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A Review on Multifunctional Excipients with Regulatory Considerations

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The practice of multifunctional excipients is gaining more and more attention as it simplifies the process of drug formulation by substituting the necessity of using mixture of many excipients. The multifunctional excipients are the class of excipients which includes pre-–processed and co-processed excipients and it provides added functionalities to the formulation. Functionality of an excipient is a useful property which helps in manufacturing and improves quality as well as applicability of the material. Researchers have identified that single component excipients may not always give the required results during development and manufacturing of definite API, hence they are concentrating to develop multifunctional excipients which will have improved quality that will fulfil the requirements of the formulation experts in terms of cost. The cost of new excipient development is very high as it demands toxicity studies, hence the industry is now focusing on co-processing of approved materials. The demand for directly compressible co-processed excipients has also increased due to the availability of high-speed tableting machines, time saving in Abbreviated New Drug Application (ANDA), simplified validation and stability of active ingredients. The intention of this review article is to highlight applicability and increasing attention focusing the benefits of co-processed excipients. Their advantages over conventional blend of excipients include development methods, testing and also highlighting their regulatory consideration.

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1. INTRODUCTION

Pharmaceutical drug products/dosage forms are formulated by blending Active Pharmaceutical Ingredients (API) with excipients. API is that which has the therapeutic action and the excipients are those which are referred as pharmacologically inactive ingredients [1]. These excipients are fused with API during development process for various functions so as to formulate a dosage form that is ready for stated use [2,3]. Co-processing of excipients would result in the enhancement and improvement in the characteristics of individual excipients as compared to the physical mixture of multiple excipients. A multifunctional excipient executes multiple functions in a dosage form [4]. The purpose behind selecting a multifunctional excipientis to give synergistic enhancement of desired characteristics and veiling the unpleasant properties of individual excipients [5]. The example of multifunctional excipient is Silicified microcrystalline cellulose which is merging of MCC and colloidal silicon dioxide. This is an example of directly compressible excipients can beneficially affect the properties of drugs [6]. The purpose for using MCC in various solid dosage form is its capability of compression, which is a direct result of its, plastic deformation, extended porous structure and surface roughness [7]. By employing these co-processed excipients, the outcome will be enhanced compressibility, porosity, flow properties, particle size distribution, shape etc. These multifunctional excipients after their evolution have to be examined using different testing techniques. Co-processed excipient is the consolidation of at least two pharmacopeial and/or non-pharmacopeial excipients to genuinely modify their properties [3]. Co-processing is a method of designing that empowers the mixture of at least two excipients to make single compound excipient with better usefulness compared with simple blend of excipients [8].

New blends of prevailing excipients are fascinating options for improving excipient usefulness since all dosage forms contain more than one excipient [9]. None of the single excipient holds all the physicochemical characteristics for the development of a formulation. Subsequently there is need to have excipients having more than one characteristics like enhanced flowability, decreased moisture sensitivity, enhanced compressibility and improved disintegration ability [10].The usefulness of the excipients can be improved by either advancing novel excipient or co-processing of prevailing excipients. Developments in drug formulations and delivery system led to the development of multifunctional excipients which have added functions apart from their main purpose. Producing the new chemical excipient is inefficient and must have to pass through various regulatory approvals which states about the safety and non-toxicity of the excipient [3].

These multifunctional excipients can be formulated by either pre-processing method or by co-processing method. Out of these two stated methods; co-processing is the widely adapted method of preparation for multifunctional excipients. Some of the methods used for preparing co-processed excipients are spray drying, agglomeration, spheronization by extrusion, melt granulation, co precipitation, roller drying etc. The accessibility of nanotechnology extendschances to elaborate on novel co-processed excipients [11].

The engineering of pharmaceutical excipients produces excipients that can come up with minimum of two functions to the formulation by using single ingredient that can be made by using novel substance excipients, new evaluation of prevailing materials, or by new mixtures of present materials [12].

Polymers built on natural resources owing to their importance can produce new excipients that have highest potential to perform unequivocal capacities , on account of their Abundance, biodegradability and non-harmful nature [13].

1.1 Types of Excipients

The excipients can be classified in the following types based upon the number and type of components used:

1. Single entity excipients: It is characterized as excipients containing single component which is the essential segment. Example: gelatin, cellulose
2. Mixture/blends of multiple excipients: Straight forward actual combinations of at least two pharmacopeial/non pharmacopeial excipients with the assistance of low to medium shear

measure where the different segments are combined as one without significant synthetic change for strong blend/mixes where the particular excipient remain genuinely separate to a particulate degree. Example: microcrystalline cellulose and lactose [14].

3. Novel excipients or new chemical entities: It is characterized as excipients which are artificially adjusted to deliver novel excipients regularly not recorded in FDA. The new excipient is any pharmacologically inactive substance which is deliberately added to the dosage form. These substances are not included in the list of inactive ingredients as per FDA [15]. Example: gelatinized maize starch with sodium carboxyl methyl cellulose and microcrystalline cellulose [12].
4. Co-processed excipients: co-processed excipients are mixture of at least two pharmacopeial or non-pharmacopeial excipients intended to truly adjust their characteristics in a way not attainable by simple blending of two or more excipients. A wide range of co-processed techniques can be used for improvement in the characteristics of individual excipients. Example: SYLOID® FP [16], Ludipress [17].

1.2 General Flow for Steps in Coprocessing of Multifunctional Excipients

Advancement of any multifunctional excipient by co-processing strategy includes steps like, determination of parent excipients according to the method as depicted in Fig. 1. The two or more parent excipients composition is made as per the requirement for production of multifunctional excipients. Further optimization of characteristics for the excipients and finally drying of optimized mixture of excipients is done [3].

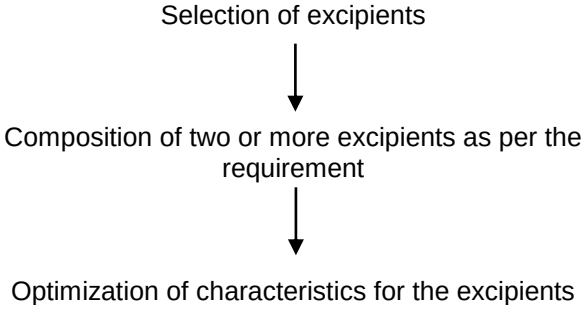

Fig. 1. Steps in Coprocessing of Multifunctional Excipients [3]

2. METHODS FOR PREPARATION OF CO-PROCESSED EXCIPIENTS

Co-processed excipients can be prepared by various methods like melt granulation, solvent evaporation, wet granulation, spray drying, freeze thawing, hot melt extrusion, extrusion spheronization etc. as depicted in Table 1.

2.1 Melt Granulation

Melt granulation has been utilized in numerous mechanical applications, including polymer, substance, metal, glass, food processing and fertilizers [18]. Melt granulation method of producing multifunctional excipients includes consolidating, the blending of excipients to be co-processed along with a meltable binder. The fusion is then heated with constant blending which breaks the mass into agglomerates which is further chilled to room temperature and eventually screened to acquire granules of required size. This technique does not utilize water or some other solvents [3].

2.2 Wet Granulation

Goyanes et al. had utilised the method of wet massing with slight modification for preparation of co-processed excipients[15]. Wet granulation technique can be completed either in fluid bed granulators or high shear blenders. Co-processing of excipients by wet granulation method involves mixing of the granule blend with a granulating liquid, passing the wet mass through sieve, drying and ultimately screening the dried granules [3]. This is the method mostly used in the pharmaceutical industries. The advantage of wet granulation over direct compression is its cost effectiveness and it is an attractive granulation method [12]. Wet granulation of α–lactose monohydrate is still a common choice for producing pharmaceutical tablets [19].

2.3 Freeze Thawing

This technique involves simultaneous crystallization and agglomeration processes in single step which has been efficaciously used for enhancement of flowability and similarity of excipients [10]. Additionally numerous biotech items are effectively put away in the frozen state [20].

2.4 Extrusion Spheronization

In this method two or more excipients are mixed to create a dry powder blend. This dry powder blend is then mixed with the liquid binder to produce a wet mass. This wet mass is then passed through the spheronizer which produces spheroids of uniform spherical size and shape. Hot melt extrusion method is most widely used among spheronization method. is a heat dependent technique which has gained interest as a novel approach for HME producing polymeric sustained release, immediate or transdermal/transmucosal delivery system. The molten polymer functions as a thermal binder hence no solvent or water is required. The HME process involves higher temperature greater than 80°C. Hence the excipient and the API must be heat labile. Schematic diagram of hot melt extrusion process is as depicted in Fig.2.

Technique is broadly utilized in moving and liquefying of polymer inside a tank by a pivoting screw. The polymer dissolve is further forced through the die which solidifies into various shapes/forms which can then be converted into tablet or granules [10].The advantages of this method is, it is reproducible, less time consuming and also, various shapes are possible, however the costs involved is higher [16]. For example, in Telmisartan antihypertensive drug, by using the hot melt extrusion technique, the properties like solubility, bioavailability, and stability were improved. This was attained by using Telmisartan (TEL) with the formulation of TEL-loaded pH-modulated solid dispersion [21].

2.5 Spray Drying

The spray drying process is a method in which continuous drying of the processed particles takes place. Spray drying technique involves spraying of the liquid feeds, i.e, solution, suspension, emulsion into hot drying medium which is converted into dried particulate matter like powder, granules or agglomerates depending on physicochemical properties of the feed and design of the dryer [22]. This method mostly involves five steps: concentration, automization, droplet air contact, droplet drying, separation, co-spray drying[16,14].Schematic diagram of spray drier is as depicted in Fig.3.

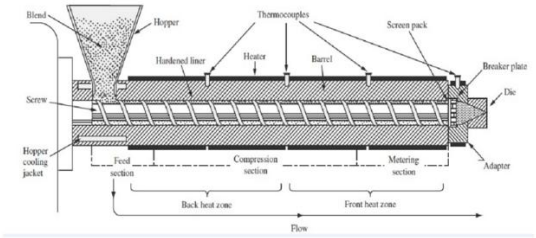

Fig. 2. Schematic diagram of hot melt extrusion process [24]

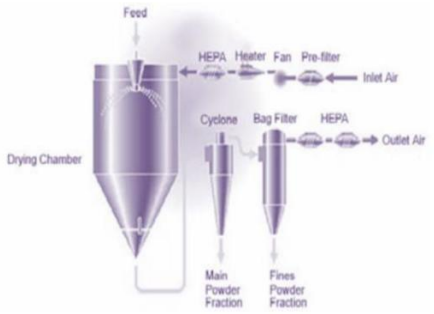

Fig. 3. Schematic diagram of spray drier [24]

2.6 Solvent Evaporation

This process involves microencapsulating the main excipient material by dissolving or dispersing it in the polymer coating solution. Further by agitation process the core material blend is distributed all over the vehicle phase to get the proper size and shape microcapsules. Then heating the above mixture results in evaporation of the solvent. On evaporation of the solvent, the liquid vehicle temperature is decreased to ambient room temperature by continuous agitation process. The core excipient materials can be either water insoluble or water-soluble materials [23]. This process is used in preparation of liquid manufacturing vehicles. The coating excipient is solubilized in a volatile solvent, which is immiscible with the liquid manufacturing vehicles [16].

2.7 Roller Compaction

It is a method of compaction of dry powder into a solid mass in the form of a ribbon. This involves feeding of powder mass into a set of directly opposed, counter rotating rollers. This process does not use any liquid as well as it is carried out at comparatively low temperature. Roller compaction method is more favourable for water or thermosensitive drugs since no use of liquid or drying is required. Flow diagram of roller compaction process is as depicted in Fig.4.

2.8 Co-Grinding and Co-fusion

In this method two or more excipients are ground or fused with each other to prepare a mixture of excipient with improved characteristics.

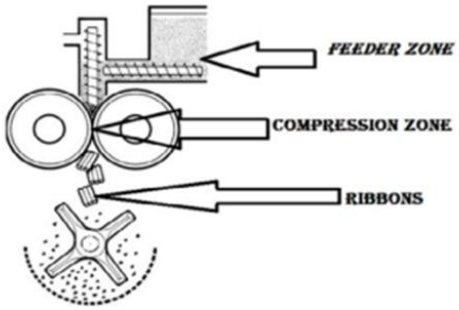

Fig. 4. Flow diagram of roller compaction process [24]

Table 1. Co-processing Methods and Outcomes [25]

Methods	Excipients involved in coprocessing	Outcomes
Melt granulation	MCC, Crospovidone, PEG-4000, dibasic calcium phosphate	Good flowability, higher disintegration, time, rapid drug release, better hardness
Solvent evaporation	Acacia gum, Maize starch	Improved flow property, better disintegration time.
Spray drying	MCC, Colloidal silicon dioxide Crospovidone, StarCap 1500 Lactose and MCC	Very good flow property, high compressibility, decreased disintegration time and good binding property, good dilution potential (up to 40%)
Wet granulation	Lactose monohydrate, MCC &Corn-starch	Superb flow property, directly compressible excipient and increased compressibility
Extrusion spheronization	MCC and Eudrajit	Strong mechanical strength, excellent flow property, improved dissolution
Roller compaction	Polyethylene oxide and HPMC K4M	Improved release retarding property, better flowability and compressibility.
Co-grinding and co-fusion	Tapioca starch & mannitol	Co-grinding less useful than co-fusion, improved flow property, improved packing and compaction property

2.9 Testing of Co-processed Excipients

Co-processed excipients differ from simple mixture of excipients which contains combination of at least two excipients. Hence, it will be important to establish the techniques for testing and analysis that will permit the composition of co-processed excipient to be estimated in a routine process. Usually, quantitative analysis of individual excipients which are used to prepare a co-processed excipient is the most preferred way of the quality control analysis. But this may not be possible for the combination of excipients when one of the component excipients is polymeric in nature. However, a suitable method must be developed which would estimate the individual components present in the co-processed excipients in a quantitative manner. Apart from the quantitative test to be performed for a co-processed excipient, few more tests also need to be considered while analysing it. These additional tests include physical tests such as particle size and distribution, water content, limit tests for individual excipients, residual solvents, elemental impurities and degradants. But still, it is mandatory to develop an analytical technique which will give clear differentiation from co-processed and simple mixture of excipients. Such a test will be important to ultimately acquire a compendial monograph for the co-processed excipient [26]. For characterization of individual excipients present in co-processed excipients, advanced analytical techniques are used like, scanning electron microscopy, differential scanning calorimetry, FTIR, X ray Diffraction technique. Following are the different analysis methods used for various co-processed excipients:

1. Solubility: Each sample was examined in three-fold and outcomes are revealed as the mean with standard deviation. e.g.Pharmaburst®500, Parteck® ODT, Ludiflash®, Disintequik™ ODTe [23].
2. Density: The density measurement is critical parameter for the co-processed excipients in the solid powdered form. The density can be estimated by using pycnometer. e.g. Alginic acid and microcrystalline cellulose (Alginate ester)
3. Particle size determination: Determination was performed using threefold and the middle particle diameter was used to indicate the size of particle. Also, particle size can be determined by methods such as Direct microscopy or Optical microscopy, Sieving method, Conductivity or Coulter counter method, Sedimentation method and LASER particle size analysis. e.g.Alginic acid and microcrystalline cellulose (Alginate ester) [13].
4. Scanning electron microscopy: the particle size distribution of an excipients has a major impact on the characteristics of a formulation, so it becomes very necessary to study the particle morphology. Scanning electron microscopy is used to study particle size, morphology with its chemical composition. The SEM instrument consists of components like the source, electromagnetic lenses, scan coils, electron detector for backscattered electrons, sample compartment, and a computer system for detection.
   SEM is classified into three types, the conventional SEM, environmental SEM, and the low vacuum SEM.This technique will acquire a mosaic image of the particles which will describe about the particle characteristics of an excipient [27,28].
   e.g. Alginic acid and microcrystalline cellulose [25] BARETab® Nutra [28], xylitol-starch [29].
1. Thermal methods: For characterization of co-processed excipients, thermal methods like Thermogravimetric analysis TGA and Differential scanning calorimetry DSC were used. e.g. Alginate ester[13], α-Lactose Monohydrate and Magnesium Silicate [13].
2. Fourier transform infrared (FTIR) spectroscopy: FTIR technique is used to study the compatibility of two excipients as well as API and excipients. This method consists of grinding of the sample and triturating with the KBr powder in the ratio of 1:100 and further compressing it into the KBr pellets using a hydraulic press. The formed pellets are thus placed in the sample compartment and scanned from 4000 to 500cm^{-1} having a 4 cm^{-1} resolution. The FTIR spectra demonstrates the change in the shape and position of the bands on the spectra due to the presence or absence of different functional groups present [30,31]. e.g. Alginic acid and microcrystalline cellulose [25]. chitin-calcium carbonate [30].

3. Powder X-ray diffraction analysis (XRPD): This technique in a generally used for phase identification of crystal material and can give information on unit cell dimension. A diffractometer is an estimating instrument for breaking down the design of a material from dispersing design, generate when a light illuminate or atom cooperate with it. e.g. Chitosan [6].
4. NMR: Carbon NMR and Proton NMR techniques are used in characterization of excipients. NMR analysis helps in determination of structure, molecular weight, water content, molecular mobility. e.g. kollidon, alginate ester [13].
5. Mass: Mass spectrometric technique is used as one of the major characterization techniques in excipient analysis. This analysis helps in structural elucidation of the compounds and its major fragments.

2.10 Regulatory Considerations

Before getting introduced in the market, every novel excipient needs to go through a few administrative endorsements and toxicological examinations to confirm safety and effectiveness. The FDA necessitates that NDA (new drug applications) and ANDA (abbreviated new drug applications) applicants give data about all constituents of the drugs as well as all excipients used. This information involves data of its composition, analytical techniques used, along with the safety. New excipients must be properly scrutinized for pharmacological action as per the ICH guidelines. These assessments can be performed through toxicological evaluations. By detailed investigations of co-processed excipients, it had observed and proved that the included excipients do not lead to any chemical changes after coprocessing, these co-processed excipients are considered as safe if the parent excipients are like wise Generally Regarded As Safe (GRAS)- certified by regulatory authorities and hence these excipients need not to undergo any further regulatory approval and toxicological evaluations. Guidelines expresses that when any one or both of the excipients used in co-processing are official in any compendia, then these excipients used will follow all the standards stated in its monograph [31]. But if one of the excipients is non compendial or it is a novel excipient then, it must be regarded as a new chemical entity which will be then subjected for detailed toxicological studies.

For any new excipient or a new combination of co-processed excipient various guidelines need to be referred. These guidelines include

- CDSCO guidelines as per D & C Act [32].
- WHO Supplementary guideline for the manufacture of pharmaceutical excipients [33].
- FDA Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients [34].
- IPEC International Pharmaceutical Excipients Council of the respective country [35].
- The IPEC Europe Co-processed Excipient Guide for Pharmaceutical Excipients [36]
- Eudralex Volume 4 guidelines for excipients [37].
- The International Pharmaceutical Excipient Council & The Pharmaceutical Quality Group the Joint Good Manufacturing Practices Guide for Pharmaceutical Excipients 2017 – (www.ipecamericas.org) [38].
- EXCiPACT™ Certification Standards for Pharmaceutical Excipient Suppliers, Issue 1, January 2012 [39].
- NSF/IPEC/ANSI 363-2016 Good Manufacturing Practices (GMP) for Pharmaceutical Excipients [40]. USP 37-NF32, General Chapter <1078> Good Manufacturing Practices for Bulk Pharmaceutical Excipients, USP Convention, Inc., Rockville MD, 2014 [41].
- International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality – M4Q(R1) [42].

For a new co-processed excipient to be approved, it should be contained within approved products regulated by the national regulatory agency (public competent expert in the European Union). There are contrasts in how co-processed excipients are taken care of in the significant areas (Europe, Japan and the United States).

Excipient Master File system, is not practised in Europe, hence the full details relating to any excipient are included in the Marketing

Application. The application, either for an Marketing Authorization should be Investigational Medicinal Product (IMP) or referenced.

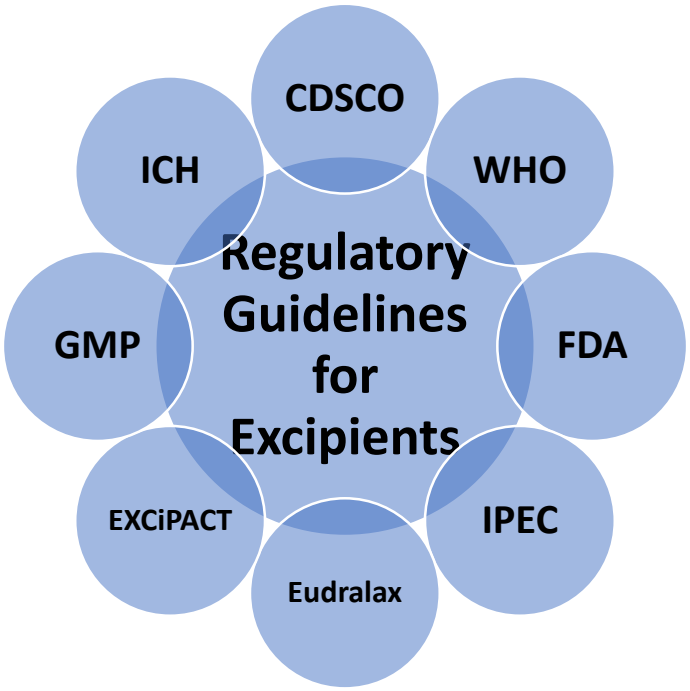

Fig. 5. Various Regulatory agencies and their guidelines for excipients

Table 2. Patent Review on Co-Processed Excipients [25]

Sr. No	Patent No	Grant year	Title
1	EP 3 682 901 A1 22.07.2020 BULLETIN 2020/30	2020	Co—processed excipient, obtained by spray—drying, usable as a pharmaceutical excipient or food additive [43].
2	WO 2017/013682 AL	2017	A co-processed pharmaceutical excipient [44].
3	WO 2016/046693 AL	2016	Process of preparation of co-processed polymer and it's pharmaceutical application [45].
4	US 8,932,629 B2 JAN. 13, 2015	2015	Co-processed microcrystalline cellulose and sugar alcohol as an excipient for tablet formulations [46].
5	WO 2014/165246A1	2014	Co-processed tablet excipient composition its preparation and use [47].
6	US 2013/0177649 A1	2013	Modified protein excipient for delayed-release tablet [48].
7	WO 2013/175405 AL	2013	High performance excipient comprising co-processed microcrystalline cellulose and surface-reacted calcium carbonate [49].
8	US20110076326, MARCH 31, 2011	2011	Microcrystalline cellulose calcium carbonate [50].
9	WO 2003/051338	2003	Microcrystalline cellulose galactomannan gum [51].
10	US4744987A 1998	1998	Mannitol-sorbitol [52].
11	US5686107A 1997	1997	Silicified mcc-a polyol and sugar with or without disintegrant [53].

Table 3. Marketed Co-Processed Excipients [16,24]

Multifunctional excipient	Trade Name	Advantages	Method of manufacturing
Sucrose 3% dextrin	Dipac	Directly compressible	Crystallization
Microcrystalline cellulose, Silicon dioxide	Prosolv	Improved flow, decreased affectability to wet granulation, improved hardness of tablet, decreased friability	Co-spray dried
Microcrystalline cellulose, Guar gum	Avicel ce-15	A reduced amount of grittiness, negligible chalkiness, more palatability	Spray dried
Calcium carbonate, Sorbitol	Formaxx	Better particle size distribution	Co-processed (unique process)
Microcrystalline cellulose, Lactose	Microlela	Potential for formulating elevated dose	
Anhydrous lactose, lactitol	Pharmatose DCL 40	increased compressibility, low lubricant sensitivity	Spray dried
MCC, colloidal Silica	Prosolv	better flow properties, better hardness, reduced friability	Co-spray dried
Lactose, 25% cellulose	Cellactose	Improved compressibility, enhanced mouth feel, improved tableting at low price	Co-spray dried

As per latest European guidelines, when a novel excipient is used in a drug formulation it must undergo detailed toxicological studies as that of an API [30] The blend of excipients was introduced as a subject to the National Formulary and was allocated an importance based on the usage of the blend in marketed formulation in which the processing has given an increased value to the excipient mixture. In this way, there is a need for an administrative dossier inside the EU region for any novel excipients [24].

In Japan, co-processed excipients are mentioned as premixed excipients. Japan has an Excipient Master File framework, and their DMF framework can be utilized for premixed excipients.

The US FDA has a grounded Drug Master File (DMF) framework for excipients. The whole data for excipients can be submitted as a Type IV DMF. The configuration for such an accommodation ought to follow the rules from the ICH M4Q(R1) guidelines [23].

2.11 Patents on Co-processed Excipients

There are various patents published and granted for no. of co-processed excipients with its method of manufacturing as depicted in Table 2.

2.12 Marketed Co-processed Excipients

With the expanding improvement of new synthetic elements, there is a colossal chance for the development of co-processed excipients. With this ever-increasing demand from manufacturing industries, many co-processed excipients were developed and marketed as depicted in Table 3 [54].

3. CONCLUSION

Formulation development mainly depends on the excipient used. Though the excipients are not active ingredients but it assumes fundamental part in design and development of dosage form. From the available dosage forms around 90% are solid dosage form with tablet being one of the main dosage forms. Hence, in development and testing of multifunctional excipient more emphasis has been put on the excipients used in tablet manufacturing. One of the major benefits in developing co-processed multifunctional excipient is that from regulatory perspective this excipient is not ideally considered as a new excipient by virtue of this these excipients don't need extra toxicological investigations. The increasing use of excipients in development of

formulation results in more economic expenditure. So, to save time and economy during the stages of Food and Drug; the concept of multifunctional excipient proved to be the most effective and beneficial.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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