Co-processed Excipients: A Revisit of Its Development in the Past Two Decades; A Review

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Abstract

A pharmaceutical excipient is a substance acts as a carrier incorporates active pharmaceutical ingredients. Excipient selection focuses on desirable characteristics of excipients. Limitations of using excipients which affect the characteristics of the granules and tablets. Co-processed excipients are produced by integrating one excipient into the other excipient at particle level. Such combination of two or more pharmacopeial or non-pharmacopeial excipients does not involve chemical reaction and only involve physical properties changes which is not possible by simple physical mixing. The introduced multicomponent-based excipients for formulation to obtain better features and tableting properties. The objectives of this revisit to discuss the development of co-processed excipients in the past two decades. This review summarizes the advantages of co-processed excipient, the manufacturing process, compilation of co-processed excipients in the literature, limitations, evaluation methods and future development of co-processed excipient. Co-processed excipients will undoubtedly attract attention from academia and pharmaceutical industry as more newer combinations of excipients and newer ways of co-processing become available Besides, rather using numerous excipients in formulation, it allows for the development and usage of single multifunctional excipients.

Keywords: Excipients, Co-processed, Tablets.

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INTRODUCTION

Excipients

A pharmaceutical excipient is defined as "a substance or a combination of substances that can form a certain volume of an agglomerating mixture, acts as a carrier and contains active pharmaceutical ingredients (APIs)." Examples of excipients include binders, fillers, super-disintegrants, lubricants and glidants. An ideal excipient is an excipient that ensures the volume, the uniformity, and the dose of the API in the drug from the manufacturing process until it is administered to the patient (Abrantes, Duarte, & Reis, 2016).

Excipients are a necessary component of pharmaceuticals. They are present in greater proportion than API in most formulations because it constitutes the main body of the formulation, so it is always crucial to choose excipient that meets the desired characteristics for such excipient. To select a desired excipient, there are many characteristics to consider such as the price, function, accessibility, material consistency, regulatory approval and sources (Airaksinen et al., 2005; Patil, 2012).

When choosing excipient for formulation development, physical and chemical features, stability and compatibility issues, pharmacokinetic properties, permeability characteristics, segmented absorption behaviour and drug delivery mechanisms are important. This can aid in assessing the API absorption issues and the required delivery platform (Airaksinen et al., 2005; Patil, 2012).

The ideal characteristic of an excipient includes the excipient should be chemically stable, non-reactive, common equipment required for manufacturing, process insensitive, inert, non-toxic, good palatability, inexpensive and efficient in their intended use are all key components for an excipient (Patil, 2012).

Type of excipients

1. Binders

Binders are the "glue" that bind powders together to form granules. They also give the necessary cohesion to bond the particles and form a tablet under compression (Alanazi, 2010). Binders are used in tablet formulation to provide plasticity and hence increase the bond strength between the particles win the tablet (Debnath Subhashis, 2019). The research and development of new excipients that may be used as a binder in tablet formulations remain of interest. This is

due to the fact that different binders can be used to achieve different mechanical strengths and drug release characteristics of tablets for different medicinal uses (Shailendra, 2012).

Example of binders are acacia, starch paste, PVP, glucose and carboxymethyl cellulose (Patil, 2012).

2. Fillers / Diluents

Diluents or fillers are medicinal chemicals that do not have pharmacological activity but are useful and required in pharmaceutical formulations. Diluents are heterogeneous groups of ingredients that are used to make up the needed bulk of the tablet when the medication dose is insufficient to produce the quality, it is designed in to improve handling of tablet during manufacturing process and ensure desired content homogeneity. Diluents are commonly added to tablet formulations to improve tablet features such as allowing direct compression to improve cohesiveness, increases flow and optimizes tablet's weight according to die capacity (Nagpal, 2016). Example of fillers are lactose, dextrose, sorbitol, MCC and dibasic calcium phosphate dehydrate (Patil, 2012).

3. Disintegrants and super-disintegrants

Disintegrants are chemicals that are added to tablet and some encapsulated preparations to help breaking up the tablet and capsule "slugs" into tiny particles in an aqueous medium, expanding the accessible surface area and facilitating faster drug release. They help the tablet matrix to absorb moisture and disperse. The main purpose of the disintegrants is to counteract the tablet binder's efficiency and the physical forces to form tablet under compression (Nagar, 2014; Pahwa & Gupta, 2011). Example of disintegrants are corn starch, clays such as Veegum HV, resins, clays and cellulose (Patil, 2012).

Super-disintegrants are the type of superabsorbent substance that disintegrates rapidly due to formulation's combined swelling and water absorption effects. The wetted surface of the carrier increases as super-disintegrants swell, promoting the system's wettability and dispersibility of the system, hence improving disintegration and dissolution. Effective super-disintegrants promote better compressibility and compatibility while having no negative effect on the mechanical strength of high dose medications' preparation (Nagar, 2014; Pahwa & Gupta, 2011). Example of super-disintegrants are CCS, crospovidone, sodium starch glycolate.

4. Lubricants

Lubricants are excipients which are used for the purpose of making the process smooth. Lubricants are used for preventing the clumping of ingredients which is used in the formulation process. The function of lubricants is to reduce the friction between the tablet's outer layer and the die wall during ejection process while still keeping adhesion of the formulation, thereby avoiding tablets from adhering to the surface of the punch. Lubricants can improve the flowability of powder by reducing inter particulate friction (Li & Wu, 2014; Poonam, Sagar, Abhishek, Yuvraj, & Pradesh, 2018). Examples of lubricants are talc, silica, stearic acid and magnesium stearate (Patil, 2012).

5. Glidants

The glidant is mixed with the formulation to improve the flowability of mixed material of the tablet core. Glidants are added into the tablet powder blend to improve flowability into the die cavity of tablet presses. Glidants reduce friction between granules to allow the tablet granulation to flow more smoothly. The role of glidants on granule flow is determined by the size and shape of the granules and the glidants particles (Advankar et al., 2019). Example of glidants are colloidal silicone dioxide, starch, talc and magnesium stearate (Patil, 2012).

Limitation of excipients

There are some limitations of using excipients which affect the characteristics of the granules and tablets. Polymer binders can cause processing issues such as fast over granulation, increased tablet hardness and reduced dissolution properties. Strong disintegrant is normally necessary in case of polymer binders, however they are expensive and have a significant effect on stability of the product (Debnath, 2019).

Disintegrants can increase the hygroscopicity of medications which can be an issue for medications that are sensitive to moisture (Ahmad, 2018). The consequence of low lubricant concentration and insufficient mixing are sticking, capping, and binding of tablets in the die cavity. On the other extreme, unusual high lubricant concentration and excessive mixing develops negative impact on product quality and processing such as low hardness and compression variability, prolonged disintegration time and reduced rate of dissolution (Li & Wu, 2014).

Co-processed Excipients

Co-processed excipients are prepared by combining one excipient into the particle structure of another excipient (Nachaegari, 2004). Co-processed excipients are the integration of two or more pharmacopeial or non-pharmacopeial excipients into a single composite material with physical properties change which is not possible achieved with simple physical mixing (Pawar, Ahirrao, Kshirsagar, City, & Knowledge, 2019).

Introduced multi-component excipients for formulation to obtain better features and tableting characteristics than a single substance or the physical mixtures (Limwong, Sutanthavidul, & Kulvanich, 2004). These were created largely to solve the flowability, compressibility and disintegration potential concerns.

Advantages of Co-processing

1. Rapid disintegration

Orodispersible tablet or orally disintegrating tablets are newer tablets that have a rapid disintegration time (Patel, 2009). Co-processed adjuvants provide fast disintegration to the established formulation due to their high solubility, swelling and wicking properties (Bin, Gaurav, & Mandal, 2019).

2. Enhanced compressibility

Compressibility will affect the tablet punching process. Powder blend with good compressibility forms a compacted tablet when the upper punch is lifted from the tablet dies. Co-processed excipients have primarily been used for direct compression since the flow characteristics increase during this process, thereby obtaining better compressibility. However, many excipients lack plasticity characteristic. Co-processed excipient is designed to overcome this. (Liew et al., 2019; Nadavadekar & Koliyote, 2014). Ludipress® is a co-processed adjuvant whose compressibility is better than a physical mixture of its component excipients (Marwaha, 2010).

3. Improved dilution potential

The capability of an excipient to sustain its compressibility when diluted with another material is known as dilution potential. Majority API and excipients have low compressibility. Co-processed excipient has a unique characteristic that even though it is diluted with other excipients, its compressibility remains high. As an example, Cellactose® in a study is proved to have larger dilution potential than the physical mixture of its component excipients (Liew et al., 2019; Desai, Chavan, Mhatre, & Chinchole, 2012; Nadavadekar & Koliyote, 2014).

4. Simplified production process

The use co-processed excipients reduce tablet processing steps significantly. Tableting process involves weighing, mixing, granulation, drying, sieving and compression. The process is time consuming and tedious and risk of errors is high in the process (Liew et al., 2019). The use of co-processed excipient can make the manufacturing process easier and reduce the error rate (Smewing, 2002).

5. Improved flow properties

By regulating the particle size distribution, the co-processed excipients have improved flowability compared to the physical mixture or the individual component. Especially in the case of high-speed rotary tablet machines, good flowability is required. The co-processing excipients improves the flowability of powder mixture (Liew et al., 2019). In comparison with microcrystalline cellulose, the volumetric flow characteristics of silicified microcrystalline cellulose have been studied. Despite of similar particle size, co-processed excipient was found to have superior flowability compared to the physical mixture. (Nadavadekar & Koliyote, 2014).

6. Affordability and economic method

The manufacturer has an option to use a single composite co-processed excipient rather than mixing a series of individual conventional excipient. This simplifies the process and reduces the labor cost. Furthermore, the formulation can be direct compressible and reduces the manufacturing time significantly. (Liew et al., 2019).

Techniques used to produce co-processed excipients

Roller compaction

Roller compaction adopts the dry granulation concept to bond particle. This method is suitable for thermolabile and moisture sensitive ingredients. Roller compaction considers as a good technique since it can help to tackle the drug with high loading, improve flowability, content uniformity and avoid the drug from segregation. The powder mixture is compressed by the counter-rotating rollers to form particles bonding. These compacted powder is then milled into suitable sized granules (Liew et al., 2019; Chang et al., 2008; Teng, Qiu, & Wen, 2009).

Wet granulation

Wet granulation is another simple method to produce co-processed excipient. Even for large drug contents, it can manage the bulk density of the product and compatibility; it allows for improving control of drug content homogeneity at low drug concentration. Fluid bed granulators and high-shear mixers can be used to perform wet granulation. The powder mix is blown up by stream of air injected upwards via the granulator's bottom screen. The binder solution is sprayed in the opposite direction of the stream air. The collision of solid particles with the liquid droplets forms granules eventually. The granules are dried partially by the air in the equipment. (Liew et al., 2019; Faure et al., 2001; Hapgood, Tan, & Chow, 2009).

In high-shear granulation, the impeller keeps the powder agitated in a closed vessel and injects the binder solution from above. The high shear force prevents the formation of big agglomerates. Drying process occurs in the same system with the innovative single-pot technology. The granules obtained have a higher density compared to those from fluid bed granulation (Liew et al., 2019; Faure et al., 2001).

Hot melt extrusion

In hot melt extrusion (HME) process, high heat (80 °C) is used hence this method is not suitable for heat sensitive material. The excipients are first melted and then extruded out and harden into a various shape through the die. HME is a

steady, easy and efficient method. No solvent is needed in this process because the molten polymer can act as a thermal binder (Liew et al., 2019; Liu, Zhang, & McGinity, 2001).

Spray drying

In spray drying, five steps are taking place namely concentration of feedstock, atomization, droplet-air contact, droplet drying and separation. By spraying a feed into a hot drying medium, the technique converts a solution, suspension or dispersion into dried particle form. During the process, the excipients form particle-particle bonds (R. P. Patel, 2009). Spherical shaped particles are generated. These particles such as Starlac® are good for direct compression and have excellent flowability. It is caused by increased droplet area and high temperature (Liew et al., 2019; Deshmukh, Wagh, & Naik, 2016).

Roller drying

The homogeneous solution or dispersion comprising the pre-mixed excipients are dried with a roller dryer (Liew et al., 2019). Roller drying is applied to co-process lactose with sorbitol and lactitol. The temperature was high enough to produce β-lactose in crystalline form (Liew et al., 2019; Sawyer et al., 1997).

Co-transformation

The use of heat or solvent effect to temporarily "open-up" (swelling) particles of excipient is known as co-transformation. The additional excipients are incorporated into the previously described excipient's "opened-up" structure. The added excipient enhance the final product's functionality (Liew et al., 2019; Staniforth, 2005).

Milling

Millers such as roller mill, ball mill and hammer will are used for the milling process. The premixed excipients are milled in a high-speed milling machine. The formation of granules happen when the particles come in contact and form bonds when they are milled. An example reported is that ball milling is used to produce co-process cross-linked PVP and calcium silicate (Liew et al., 2019; Rao et al., 2012).

Melt granulation

The excipients were mixed with a meltable binder which is generally solid at temperature below 80˚C. To split the mass into agglomerates, the mixture heated above the melting point of the binder while being continuous blended. Finally, the cooled agglomerates are sieved to obtain granules with appropriate particle size (Liew et al., 2019; Gohel & Jogani, 2005; Incorvia, 2015).

Solvent evaporation

In a liquid manufacturing vehicle, solvent evaporation was happened. After dissolving coating excipient in a volatile solvent that is immiscible with the liquid production carrier, the core excipient is dissolved or dispersed in the coating solution. To achieve the appropriate encapsulation size, agitation force is utilised. The solvent is evaporated by using heat (Liew et al., 2019; Chaudhari, Phatak, Desai, & Excipients, 2012; Deshmukh et al., 2016).

Co-processed excipients in literature

Co-processed excipient ingredients	Technique used	Advantages	Reference
Lactose, PVP and crospovidone	Spray drying or wet granulation	Good flowability, compressibility and disintegration time	(Hatcher, 2011)
MCC and calcium carbonate	Spray drying	Economical and low lubricant sensitivity	(Citra et al., 2013) (Kenneth et al., 1988)
Corn-starch and PVP	Fluid bed spray granulation	Good flowability and compressibility	(Menon et al., 1994)
Colloidal silicon dioxide and MCC	Roller compaction or wet granulation	Good flowability, disintegration time and compressibility	(Sherwood et al., 1996)
Guar gum and MCC	Spray drying	Enhanced compressibility and palatability	(Ratnaraj et al., 1991)
Directly compressible sucrose (95% sucrose & 5% maltodextrin)	Direct Compress	Palatable and good flowability and compressibility	(Bowe, 1998)
MCC and methylcellulose	Wet granulation	Complete taste masking of a bitter drug	(Augello et al., 1991)
MCC and maltodextrin	Spray drying	As a stabilizer in food and cosmetic application	(Buliga et al., 2015)
Rice starch and MCC	Spray drying	Great compressibility	(Limwong et al., 2004)

Calcium phosphate and fatty acid wax	Melt granulation	Solved abrasiveness and capping issues of calcium phosphate	(Cucala Escoi, Luengo, & Lana, 2006)
Crospovidone and sodium starch glycolate	Wet granulation and tray drying	Good flow property, compaction and disintegration property	(Gohel, Parikh, Brahmbhatt, & Shah, 2007)
MCC and mannitol	Spray drying	Better compatibility and lubricant sensitivity	(Li, 2008)
Mannitol and cellulose	Freeze-thawing method	Improvement in flowability, compatibility and dissolution rate	(Patel SS, 2007)
Povidone and glyceryl behenate	Hot melting method	Good flow and compressibility	(Ayyappan, Umapathi, & Quine, 2010)
Sodium carbonate and polyethylene glycol	Fluid bed spray granulation method	Reduced caking issue	(Davar, Kavalakatt, Pather, & Ghosh, 2010)
Lactose, MCC and cornstarch	Wet granulation	Excellent flowability, compressibility, and disintegration time	(Akram, Naqvi, & Gauhar, 2011)
α-chitin and mannitol	Fluid bed spray granulation	Improved physical charactersitics such as hardness, friability, easier ejection and disintegration time	(Al Omari, Badwan, & Daraghmenh, 2011)
MCC and hypromellose	Spray dry granulation	Improved flowability, compatibility, drug loading and blendability	(Deorkar, 2010)
Dibasic calcium phosphate, hypromellose and crospovidone	Spray dry granulation	Increase flowability, API loading, and blendability and high compatibility	(Deorkar, 2010)
Lentinus tuber regium, sodium bicarbonate, tartaric acid and citric acid	Solvent evaporation	Improve flow property, compressibility, and dilution potential	(Ugoeze & Nkoro, 2015)

(Liew et al., 2019)

Limitation of co-processed excipient

Despite of the improved functionalities, co-processed excipient has few limitations as well. In establishing an innovative formulation, the proportion of the excipients in a mixture is fixed. The user does not have an option to adjust the ratio of the excipient. Furthermore, the pharmacopeia does not recognise co-processed adjuvant (Kumari et al., 2013). For this reason, the pharmaceutical industry generally does not accept a co-processed excipient unless it is proved to show significant improvement compared to the physical mixtures of the excipients (Liew et al., 2019).

Evaluation Method of co-processed excipients

There are various ways to test the co-processed excipients such as angle of repose, Hausner ratio, Carr's index, sieve analysis, friability test, swelling index and loss on drying. There are three common methods to determine the flowability namely angle of repose, Hausner ratio and Carr's index.

i. Angle of repose

Angle of repose is a property linked to inter-particulate friction or movement resistance between particles (United States Pharmacopeia, 2016). It can determine the granules' flow characteristics.

ii. Hausner ratio and Carr's index

The compressibility index and the Hausner ratio have become common approaches for forecasting powder flow properties because they are simple, quick and easy ways. Since all of these factors can affect the observed compressibility index, the compressibility index is proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials (United States Pharmacopeia, 2016).

iii. Sieve analysis

A set of stainless-steel sieves with apertures ranging from 0.025 to 0.800 mm were placed on a vibrating sieve shaker to determine the particle size distribution. On each of the sieves, the percentage weight of the mass retained was calculated (Svačinová et al., 2019).

iv. Friability test

The friability can be determined using friabilator. The test was conducted by rotating granules in a friabilator for 4 minutes or 100 revolutions. The weight of granules before the test was compared against the weight after the test and % friability is calculated using the formula below (Pusapati et al., 2014):

$$\%\ friability = \frac{Initial\ weight - final\ weight}{initial\ weight} \times 100$$

(Pusapati et al., 2014)

v. Swelling index

The initial volume was determined by placing a known volume of powder a graduated cylinder. Enough water was added to the cylinder and shaken vigorously. It was set for a period of 24 hours. After 24 hours, the powder's volume was measured. It is calculated as (As, 2016) :

$$Swelling\ index\ = \frac{Final\ volume - Initial\ volume}{Final\ volume} \times 100$$

(As, 2016)

vi. Loss on drying

1 gram of powder was heated for 1 hour at 100°C in hot air oven. After that, weight of powder was measured. It is calculated as (As, 2016):

$$Loss\ on\ drying = \frac{Intial\ weight - Final\ weight}{Initial\ weight} \times 100$$

(As, 2016)

Evaluation Method for tablets

Uniformity of weight, hardness, friability, and disintegration test can be used to test the tablets which need to meet the specification stated by pharmacopoeias.

Weight Variation / Uniformity of weight

Weight uniformity is a determined by granulation quality, flow of granulation and mechanical performance. Weight uniformity test is important to ensure the actual content of drug in a tablet is the same as it is claimed.

As indicated in Table 1, the British Pharmacopeia (BP) has provided some tolerance for the average weight of uncoated compressed tablets. To ensure the sample meets the BP requirement, there is no more than two tablets are exceeding the percentage difference and no tablet doubled the times of this percentage difference.

Table 1: BP tolerance for the average weight for uncoated compressed tablets

Average weight	Percentage difference (%)
Less than 80 mg	10
More than 80 – 250 mg	7.5
More than 250 mg	5

(British Pharmacopoeia, 2011)

Content uniformity test

Content uniformity is required to ensure batch to batch consistency in terms of drug content. Content uniformity test determines whether the dose of the medicinal ingredient complies to the specified acceptance limits. The amount of active substance in tablet should be between 85% to 115% of the label claim (Journal et al., 2013).

Thickness test

The diameter of the tablets determines the thickness test. Within a ±5% variance of a standard value, the thickness should be maintained (British Pharmacopoeia, 2011). Due to differences in the granulation and pressure applied to the tablets, wear and tear on the length of punches and velocity of tablet compression, the thickness may vary with no change in weight. The thickness of tablet is usually managed to avoid appearance issues and to ensure that tablets fit into the container or packaging (Ahmed, Ali, Hassan, Ali, & Haque, 2001).

Hardness / Tablet Breaking Force

Tablet breaking force measures the amount of force required to break a tablet. In addition, a tablet's hardness is affected by the concentration of binders used and the compression force. Conventional tablets must be able to sustain the extremes of handling and shipping in the manufacturing plant, in drug distribution system and at the hand of end users (British Pharmacopoeia, 2011). Tablets which are too soft will be unable to withstand handling and further processing such as coating and packaging whereas tablets which are too hard are unable to undergo disintegration to meet the disintegration specifications.

Friability

Friability determines how resistant tablets or granules are to abrasion or fracture during coating, packaging, handling, and shipping processes. Friability of the tablets refers to the proportion of weight loss after tumbling. A maximum mean weight loss of one percent from the three samples considered acceptable (British Pharmacopoeia, 2011).

Disintegration

The disintegration test is used to mimic the disintegration of the tablet in the body. Disintegration is the first physical change detected for a medicine when it enters the body. The disintegration test is just a measurement of the time that it

takes for a group of tablets to disintegrate into particles in a certain set of conditions. The disintegration of tablets does not imply the availability of absorption. The rate of water inflow into the tablets and the porosity of the tablets influences the rate of disintegration. Swelling of the disintegrant results in the creation of swelling force, capillary action and annihilation of intermolecular interactions which then results in the production of repulsive force between particles are basic mechanism of the disintegration proposed.

Dissolution test

The effectiveness of dosage forms is influenced by the dissolution rate at which a medicine dissolves in the fluids of the gastrointestinal system. The pharmaceutical industry tries to maximize the amount of medicine that can be absorbed by the body. In-vivo or in-vitro testing can be used to determine the amount of medicine released. The dissolution test is a well-known in-vitro test. The dissolution test is a standardised method for determining the rate at which the medicine is released from a dosage form. It is also used to find out and determine the availability of active drug ingredient in their delivered form (Aulton, Michael E., 2013).

Future development of co-processed excipient

The limitations of the conventional individual excipient have alarmed the formulators to develop newer enhanced functionality material to cater the needs of the industry. The development of co-processed excipient has no doubt gain interest of experts in the field as an alternative to obtain high functionality material. Increasing use of co-processed excipients has several benefits such as easy and cost-effective production processes and reduced data burden. The development of new co-processed excipients need complies with safety, performance and regulatory issues is a current and future trend in excipient technology. Co-processed excipients will undoubtedly attract attention from academia and pharmaceutical industry as more newer combinations of excipients and newer ways of co-processing become available (Liew et al., 2019; Garg, Dureja, & Kaushik, 2013). Besides, rather using numerous excipients in formulation, it allows for the development and usage of single multifunctional excipients. (Kumare, 2013).

CONCLUSION

The co-processed excipients have definitely positioned itself as an newer alternative to replace the conventional excipient as its offers improvement in physical properties of the product developed. These improvements include better compressibility, palatability, disintegration and dissolution than conventional individual excipients. It is expected that co-processed excipient technology will remain as a trend and continue to evolve to meet the needs of in the pharmaceutical industry (Liew et al., 2019; Parfati N, Rani KC, 2018).

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