulation and development.

Keywords
co-processed excipient, Novel dosage form, Multifunctional excipients, commercial status.

Introduction

From ancient to recent times excipients are the largest components and plays important role in any pharmaceutical formulations[1]. The definition of co-processed excipient provided by the International Pharmaceutical Excipients Council (IPEC) as, "combining of two or more non- compendial/compendial excipients designing in such a way that it will modify their properties physically, which cannot be achieved via simple physical mixing"[2]. Excipients are the second important parameter after the API to study any pharmaceutical formulation. An excipient is that material which has been used to carry out the evaluation studies, also purposefully impactthe drug delivery system, provides good support, and also helps to achieve better bioavailability, drug release profile, stability, patient compliance and improves the technological performance of formulation[3].

In the last ten years, Scientist attention moves towards not only the formulation but also the development of novel dosage form. Various forms of excipients must be added to API to obtain the desired physicochemical properties, such as disintegration, dissolution, compressibility, and stability. The Co-processed excipient has a multifunctional property that raises the drug formulation innovation and development with lowering cost[2]. There is no single component that satisfies all requirements of formulation therefore, there is a need of developing a new chemical entity excipient but it requires a very huge amount to be invested so, to overcome this issue, formulation scientist studied and has introduced a novel concept i.e. Co-processing of excipients[4]. In the manufacturing of dosage forms like capsules, tablets, powders, ointments, and creams, among others, Co-processed excipients have gained more attention. A combination of functional material with an economical excipient produces an integrated product that possesses superior quality and functionality as compared to the single excipient. Co-processing usually does not involve chemical change as the functionality is enhancing by the change in physical properties of excipients particles. Spray drying, melt granulation, hot-melt extrusion, solvent evaporation, roller compaction, wet granulation are various methods used for manufacturing of co-processed excipient[2].

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Literature Survey

Wang S et al. (2015) Using spray drying, developed a co-processed excipient of lactose monohydrate (filler), HPMC E3 (binder) & PVPP (super-disintegrant). They concluded that as the percentage of HPMC & lactose increases up to a particular limit, the compatibility and tableting properties improve. Developed co-processed excipients show much higher working efficiency and lowering yield pressure compared to α-lactose monohydrate[5]. Norman et al. (2006) studied and developed a blended mass of sorbitol &mannitol. Solution of powdered mannitoland sorbitol was prepared. This solution was then dried air stream. For orally disintegrating tablet(ODT)this invention is suitable[6]. Nagendrakumar et al. (2009) mixed cros-carmellose sodium and cross-povidone in ethanol. The mixture was stirred till the ethanol get evaporated and then the obtained wet uniform mass was sieved and dried using a hot air oven. The invention was achieved as a co-processed super disintegrant. It was used in granisetron fast dissolving tablet formulation[7]. Pawar et al. (2014) prepared a co-processed excipient of Eudragit S-100 and chitosan using solvent evaporation technique. Venlafaxine HCl sustained-release tablet was prepared using this co-processed excipient via direct compression method[8]. Gandhi PP and Mundada AS (2016) prepared a formulation of mouth dissolving tablet of Terbutalinesulphate using the Solvent evaporation method. In this formulation, the co-processed prepared using*Oscimumbascillum* mucilage and Mannitol which acts as a super disintegrant and also improves tableting property[9]. SILVIA SURINI et al. (2019)developed a transdermal dosage form in which co-processed of Xanthan gum and cross-linked Amylase is used. The transdermal formulation of Hydrogel containing Diclofenac sodium is prepared[10]. Mohammad Chaheen et al. (2018) studied chitin &calcium carbonate (CaCO3). Different methods were used for the precipitation of CaCO3 on the chitin particle surface. The CaCO3 polymorph interacts with the chitin molecule at amide and carbonyl group. The results were showed improved true density, the flowability of powder and tablets were seen to be improved tensile strength and disintegration time(2-4sec.)[11]. Saurabh Patil et al. (2021) developed and studied theChitosan-based co-processed excipient that improved tableting. They used chitosan 50%, mannitol 43%, and crospovidone 6.5% to formulate Paracetamol using direct compression method, hardness of 100 N and disintegration time <25 sec were applied. The developed co-processed excipient achieved better tableting results and high applicability in drug delivery and potential for scale-up process[12].

Advantages of Co-Processed Formulation

1. Multi functionalities can be achieved by a single co-processed excipient.
2. Compressibility of Tablet improved.
3. Lubricant sensitivity can be reduced, e.g. co-processed of MCC &calcium carbonate.
4. Improvement of flow properties.
5. Desirable properties can be incorporated and undesirable properties can be removed.
6. Co-processed excipients reduces the risk of wear & tear of dies and punches during tablet manufacturing.
7. Co-processed excipient use in the pharmaceutical industry has grown as their physicochemical properties have improved.
8. Improvement palatability and mouthfeel.
9. Dilution potential can be enhanced, e.g. co-processed of lactose &sorbitol.
10. Minimal weight variation during direct compression.
11. Designing tailor-made excipients are possible due to Co-processing of excipients.

Disadvantages of Co-Processed Formulation

1. Advancement of equipment and high-temperature processing is required.
2. Process is expensive as considered as novel process and more labor and energy requirement.
3. Materials may be a loss at various stages of processing.
4. Thermolabile and moisture-sensitive material not satisfied completely.
5. The process is time-consuming.
6. Some lipidic excipients are not tolerated by pre-clinical species.

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Steps Involve in Co-Processing of Excipient

The following steps are involved in Co-processed excipient development (Figure1)

1. For developing the co-processed first study the functionality requirement and characteristics of material and identification of material is required for co-processed development[4].
2. Choosing the required proportions of different types of excipients[13].
3. The particle size of excipients should be studied before and after dispersion. This defines whether the dispersion was properly prepared or not[4].
4. Choose a suitable drying method, such as spray drying or flash drying, and optimize the process[1].

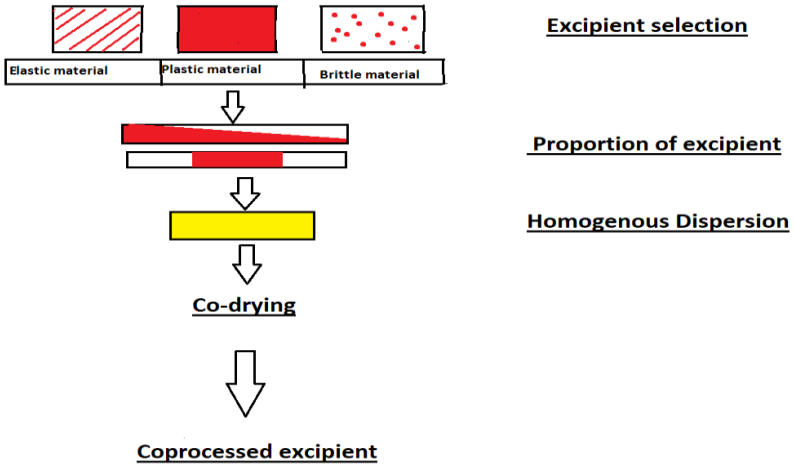

Figure 1: Schematic representation of the co-processing method

Methods to Prepare Co-Processed Excipient

Roller compaction: This method is used for moisture and heat-sensitive excipients. In this technique, dry granulation principle is followed for takes place bonding between the particles. The uniform mixture of powder blend is taken and later on compressed between the rotating rollers which give the solid ribbon of compacted material and later this material milled into appropriate particle sizes of granules[14]. Daraghmeh N Patel et al. (2015) studied developed co-processed excipient named Cop–CM using chitin and mannitol as raw material by roller compaction method.This Cop-CM is used in orally dispersive tablets (ODT)[15].

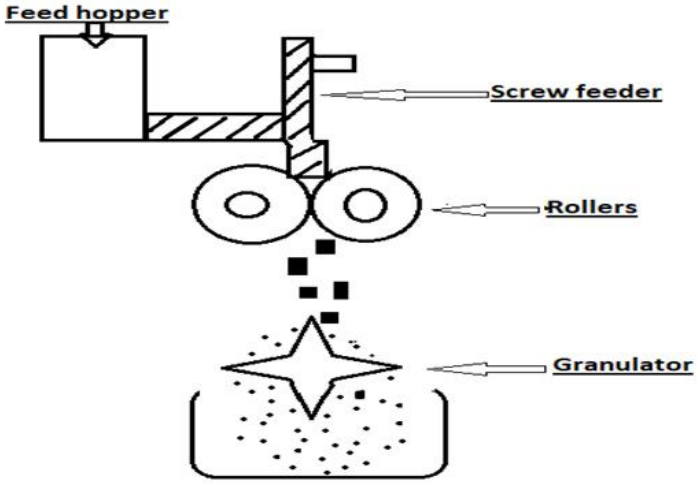

Figure 2: Roller compaction method

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Wet granulation ion method: Wet granulation method is a conventional and simple type of method used for co-processed excipient manufacturing. This process is based on high shear mixers or fluid-bed granulators. In a fluid-bed granulator, the powder material is introduced to fluidization by providing an upward flow of air from the granulator's bottom screen and then binding solution sprayed in opposite direction to the powder bed. The liquid droplets and solid particles are mixed together thus, results in adhesion, and further granulesformation takes place[4].

Melt granulation technique: In this technique, the meltable binder is used to mixing the co-processed excipients utilizing water bath, agglomerates then cooledand solidified mass further passing through a sieve to achieve the granules of co-processed excipients. We can carry out this technique within a short processing time and this technique is solvent free[2]. Kothiya M. et al. (2015) studied co-processed excipients for Irbesartan rapid dissolving tabletsusing the 'Melt granulation method'. In this co-processed study, diluent (lactose monohydrate, mannitol) and binder (Polyethylene glycol 4000) were selected. Functionality improved by adding crospovidone (8%)[16].

Hot-melt extrusion: HME consist of one barrel and a rotating screw. Inside the barrel melting of the polymer takes place and for transferring of polymer rotating screw is used.This melted polymer is further pressurized through the required shape and size of the die. This Extrusion is processed into tablets, granules, or pellets[4].

Spray drying: The technique in which fluid state material is sprayed in a hot drying medium and further converts into a dry particulate form.A feed can be in the form of emulsion, suspension, solution, or dispersion. Based on the requirement of formulation, Physico-chemical properties of a material, and dryer design, the dried product can be in the form of agglomerates, granules, or powders[5].

Solvent evaporation method: This method takes place in a liquid vehicle. First dissolved the coating excipient and volatile solvent (immiscible in liquid vehicle base). The chief excipient which will further form microecapsules is dispersed or dissolved in the solution of coating polymer by providing agitation. The desired size of microencapsules are obtained by dispersed the mixture of core-coating material in a liquid manufacturing vehicle. Solvent evaporation takes place via heating and reduction in temperature is achieved by continuous agitation[2].

Properties of Co-Processed Excipient

1. **No significant chemical change:** Many studies have been conducted to study the chemical change. These studies revealed,no significant chemical change in co-processed excipients. A study of Silicified microcrystalline cellulose conducted using Nuclear magnetic resonance(C13), Infrared spectroscopy, XRD, Raman spectroscopy evaluated no significant chemical changes[11].
2. **Physico-mechanical properties:**

2.1 Improved Flowability: co-processed excipients show superior flowabilityas compared to the simple excipients. Volumetric study of Silicified microcrystalline cellulose wasconducted in comparison to and Microcrystalline cellulosefollowed by similar particle size same as parent excipient. This study revealed that the flow of SMCC was superior to that of MCC[2].

2.2 Improved compressibility: Compressibility of co-processed excipient seen to be improved mainly in tablet manufacturing via direct compression.If we carry out the study of pressure–hardness relationship plot of co-processed excipientsand simple physical mixture of excipients the compressibility profile of co-processed excipient seems to be improved e.g. The compressibility profile performance of Cellactose16, SMCC17, 18 and Ludipress19 showed a better result than of simple physical mixtures of excipients[13].

2.3 Better dilution performance: Dilution capacity refers to an excipient's ability to keep compressibility after being diluted with other material.The majority of active pharmaceutical ingredients are poorly compressible. Cellactose showed better dilution performance than simple physically mixed excipients[4].

3. **Improved organoleptic properties:** Co-processed excipients improve organoleptic character as there is no need for use of separate organoleptic excipients.Avicel CE-15 is a co-processed excipient of microcrystalline cellulose & guar gum developed by FMC Corp., Philadelphia, PA., exhibit advantages in chewable tablets as it decreases grittiness, chalkiness, also improved palatability of tablet and mouth feel property[17].

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Commercial Status of Co-Processed Excipients

In the past few years, many co-processed excipients have been launched in the market and a few formulations are commercially available. The list of such co-processed excipients is given in Table 1

Table 1: **Commercial available co-processed excipients**

Trade name	Excipients	Manufacturers	Advantages	Reference
Ludipress	Lactose, kallidon30, kallidon CL	BASF, Germany	Good flowability, low degree of hydroscopicity.	18
Cellactose	Lactose and cellulose	Meggle, GmbH Germany	High compressibility, Better tableting and better mouth feel	19
Starlac	Maize starch and Lactose	Meggle, GmbH Germany	Rapid disintegration, good flowability due to spray drying, an acceptable crushing force due to lactose content.	20
Microcelac	Microcrystalline cellulose and lactose	Meggle, GmbH Germany	High dose can be formulated.	21
Formaxx	Calicum carbonate and sorbitol	Merck	taste masking, improve content uniformity, high compressibility, controlled particle size distribution.	22
Avicel ce 15	MCC and gaur gum	'FMC' Corporation., USA	Minimum chalkiness, minimum grittiness.	23
Dipac	Sucrose and dextrin	Penwest Pharmaceuticals Co. USA	Directly compressible grade	24
Prosolav	MCC and silicon dioxide (SiO_2)	Penwest Pharmaceuticals, USA	Better flowability, better hardness of tablet, less grittiness and minimum chalkiness.	25
Pharmatose DCL 40	Anhydrous lactitol and β-lactose	DFE Pharma	Good flowability, good binding property and not hygroscopic,Uniform and Spherical particle shape	26
Pearlitol SD	Granulated mannitol	Roguette	Suitable for chewable tablet application with good mouth feel and palatability	27
Advantose FS-95	Starch and fructose	S.P.I Polyols	Fast disintegration property, Suitable for nutraceuticals and chewable vitamin applications	22
Finlac DC	Directly compressible lactito	Cultor Food Science	Direct compression grade. Good mouth feel and rapid disintegration property. Used for nutraceuticals and chewable vitamin applications	28
Fujicalin	DCP anhydrous	Fuji Chemicals	Directly compressible, rapid disintegration	29
Neusilin	Amorphous magnesium aluminometasilicate	Fuji Chemicals	Superior flow property, anti-caking, good Compressibility and can beuse for solid dispersion	30
Tap 400	Tartaric acid (processed)	Pellet Pharmaceuticals	Used in drug delivery technology to improve acidic core of formulation	31
Vitacel VE-650	Microcrystalline cellulose and calcium carbonate	FMC Biopolymer	Suitable for direct compression and encapsulation	32
F-Melt	Carbohydrate, disintegrant and DCP	Fuji Chemicals	High flowability, reduces sticking and capping problems, directly compressible, orally disintegrating(less than 30 sec)	33

Sepitrap-80	Polysorbate 80	Seppic	Enhance bioavailability of low solubility API'S, meant for direct compression processes	34
Sepitrap 4000	Ethoxylated hydrogenated castor oil	Seppic	Enhance bioavailability of low solubility API'S,directly compressible	34
Copovidone	Kollidon VA 64 and plasdone S630	Ashland	Excellent flow properties and dry binder	35
Ludiflash	Mannitol, crospovidone and polyvinyl acetate	BASF	Suitable for high-speed tableting, low friability, and good flowability	36

Regulatory Perspective Regarding Co-Processed Excipient

To evaluate the safety of pharmaceutical excipients there is no such process as the excipients are only approved as a component of a new drug product.

- Co-processed excipients can be taken under "Generally Regarded as Safe (GRAS)" category only when regulatory agencies "GRAS-certified" the parent excipient. Therefore, no additional toxicological studies have to be conducted for co-processed excipients[13].
- Co-processed excipients still not received the place into official pharmacopoeial monographs, this could be a major obstacle in the success of co-processed excipients. In the recent era, co-processed excipients have been achieved a valuable and higher position in excipient development[4].

Conclusion

The Co-processed excipient helps to overcome the problem related to the use of a single excipient and gives rise to the preparation of various novel formulations. This plays an important and significant role in improving and enhancing the physical, chemical & mechanical value of the drug delivery system and also in formulating stable formulation.Co-processed excipients deal with the problem related to pre-compression, palatability, dissolution, compressibility, and sticking. There is vast scope in co-processed development as the demand for formulations is increasing. We can achieve the best place in formulation &development gradually by developing co-processed excipients. As official acceptance in Pharmacopoeia, co-processed adjuvant lacks this could be the hurdle for success in pharmaceutical market-place value.

Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper

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