

CO-PROCESSED EXCIPIENT: AN OVERVIEW**Bhagyashree A. Pakhale^{1*}, D M.Shinkar¹, R B. Saudagar²**

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ABSTRACT

Co-processed excipients, wherever, excipients are intermixed by ideals of sub-molecule level cooperation have given an alluring device to creating high usefulness excipients. The multifold points of interest offered by co-processed excipients, for example, yield of synergism in usefulness of mortal parts, decrease of organization's administrative concern on account of nonattendance of concoction procedure amid co-handling and change in physico-chemical properties have developed their utilization in the pharmaceutical business. The excipient business, which bears to a great extent involved an expansion of the nourishment business, has embraced the novel utilization of molecule designing and material sciences to make ready for a Modern classification of useful excipients called co-processed multifunctional

excipients. The co-processed embodies the most broadly investigated system for the detailing of specifically compressible adjuvants on the grounds that they are financially effective and might be arranged in-house focused around the usefulness needed. This reassessment article is in compatibility of bearing explained data on the wellsprings of new excipients, potential focal points of co-processed excipients, material qualities needed for co-processing, routines for planning different co-processed excipients for direct compression accessible in the business.

KEYWORDS: co-processed excipients, co-processing, High Functionality excipients, molecule building.

History of Co-Processed Multifunctional Excipients

Co-processing of excipients in the pharmaceutical business could be gone once more to the late 1980s with the presentation of co-prepared microcrystalline cellulose and calcium carbonate, took after by cellactose in 1990, ^[1] which is a co-processed synthesis of cellulose and lactose yet Co-processing was at first utilized by the food business to enhance stability, wettability, and solubility and to improve the gelling properties of food ingredients, for example, coprocessed MCC and glucomannan, glucomannan and galactomanan. ^[2,3]

What is Co-Processing

Co-processing is an alternate way that new excipients are coming to market without experiencing the thorough wellbeing testing of a totally new chemical. It could be characterized as consolidating two or more settled excipients by a fitting procedure. Co-processing of excipients could prompt the development of excipients with better properties thought about than the basic physical mixtures of their components. ^[4]

Aim and Object of Co-Processing

The primary point of co-processing is to acquire a product with added worth identified with the degree of its usefulness/cost. The component that happens amid the co-processing strategy is not completely seen however seems to yield a particulate product in which the parts are in personal relationship with one another. This close affiliation can't be attained through basic dry mixing of segments, yet rather obliges that they might be coprocessed by a fitting methodology. Improvement of coprocessed straightforwardly compressible adjuvant begins with the choice of the excipients to be consolidated, their focused on extent, determination of readiness technique to get improved product with coveted physico-chemical parameters and it closes with minimizing avoidance with batch to-batch varieties. ^[5]

Co-Processed Excipients

The IPEC- piece aide draft characterizes coprocessed excipients are co-processing of two or more than two compendial or non-compendial excipients. They are intended for alteration of physical properties which was not achievable by basic physical blending. Excipients with enhanced usefulness could be acquired by creating new synthetic excipients, new evaluations of existing materials, and new combos of existing materials. ^[6] Developing another substance excipient is uneconomical and must experience different phases of administrative endorsement go for tending to issues of security and lethality. Creating new evaluations of existing excipients (physicochemical) has been the best method for the advancement of new

excipients in recent decades like pregelatinized starch, croscarmellose, and crospovidone. Be that as it may, usefulness could be enhanced just to a certain degree in view of the restricted scope of conceivable adjustments. New mixtures of existing excipients are an intriguing alternative for enhancing excipient usefulness on the grounds that all plans contain different excipients. Consolidation excipients fall into two general classes: physical mixtures and co-prepared excipients. Presently a day's co-processing appears to be intriguing chance on the grounds that the multifunctional excipients are arranged in a unique manner physically adjusted without changing the substance structure and dependability. Co-processing of excipients prompts the development of excipient crushes with predominant properties contrasted and physical mixtures of parts or with individual segments. They have been produced fundamentally to address the issues of flowability, compressibility, and disintegration potential, with filler– binder mixtures being the most ordinarily attempted. ^[7,8]

Need for Developing Multifunctional Excipients

The proceeded with popularity of solid dosage forms, a slender pipeline of new chemical excipients, and an expanding inclination for the direct compression procedure makes an opportunity for the advancement of high-usefulness excipients. The improvement of new excipients to date has been business sector driven (i.e., excipients are created in light of business interest) as opposed to advertising driven (i.e., excipients are produced first and business interest is made through showcasing methodologies) and has not seen much movement as demonstrated by the way that, for the past numerous years, not a single new chemical excipient has been brought into the business. The essential explanation behind this absence of new chemical excipients is the generally high cost included in excipients revelation and improvement. On the other hand, with the expanding number of new medication moieties with changing physicochemical and stability properties, there is developing pressure on formulators to search down new excipients to accomplish the desired set of functionalities.

Different elements driving the search for new excipients are:-

- 1) The developing ubiquity of the direct-compression procedure and an interest for a perfect filler–binder that can substitute two or more excipients.
- 2) Tableting machinery's expanding speed capacities, which require excipients to keep up great compressibility and low weight variety even at short stay times.

- 3) Shortcomings of existing excipients, for example, loss of compaction of microcrystalline cellulose (mcc) upon wet granulation, high dampness affectability, and poor die filling as a consequence of agglomeration.
- 4) The absence of excipients that address the needs of a particular patient, for example, those with diabetes, hypertension, and lactose and sorbitol affectability.
- 5) The capability to regulate the solubility, permeability, or stability of drug molecules.
- 6) The developing execution desires of excipients to address issues, for example, disintegration, dissolution and bioavailability.

Preferences, Properties and Limitations of Multifunctional Excipients

Co-processing excipients prompts the development of excipient granulates with prevalent properties contrasted and physical mixtures of segments or with individual parts. The methodology is completed to achieve a synergistic change in the individual undesirable property or enhance the same. The accompanying properties are constantly the criteria;

Improved Flow Properties

Co-processed excipients show prevalent flow properties by controlled ideal molecule size and particle-size dissemination. Ex: cellactose shows preferred stream qualities over lactose or a mixture of cellulose and lactose.^[9]

Improved Compressibility

There is a colossal change in the pressure–hardness connection of co-prepared excipients, as contrasted and basic physical mixtures. The co-processed excipients demonstrating a checked change in the compressibility profile.

Ex: Cellactose, SMCC and Ludipress shows prevalent compressible properties than straightforward physical mixtures of their constituent excipients.

Better Dilution Potential

Dilution potential is the capability of the excipient to hold its compressibility actually when diluted with an alternate material. Most dynamic drug substances are poorly compressible, and thus, excipients must have better compressibility properties to hold great compaction actually when weakened with a defectively compressible agent. Cellactose is demonstrated to have a higher weakening potential than a physical mixture of its constituent excipients.^[10]

Reduced Lubricant Sensitivity

Most co-processed products comprise of a generally vast measure of weak material, for example, lactose monohydrate and a more modest measure of plastic material, for example, cellulose that is settled between or on the particles of the fragile material. ^[11] The plastic material gives great holding properties in light of the fact that it makes a constant framework with a vast surface for holding. The substantial measure of weak material gives low lubricant affectability because it prevents the formation of a coherent lubricant network by forming newly exposed surfaces upon compression, thus breaking up the lubricant network.

Fill Weight Variety

Generally, materials for direct compression have a tendency to show high fill weight varieties as a consequence of poor flow properties, however co-processed excipients, when compared and simple mixtures or parent materials, have been indicated to have less fill-weight variety issues. The essential purpose behind this wonder is the impregnation of one molecule into the network of an alternate, which decreases the harsh molecule surfaces and makes a near-optimal size circulation, bringing on better flow properties. Fill-weight variety has a tendency to be more noticeable with high-speed pressure machines. Fill-weight variety was examined with different machine speeds for SMCC and MCC, and SMCC indicated less fill-weight variation than MCC.

Co-processed excipients offer the accompanying extra points of interest:

- 1) Pharmaceutical manufacturers have the choice of utilizing a single excipient with various practical properties, thereby diminishing the quantity of excipients in stock.
- 2) Some expense, the general product cost diminishes due to enhanced usefulness and less test prerequisites contrasted with individual excipients.
- 3) Co-processing excipients help in planning tailor-made excipients. They can hold functional points of interest and specifically decrease drawbacks.
- 4) Reduction being developed courses of events and procedure approval exertion.
- 5) Co-processed excipients by virtue of non-obvious advantages hold the possibility of patenting the dosage form.

Limitations

Real restriction of co-processed excipients mixture is the degree of the excipients in a mixture is settled and in creating another definition, an altered proportion of the excipients may not be

an ideal decision for the API and measurement for every tablet being worked on. Co-processed adjuvant fails to offer the official acceptance in pharmacopeia.

Steps Involved in Co-Processing

The genuine procedure of creating a co-processed excipient includes the accompanying steps:

- Identifying the group of excipients to be co-processed via carefully studying the material characteristics and usefulness prerequisites.
- Selecting the extents of different excipients.
- Assessing the molecule size needed for co-processing. This is particularly essential when one of the parts is handled in a scattered stage. Post transforming the molecule size of the recent relies on upon its introductory molecule size.
- Selecting a suitable methodology of drying, for example, spray or flash drying.
- Development of controlled generation parameters to avoid batch to batch variation.

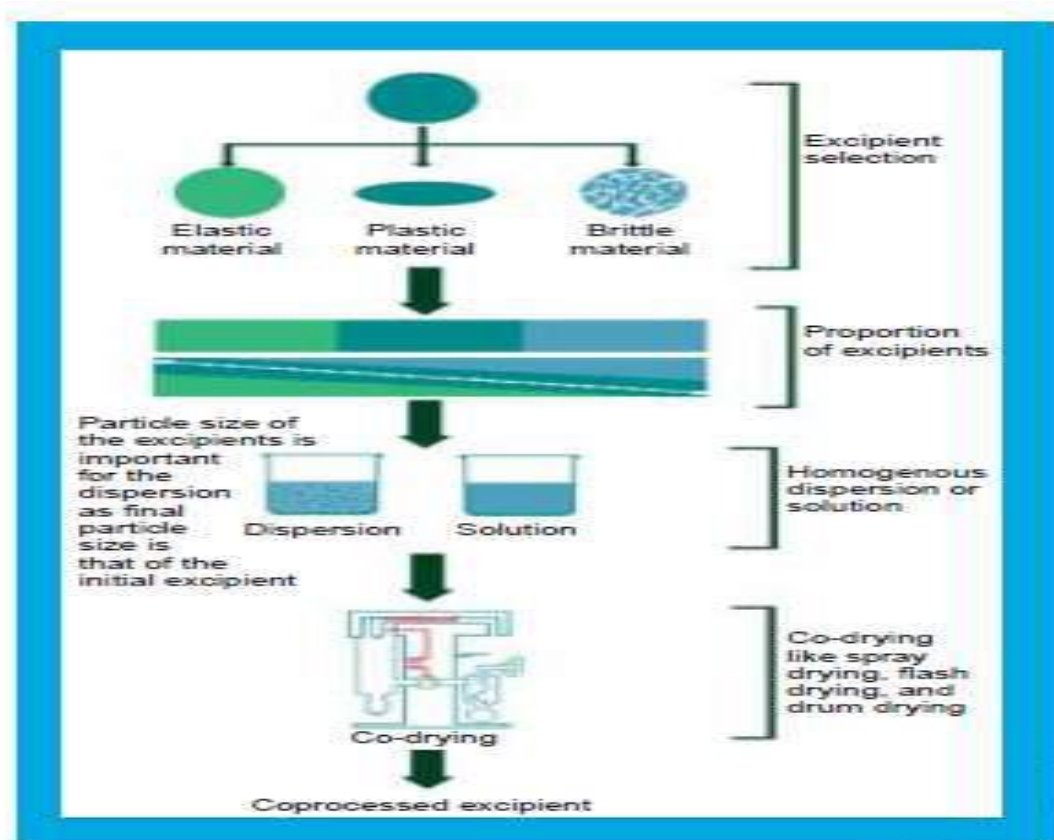


Figure 1: Schematic representation of steps involved in co-processing

Characterization of New Co-Processed Excipient Prepared

The new co-processed excipient prepared was evaluated for the following:

- 1. Solubility:** Solubility of coprocessed excipient was tested in water, aqueous buffers of pH 1.2, 4.5, and 7.4 and organic solvents such as alcohol, dichloromethane, chloroform, acetone and petroleum ether.
- 2. pH:** The pH of 1% w/v slurry was measured.
- 3. Melting Point:** Melting point was determined by using melting point apparatus (Digimelt).
- 4. Swelling Index ^[12]:** The new excipient prepared (200 mg) was added to 10 ml of water and light liquid paraffin taken in two different graduated test tubes and mixed. The dispersions in the tubes were allowed to stand for 12 h. The volume of the sediment in the tubes was recorded. The swelling index of the material was calculated as follows.

Volume of sediment in water – Volume of sediment in light liquid paraffin

$$\text{S.I (\%)} = \frac{\text{Volume of sediment in water} - \text{Volume of sediment in light liquid paraffin}}{\text{Volume of sediment in light liquid paraffin}} \times 100$$

- 5. Moisture Absorption:** The hygroscopic nature of the new excipient prepared was evaluated by moisture absorption studies in a closed desiccator at 84% relative humidity and room temperature.
- 6. Particle Size:** Particle size analysis was done by sieving using standard sieves.
- 7. Density:** Density (g/cc) was determined by liquid displacement method using benzene as liquid.
- 8. Bulk Density ^[13]:** Bulk density (g/cc) was determined by three tap method in a graduated cylinder.
- 9. Angle of Repose ^[14]:** Angle of repose was measured by fixed funnel method.
- 10. Compressibility Index ^[15]:** Compressibility index (CI) was determined by measuring the initial volume (V_0) and final volume (V) after hundred tapings of a sample of modified starches in a measuring cylinder. CI was calculated using the equation

$$\text{Compressibility index (CI)} = \frac{V_0 - V}{V_0} \times 100$$

Selection of the Excipients to be Coprocessed

Excipients selection is most imperative assignment to try for co-processing method. Materials, by virtue of their reaction to connected strengths, could be named flexible, plastic, or weak /brittle material. However, pharmaceutical materials display each of the three sorts of conduct, with one sort being the transcendent reaction. This makes it hard to outline which property is useful for compressibility. Maarschalk reports co-processing performed with a lot of brittle material and a little measure of plastic material, as exemplified by Cellactose (Meggles Corp.) in which 75% lactose (fragile material) is coprocessed with 25% cellulose (plastic material). This specific blend keeps the capacity of an excess of elastic energy amid compression, which brings about a little measure of anxiety unwinding and a diminished tendency of capping and lamination. Notwithstanding, cases of the other amazing additionally exist (e.g., SMCC has a lot of MCC [plastic material] and a little measure of silicon dioxide [brittle material]). These two circumstances exemplify the way that co-processing is by and large performed with a synthesis of materials that have plastic deformation and brittle fragmentation qualities. Consequently, co-processing these two sorts of materials delivers a synergistic impact, regarding compressibility, by specifically overcoming the disadvantages. Such combinations can help enhance functionalities, for example, compaction performance, flow properties, strain-rate sensitivity, lubricant sensitivity or sensitivity to moisture, or decreased hornification. A couple of illustrations of co-processing excipients that are created by co-processing brittle and plastic materials are enrolled in Table 1. However, co-processed excipients are also developed by co-processing of two plastic materials or two brittle materials (for example Dipac). Table 2 provides a list of co-processed excipients that are developed by co-processing of two or three plastic materials.

Table 1: Co-processed excipients developed by co-processing brittle and plastic materials

Excipients Co-processed		Improved properties compare to physical Brittle blend	Reference
Brittle blend Reference Component	Plastic Component		
Colloidal silicon Dioxide	MCC	Novel MCC based excipient is free flowing ,posses excellent disintegration properities has improved compressibility relative to normal off the shelf commercially available MCC.	29
Dibasic calcium Phosphate	HPMC Crospovidone	Has increased flowability ,an increased API loading and blendin and higher compactability	30
Calcium Phosphate	MCC	Novel MCC based excipient has improved compactability and recompactability	31
β lactose	Sorbital	Produce tablet with improved recompactability	32
Calcium Carbonate	MCC	Novel MCC based excipients has improved recompactability	33
Lactose	Polyviny Pyrrolidine (PVP) Crospovidone	Novel excipient possess good flowability and good compressibility under low pressure Produce tablets that exhibit excellent disintegration properties coupled with great hardness and low abrasion	34

Table 2: Co-processed excipients developed by co-processing two/three plastic materials

Excipients Co-processed	Improved properties over physical blend	Reference
MCC Guar gum	Improved smell, taste, texture and mouth feel.	35,36
Mannitol, Sorbitol	Good compactability and less hygroscopicity	37
MCC HPMC	Better flowabilty and higher compactability. Retains compressibility on wet granulation	38
MCC HPMC Crospovidone	Exhibit enchanced flowability, excellent compactability, increased API loading and blendability	39

Strategies for Coprocessing

Co-processing systems are by and large straightforward, adaptable and well known. Co-processing strategy, alongside its trial conditions assumes an extremely basic part in the improvement of co-processed excipients. The techniques utilized for co-processing of excipients are

- 1) **Spray Drying:** Co-processing of excipients utilizing spray drying system includes atomizing the result or homogenous scattering of the excipients to be co-processed into fine droplets. Fine droplets are then tossed radially into moving stream of hot gas. The expanded droplet surface territory and high temperature causes the creation of spherical particles, which makes them suited for the immediate layering methodology. Exact control of different spray drying procedure parameters like inlet air temperature, atomization air force, feed rate, fluid consistency, solid substance in the feed, disc speed can help in planning particles with desired qualities. Spray drying by excellence of exact control over molecule attributes and simple scale up has been broadly utilized for the generation of co-processed excipients. ^[16]
- 2) **Fluid Bed Spray Granulation (FBSG):** FBSG system for co-processing includes spraying a solution of one excipient onto a liquid bed of other excipient, drying and alternatively screening to obtain the granules of coprocessed excipients. Menon et al. depicted FBSG for co-processing of corn starch and polyvinyl pyrrolidone. The created co-processed excipient is free flowing and show great compressibility. ^[17] Davar et al. portrayed co-processing of sodium carbonate with poly ethylene glycol utilizing FBSG procedure. Co-processing of sodium carbonate with poly ethylene glycol secure it from dampness, consequently, avert building up of sodium carbonate. The created co-prepared excipient was utilized as pH adjusting operator as a part of noneffervescent pharmaceutical synthesis of zolpidem or scopolamine. ^[18] Al Omari et al developed co-processed excipient containing α -chitin and mannitol. Co-processed α - chitin and mannitol was utilized as a part of the planning of orally deteriorating tablets. Tablets made with this progressed composite display low friability, low launch energy and hardness sufficient to be prepared in fast tableting machines, while holding quick disintegration or dissolution properties.^[19]
- 3) **Wet Granulation:** Co-processing of excipients utilizing wet granulation procedure basically includes wet massing of the blend of the excipients to be co-processed with a

granulating fluid, wet sizing, drying and lastly screening of dry granules. Wet granulation is a practical strategy for co-processing as it can be embraced for traditional supplies like a planetary blender/high shear blender and obliges approval of less process variables.^[20]

- 4) **Dry Granulation/Roller Compaction:** In this system an uniform powder blend of the excipients to be co-processed is compacted between counter rotating rollers to form ribbon of compacted material that is then processed into granules. Roller compaction is suitable for co-processing of moisture or high temperature sensitive excipients on the grounds that there is no drying. Bauer et al. portrayed co-processed excipient derived from a polysaccharide product and an insoluble disintegrating agent. The polysaccharide is powdered and/or MCC and insoluble deteriorating excipients include acrylamide homopolymer, acrylic corrosive homopolymer and/or acrylic corrosive acrylamide copolymer. The polysaccharide based coprocessed excipient was utilized as tablet disintegrant and as dispersion or suspension stabilizer in the production of liquid and semisolid preparation.^[21]

- 5) **Melt Granulation:** Melt granulation strategy for co-processing includes blending, the blend of excipients to be co-processed, with an balanced amount of meltable binder (that is binder is in solid state at room temperature yet softens in the temperature scope of 50-800c). The mixture is then warmed with constant mixing so as to break the mass into agglomerates. The agglomerates are then cooled to room temperature lastly screened to acquire the granules of desired size. Melt granulation method dispenses with the utilization of water or another solvent, requires just a short preparing time and could be received for customary supplies. Cucula et al. depicted melt granulation procedure for coprocessing calcium phosphate with unsaturated fat wax. The unsaturated fat wax is ideally glyceryl behenate or glyceryl palmitostearate.^[22] Co processing of calcium phosphate with unsaturated fat wax conquers the abrasiveness and capping issues typically connected with calcium phosphate. Coprocessed calcium phosphate and unsaturated fat wax is utilized as a part of the planning of venlafaxine Hcl adjusted discharge tablet and venlafaxine besylate extended release tablet^[23].

- 6) **Roller Drying:** Co-processing of excipients through roller drying includes setting up a homogenous solution or dispersion of the excipients to be co-processed and after that drying of the resultant solution or dispersion on a roller dryer. This method has been received by Meggelaars et al. for co-processing lactose with sugar liquor. The sugar

liquor is ideally sorbitol or lactitol. In this specific case, the rolling temperatures to be sufficiently high, to acquire a product that comprises basically of β -lactose in crystalline structure. Novel co-processed β -lactose and sugar liquor is utilized as pharmaceutical excipient within the arrangement of direct compression tablets with enhanced hardness.

- 7) **Co-precipitation:** Co-processing of excipients by means of co-precipitation may incorporate any modern method referred to, for example, wet or dry granulation, pH change co-precipitation, shower drying, stop drying or basic result blending. Co-precipitation by pH change has been embraced by Badwan *et al.* for co-processing starch (corn starch) with silica (colloidal silica). The technique includes arrangement of a basic result of colloidal silicon dioxide to which corn starch was gradually included with vivacious mixing. The pH of the mixture was balanced with hydrochloric acid to pH 7.0. The solid particulates of silicate starch were then filtered out and dried up in the oven. The novel silicate starch is used as filler and disintegrant in immediate release solid dosage forms. ^[24]
- 8) **Co-transformation:** Co-processing of excipients *via* co-transformation involves the application of heat or a solvent to temporarily “open-up” the particles of one excipient and then adding another excipient into the “opened-up” particles. This technique has been adopted by Staniforth for co-processing superdisintegrant with an augmented agent. The superdisintegrant is preferably sodium carboxymethylstarch cross-linked or sodium carboxymethylcellulose cross-linked. The augmenting agent can be a water soluble polymer such as maltodextrin, surfactant such as poloxamer, oil such as stearic acid or a mixture of the above mentioned augmented agent. The co-transformed superdisintegrant has improved compressibility and can, therefore, be used in the formulation of high dose drug. ^[25-27]
- 9) **Milling:** Milling or dry grinding for the production of coprocessed excipients may be carried out in a roller mill, a ball mill, a bead mill, a millstone mill, a jet mill, and a hammer mill. Ball milling has been adopted by Rao *et al.* for co-processing cross-linked polyvinylpyrrolidone and calcium silicate. In this particular case, ball mill was operated for hours at a speed of 200 rpm using 25 stainless steel balls. The co-processed binary mixture of cross-linked polyvinylpyrrolidone and calcium silicate enhances the rate and extent of dissolution of a poorly soluble drug. ^[28]

Administrative Perspective of the Coprocessed Excipient

Combinations of excipients via co-processing do not produce any chemical change in the incorporated excipients and all the reflected changes are at the physical level. Otherwise stated, in case of co-processed excipients, the components, the component combination and the manufacturing process are not novel. The only novel parameters are the physical form and the improved functionality. Hence, the coprocessed excipients do not require any toxicological assessment and can be considered as safe if the parent excipients are generally regarded as safe (GRAS) by the regulatory agencies. A very limited number of co-processed excipients are described in official monograph for example Dispersible Cellulose (British Pharmacopoeia), Compressible Sugar (United States Pharmacopoeia/National Formulary). Their non-official status is the major hindrance to their success in the market place. This obstacle is likely to be overcome in the near future as with IPEC New Excipient Safety Evaluation Procedure (NESEP), excipients now could be reviewed outside the FDA drug approval process (NDA). Positive feedback from IPEC expert committee will limit the risk of FDA rejection of drug based on excipient and could encourage innovation in the excipient industry. ^[40]

Current & Future Developments

The continued popularity of solid dosage forms, introduction of high speed tablet machines, and an increasing preference for the direct compression process creates a wonderful opportunity for the development of high functionality excipients. A narrow pipeline of new chemical excipients and improved grades of existing excipients has opened the door for the increased use of co-processed excipients. Co-processed excipients offer numerous advantages, especially, simple and cost effective methods of production and reduced data burden. Owing to their nonofficial status, co-processed excipients are still not widely accepted by the pharmaceutical industry. Considering IPEC initiative in terms of NESEP, the future for co-processed excipients looks very promising. With upcoming newer combination of excipients and newer methods of co-processing, co-processed excipients are for sure going to gain attraction both from academia and pharmaceutical industry.

CONCLUSION

Co-processed excipient includes joining together two or more compendial or non-compendial excipients arranged to physically change their qualities in a manner not accomplishable by basic physical blending and without considerable synthetic methodology. Co-processing is

experiencing calculable support since the individual constituents are added to in an exceptional procedure without adjusting the substance structure. Co-processing of excipients constrained out excipients with better characteristics compared than the basic physical mixtures of their constituents. The essential seek of co-processing is to discover a product with bestowed survey going hand in hand with the proportion of its usefulness/taken a toll. Very nearly plans include excipients at a more famous focus than the dynamic pharmaceutical fixing (API) and therefore excipients help discriminatingly towards handling, soundness, wellbeing and working of strong measurements structures. Most of the excipients that are as of now reachable neglect to meet the wanted set of functionalities in the imagining of distinctive measurement structure fundamentally tablets. Likewise, make urging for the improvement of high usefulness excipients.

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