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PELLETS IN PHARMACEUTICALS: AN OVERVIEW OF PELLETIZATION TECHNIQUES AND EXCIPIENTS FOR OPTIMIZED DRUG DELIVERY

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ABSTRACT:

In recent years, pellets have emerged as a preferred alternative to traditional tablets and capsules in pharmaceutical formulations due to their numerous advantages. These small, free-flowing spherical particles, commonly referred to as beads, seeds, or nonpareils, offer benefits such as uniform size distribution, enhanced flowability, and improved packing characteristics. Unlike traditional solid dosage forms, pellets enable better drug distribution in the gastrointestinal tract, reducing variability in drug absorption and minimizing irritation to the stomach lining.Pelletization involves various techniques, each with its own merits and applications. Conventional methods like powder layering, extrusion-spheronization (ES), and solution/suspension layering are widely used in industrial settings. ES, in particular, is favored for its reliability and scalability in producing drug-loaded or neutral pellets. Additionally, advanced techniques such as wet spherical agglomeration, crystallo-co-agglomeration, melt pelletization, cryopelletization, and freeze pelletization have expanded the possibilities for pellet formulation, offering solutions for immediate and controlled drug release.Natural polymers and excipients, including sugar, starch, chitosan, pectin, carrageenan, alginates, xanthan gum, and talc, play a crucial role in pellet formulation. These materials contribute to the mechanical stability, sphericity, and release characteristics of the pellets. Semi-synthetic excipients like cellulose derivatives (HPMC, HEC) and synthetic polymers such as crospovidone, carbopol, polyethylene glycol, and polyethylene oxide have also been explored for their potential to enhance pellet properties.This review provides a comprehensive overview of the various pelletization methods, with a focus on the extrusion-spheronization technique, and discusses the potential excipients used in pellet formulation. The discussion highlights the importance of selecting appropriate methods and materials to achieve desired pellet characteristics, ensuring consistent drug delivery and therapeutic outcomes.

Keywords: Extrusion Spheronization (ES), Wet Spherical Agglomeration (WSA), Natural Polymers, Polyethylene Glycol (PEG), Pharmaceutical Excipients, Drug Delivery Systems.

1.INTRODUCTION

In place of traditional tablets and capsules, pellets have become a popular pharmaceutical solid unit dose form in recent years. A multiple unit particulate system (MUPS) is a dose form that uses pellets and ranges in size from 250 to 2000 millimeters [1]. Names for these free-flowing granules/spheres include beads, seeds, spherical agglomerates, nonpareils, spheres, globules, and so on. They have a uniform and narrow size distribution. When compared to powder and granules, the main benefits provided by these spheres are low surface area to volume rates, which in turn reduces the intra- and inter-subject variability of plasma profiles [6]. In conclusion, pellets are favored over traditional tablets and capsules because they enhance the technological and medicinal aspects of the dosage form. The current paper provides a brief overview of the many pelletization methods that are employed, as well as potential excipients for the extrusion spheronization (ES) process of all the strategies proposed, ES is the only reliable method that has been implemented and used in a large-scale industrial setting [7].

2.PELLETIZATION METHODS

For pelletization, several methods have been developed to far. While high shear pelletization [8], wet spherical agglomeration [9], spherical crystallization , crystallo-coagglomeration , melt pelletization, cryopelletization, freeze pelletization , and other techniques are alternative methods, solution/suspension layering , powder layering , and ES [10] are the conventional ones.

2.1. Powder Layering

The procedure entails applying binding liquid and dry powder made of excipients to inert starter seed material at the same time. Here, the dry-milled excipient powder causes the production of solid bridges after the formation of liquid bridges between the binders. In a pan or drum coater, the operation is repeated until the required size is reached [11].

2.2. Extrusion/Spheronization

Pellet manufacturing on an industrial basis makes extensive use of the ES technology. It makes two different kinds of pellets. Drug-loaded pellets have the drug matrixed inside them, as opposed to neutral pellets, which are drug-free. Direct pelletization is the term for the latter method. There are four steps to this approach. Using a wetting agent or plasticizer, a uniform powder blend of excipients and medication is first granulated in a planetary mixer, high shear mixer, or continuous granulator [12]. Using an extruder, moist coherent mass is extruded in the second stage to create cylindrical extrudates. To do the same, ram extruders, sieves, and screws are used. Wet extrudates are then fed into a spheronizer with a surface plate that has grooves to increase frictional forces, which causes the extrudates to break down into spherical pellets. Lastly, a hot air oven or fluidized bed drier is used to dry the wet spheres at room temperature. As a result, this process produces pellets that have low

friability, quiet dense, narrowly distributed in size, and well spherical. If the direct pelletization technique is used, the ES procedure permits high drug loading [13].

2.3. Solution/Suspension Layering

Using this method, initial beginning solid cores are treated with a suspension or solution of sugar-binder, preferably sugar. During the drying process, the sprayed excipient crystallizes after spreading out as droplets on the starting cores. Its cohesion and strength are increased as a result of the solid bridges that form between the particles at the surface during the drying process. A pan coater or a fluidized bed processor can be used to carry out the procedure [14].

3. ADVANCED TECHNIQUES

3.1. Wet Spherical Agglomeration

The wet spherical agglomeration (WSA) approach involves the creation of liquid suspension agglomerates and their separation from suspending liquid through the addition of a bridging liquid that serves to wet the solid surface. The WSA technique was created by Smith and colleagues and is applied in two different ways in a cylindrical tank that has a revolving agitator [15]. It was discovered that the energy input throughout the procedure determines the size of the agglomerates. Nonetheless, a few experimental parameters, such as the volume of bridging liquid, the rate of agitation, and the duration of agitation, can regulate the size. When a significant amount of particles are suspended in a bridging liquid, some of the particles dissolve fully and some partially, but the undissolved particles are transformed into spherical agglomerates as a result of constant stirring [16].

3.2. Crystallo-Co-agglomeration

A unique method for increasing the size of particles, known as crystallo-co-agglomeration (CCA), can be applied to increase the size of one, two, or more medicines at low or high doses, either with or without diluents [17]. In essence, this can be viewed as a development of the SC methodology. CCA was created by Kadam et al. with the specific goal of size augmentation [18]. However, in the last ten years, it has been investigated as a technology to create the spherical agglomerates needed for MUPS design. The micrometric, mechanical, and compressional properties of the agglomerates produced using this method have improved . Modified drug release can also be obtained from the intact pellets or compacts thereof by using appropriate excipients and polymers. Additionally, the agglomerates produced using this method can be utilized as spheres that need to be encapsulated or as immediately compressible tablet intermediates. As a result, CCA-prepared spherical agglomerates and pellets can have many benefits over spheroids, including consistent size distribution, superior flow characteristics, and repeatable packing and filling [19].

3.3. Melt Pelletization

Melt pelletization is a method that creates pellets without the need of a granulating agent or solvent by using molten liquid as a binder. In contrast to the traditional method of binding, which involves using organic or aqueous solvents, the binding liquid in melt procedures stays a part of the formulation . The melt extrusion process is divided into three phases:

Melting a solid substance is step one. Mixing the molten mass with solids is step two. Shaping the molten material and solidifying it into the desired shape is step three. It is necessary to keep the temperature in the spheronizer high enough to partially soften the extrudate, aid in its deformation, and eventually cause the formation of a spheroid [20]. Due to the high temperatures required, this approach has the drawback of being inapplicable to heat-labile materials [21].

3.4. Cryopelletization

Pellets of solution, suspension, or emulsion are created during cryopelletization by allowing them to come into contact with liquid nitrogen, which is utilized as a solidifying medium, at a temperature of -160°C. Rapid freezing happens as a result of the droplets' quick heat transfer with the liquid nitrogen. Water and organic solvents are eliminated from droplets by lyophilization or freeze-drying. A crucial stage in the process, droplet formation is determined by formulation characteristics such equipment design and related processing variables. Drug-loaded pellets for both immediate and controlled release formulations can be made using this method [22].

3.5. Freeze Pelletization

By using this method, spherical pellets of molten solid carrier matrix—which is immiscible with molten matrix—are produced in the liquid. The molten pellet matrix can be made to flow uphill or downward through the liquid in the column based on its density. It can also be exposed to varying temperatures during its journey, solidifying at the exit. Using a cooling mixture of acetone and dry ice, the initial portion, from which the molten solid carrier is delivered, is kept between 25 and 100°C, and the cooling portion, where droplet solidification takes place, is kept between 0 and -40°C [23]. The molten solid-carrier matrix is made up of excipients such as diluents, disintegrants, surfactants, or release modifying agents, as well as dissolved or distributed actives. When producing pellets, it is recommended to utilize hydrophilic or hydrophobic carriers that melt below 100°C and solidify at room temperature. Polyethylene glycol (PEG), polyvinyl alcohol, xylitol, dextrose, maltose, high HLB gelucires, and derivatives of polyethylene oxide are examples of potential hydrophilic carriers. Column liquid (immiscible with carrier) silicone oil, mineral oil, and vegetable oil can be used for these [24].

4.NATURAL POLYMERS/EXCIPIENTS

4.1. Sugar/Sucrose

Sugar spheres, also known as nonpareils, have been officially recognized in monographs and have been routinely utilized as initial substrates in pellet-based drug delivery over the past 20 years [25]. Pellets are functionalized and the medicine is put on top of it. Basically, sucrose and maize starch are combined to create sugar pellets, which are produced through a stacking process that is covered under pelletization procedures. They possess the necessary mechanical stability for additional processing. They exhibit low compressibility and outstanding flowability [26]. Nevertheless, the primary ingredient in non-pareils, sucrose, has a few well-known disadvantages, such as its tendency to hygroscopicity and a rough surface that requires more polymer to be applied during

base coat application. It is commonly recognized that the pellet's surface roughness determines how much interparticulate friction there is. The rough surface of sugar pellets has been disclosed by optical microscopic and SEM pictures [27] illustrates. Sugar pellets are not suitable for use in the production of tablet formulations because of their weak compressibility. The use of them in tablet formulation design is suggested by Martinez et al.'s work, which attributes this to the impact of particle size. In the cushion beads, smaller pellets stay compact and undamaged whereas bigger pellets break [28]. Another significant drawback of sugar spheres is the difficulty in producing small spheres through stacking; this results in significant losses and weak little pellets. Additionally, giving sugar spheres to diabetics may have negative consequences [29]. Due to its carbonyl functionalities, sucrose is prone to react (maillard reaction) with excipients and/or drugs that contain amine groups. It has

been shown that when sucrose, a water soluble core, is utilized, dosage dumping may occur. Because sucrose can create a high osmotic pressure, it obstructs the release of the medication [30]. Owing to the aforementioned drawbacks and unsuitability for the ES process, MCC has gradually taken its position.

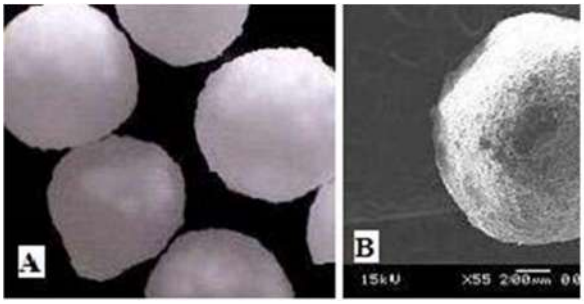

Figure.1 Sugar bead photomicrographs captured at different magnifications (A) 4X (B) 55X using a digital microscope and SEM.

4.2. Starch

The polysaccharide starch is made up of the molecules amylopectin and amylose. Due to its low water holding capacity, weak wetted mass flexibility, and poor strength imparted to pellets, it has limited potential as a pelletization aid [31]. Despite the fact that a number of writers have discussed using starch as a binder for MCC pellets, neither non-gelatinized nor pre-gelatinized starches have shown to be an effective assistance in pelletization. Only crystalline or high-amylose starches produce pellets with acceptable qualities among the different kinds of starches that are available. The pellets with a high concentration of theophylline anhydrous (25% w/w) and high amylose starch had a complete drug release in 20 minutes, a fast disintegration time of less than 10 minutes, an acceptable sphericity (AR<1.2), and a high pellet yield (>90%). In order to increase wettability and plasticity, sorbitol was utilized as a surface texture modifier and hydroxylpropyl methyl cellulose as a binder [32]. Hydrochlorthiazide and piroxicam, two poorly soluble medications, were shown to release their contents immediately in similar investigations conducted on the extracellular matrix (ES) of modified starch-containing dogs . To increase wetting and plasticity, Junnila et al. have proposed adding Polysorbate 80 as a surface active agent in addition to MCC and starch (30%, w/w) [68]. It has been shown in another investigation that MCC pellets can contain up to 50% waxy maize starch as a co-

filler. In which case it was discovered that the pellets' aspect ratio fell within an acceptable range [33]. With the exception of pellets made from a combination of starch and white dextrin, pellets made from maize and wheat starch in addition to white or yellow dextrin exhibited very weak sphericity. Theophylline pellets (10% w/w) have been reported to be prepared using a combination of lactose (63% w/w) and starch (27% w/w). The amount of water in the binder solution was shown to have an impact on the spherical granule's internal porosity, increasing as internal porosity decreased. Additionally, the amount of water that was added to the pellets affected their mechanical strength [34]. For all starches to have the appropriate sphericity and consistency, the pellet formulation needs to include extra binder. Because of their limited range of ideal water content, starch-based formulations have been proven to be less resilient than MCC-based formulations [35].

4.3. Chitosan

The primary byproduct of alkaline deacetylation of chitin, a key structural polysaccharide present in crustaceans, insects, and lower plants, is chitosan, a cationic polymer with 1-4 glucosidic linkage. It is soluble in acidic pH but insoluble in neutral and alkaline pH, biocompatible, biodegradable, and non-toxic. Its solubility profile, which is dependent on pH, has restricted its use as a pelletization aid.Nevertheless, a great deal of research on the pelletization of chitosan in combination with different binders, diluents, and polyelectrolyte complexes has been published. To make MCC-free pellets, its polyelectrolyte complex containing an anionic alginate has been pelletized. Because lactose monohydrate is used as a filler, it has been shown that the model medication, acetaminophen, releases from these pellets quickly [36]. When alcohol/water mixture 50% (v/v) was used as a binding solvent during ES, chitosan pellets with satisfactory physical qualities were formed. According to a different study, utilizing a 20% (v/v) alcohol/water mixture and a high chitosan concentration produces spherical and mechanically stronger pellets. Acceptable yield, size, sphericity, and decreased friability were seen when chitosan (15% w/w) pellets were made using HPMC (10% w/w) as a binder, and drug (caffeine) release was not prolonged [37]. Research has also been done on the effects of chitosan types with varying molecular weights—190 and 419 kDa—on the characteristics of pellets made with ES. The formulations, which include water as a granulating liquid, chitosan, MCC, DCPD, and acetaminophen as the model medication, have been developed. The manufacturing of acceptable pellets with chitosan at a maximum of 60% w/w and not more than 30% w/w of MCC was demonstrated by the results. Recent research on the impact of chitosan's degree of deacetylation on the characteristics of pure chitosan pellets was conducted by Jess and Steckel. The maximum amount of deacetylation (99.9%) in the chitosan resulted in pellets with suitable size, sphericity, friability, mechanical strength, and surface characteristics. Research on formulation and process variables has shown that the dissolving medium has no effect on the release from pellets, but the inclusion of chitosan prolongs the release of diclofenac sodium. Its cationic character and pH-dependent

solubility have led to limited investigation of chitosan as a pelletizing aid in the current situation. Ionic medications cannot be combined with chitosan due to potential interactions; therefore, in order to produce high-quality pellets, a second polymer or binder must be added[38].

4.4. Pectin

Made mostly of polygalactouronic acid, pectin is a gel-forming polysaccharide that is somewhat soluble in water [39]. Because of its various qualities, which are indicated by varying degrees of amidation and methoxylation, it has been thoroughly investigated as a pelletization aid [40]. Research utilizing liquids such as water, calcium chloride, citric acid, and ethanol to granulate three different forms of pectin with varying degrees of amide and methoxyl substitution revealed that ethanol, when used as a granulating agent, lessens the stickiness of the pectin and produces spherical pellets. Shape and size were improved by adding MCC as an extrusion aid. Nevertheless, the resulting pellets were more prone to dissolve and had a tendency to be mechanically weak. While amidation of the low-methoxylated pectin appears to have a positive effect on the production of short pellets, a high degree of methoxylation is not conducive to the formation of products. An analogous investigation was conducted to examine the impact of additive concentration in the granulation liquid on the extrudate's moisture content and how it affected the pectin pellets' size, shape, and mechanical stability. It was found that the type of pectin used influences the improvements in the pellet properties. Compared to high-methoxylated pectins, the two low-methoxylated pectins were more susceptible to concentration variations [41]. Using quantum chemical descriptors, a quantitative link between granulation liquid and particle size was established, leading to the conclusion that the granulation liquid should consist of tiny, polar molecules . Pectinic acid has a high capacity as an extrusion aid; a study using a pectinic acid and lactose blend with 1% riboflavin revealed that even pellets with only 20% pectinic acid could achieve appropriate sphericity. It has demonstrated sufficient mechanical stability, with an aspect ratio of roughly 1.15–1.20, and it has released 30–60% of a medication with limited solubility within 15 minutes in both intestinal fluid (pH 6.8) and simulated stomach acid (0.1 M HCl) [42]. Another study found that pectin pellets allowed for a high riboflavin load of 1-80% and created mechanically stable pellets that quickly disintegrated, making them ideal for the quick delivery of medicines that are poorly soluble in water [43].

4.5. Carrageenan

An anionic polysaccharide that occurs naturally and is extracted from red sea weed is called carrageenan. The market offers three major forms of carrageenan: kappa (), iota (), and alpha (). These types differ in terms of the number and location of sulfate ester substitution. While kappa is insoluble in water, the and carrageenans are soluble in it. Garcia and Ghaly [44] were the first to report on the use of carrageenan in ES. Carrageenan was employed as a binder to MCC (> 50%), not as an MCC replacement. It was subsequently thoroughly examined as a pelletization aid in 2005. It was

discovered that the -type may substitute the often used MCC in a variety of formulations to produce pellets with a quick drug release and acceptable quality during the wet ES process. It exhibits appropriate flexible and brittle qualities for the subsequent spheronization procedure because of its insoluble nature. On the other hand, extrudates made of soluble -and -carrageenans are not spheronized. Using a high drug load of 80% hydrochlorothiazide, another investigation on -carrageenan produced pellets with acceptable forms, diameters, and size distributions. These pellets' characteristics were comparable across a water content range of 90 to 105% [45]. A separate investigation yielded 36 formulations with carrageenans, four distinct fillers (lactose, mannitol, dicalcium phosphate dihydrate, and maize starch), and four distinct medications (acetaminophen, theophylline, mesalamine, and hydrochlorthiazide) Pellets with good size and shape were produced by all formulas. With the exception of mechanical strength, pellets released drugs more quickly than MCC. Carrageenan is a pelletization aid that possesses all the necessary characteristics. Carrageenan-based pellets have an advantage over MCC pellets in that they release the medicine quickly, which makes them suitable for pharmaceuticals that are poorly soluble. It has been observed that the presence of cations and the drying conditions have an impact on the characteristics of pellets made with carrageenan [46]. Above 70 °C, thermal degradation was noted, which decreased mechanical strength and accelerated the rate of breakdown. Because of ionic interactions, calcium ions have been discovered to decrease drug release and increase the mechanical strength of pellets. Nevertheless, it was shown that this pelletization aid's limitations were caused by an ionic interaction between carrageenan and alkaline drugs like dimenhydrinate and lidocaine as well as low mechanical stability [47]. When carrageenan was added to pellet formulations as a pelletization aid, the compression behavior of both high and low drug strength pellets was studied. It was discovered that all pellet formulations showed little to no fragmentation and underwent compression by deformation, which was supported by the pellets' increased equivalent diameter and aspect ratio and decreased roundness factor. Because ES-based carrageenan pellets demonstrated quick drug release, good sphericity and aspect ratio, poor drug adsorption, and deformability under compression, they can be ranked highly among pelletization aids. More water was bound by the new extrusion aid, carrageenan, which could result in an expensive drying process and stability issues for medications that are sensitive. Conversely, the wide range of ideal water content increases the pelletizing process' resilience because minor variations in the rate of powder and liquid feed won't have an impact on the final product's quality. Therefore, it may be said that carrageenan is a viable substitute for MCC [48].

4.6. Alginates

Brown seaweed contains linear, unbranched polysaccharides known as alginates or alginic acids. This polymer is made up of two distinct monomers in different ratios: D-mannuronic acid and L-guluronic acid, which are joined by - or -1,4 glycosidic linkages to form

homopolymeric blocks of either monomer, or heteropolymeric blocks that alternate between the two [49]. The molecular weights of alginates range from 20 to 600 kDa. Alginate's gelling qualities are caused by guluronic residues, which, when left to react with polyvalent ions like calcium or aluminum, cause the polymer to cross-link, resulting in the creation of gels that can be used to create matrices and pellets. The impact of granulating liquid type on the pelletability of alginate (30%), MCC (50%) and theophylline (20%) has been studied by Pornsak Sriamornsak et al. Using a viscous granulating liquid, lengthy, dumbbell-shaped pellets were produced in this instance. Using a watery granulating liquid and calcium chloride to lessen sodium alginate's capacity to swell, spherical pellets were produced. But in under 60 minutes, these pellet formulations released 75–85% of the medication [50]. Gowda et al. assessed the olanzepine matrix pellet made using a combination of sodium alginate, glyceryl palmito stearate, and MCC as a spheronization booster. Fickian diffusion was observed in the regulated release of the drug from these pellets. Oral dosage dumping is encouraged by conventional alginate pellets because of their quick breakdown of the medication and loss of multiparticulate properties such aggregation in acidic media.Because alginate pellets are acidic by nature, they may interact with alkaline drugs, so their application is restricted to alkaline pH only [51].

4.7 Xanthan Gum

Xanthamonas campestris is a microbe that is used in the pure culture fermentation of carbohydrates to create xanthan gum, a high molecular weight heteropolysaccharide [52]. Xanthan gum pellets are typically employed to regulate medication release. The formulation of xanthan gum (16%) with MCC in the presence of various fillers, such as lactose monohydrate, tribasic calcium phosphate, and cyclodextrin, resulted in spherical pellets with sufficient tensile strength. Xanthan gum did, however, restrict the release of diclofenac sodium for a prolonged period of time when it was in compacted form rather than in a pellet form. It was notable that the pellets permanently deformed instead of breaking during compaction. It was believed that fragmentation did not exist. We conclude that xanthan gum-based pellets may be a potential excipient in the creation of deformable pellets [53].

4.8 Isomalt

Isomalt is a disaccharide sugar alcohol derived from beet that is used as a sugar substitute and pharmaceutical excipient [54]. Because it lacks the carbonyl group that causes the maillard reaction when amines are present, it is more chemically stable than other saccharides. It can be administered to diabetic individuals because of its modest insulinemic and glycaemic responses. When isomalt, sugar, and MCC pellets are compared, it can be shown that while all pellet types exhibit an appropriate aspect ratio, MCC has a higher tensile strength than starting sugar and isomalt cores. Diclofenac sodium was found to release slowly from MCC layered pellets, while it released quickly from sugar cores and isomalt because of their soluble nature, which created an osmotic gradient across the polymer coat. Thus, it was reiterated that the sort of starting pellet used mostly determines the

release mechanism [55]. Given the new preparation and investigation of isomalt pellets, further research about its pellet performance is required.

4.9 Talc

Layers of silicate and brucite combine to form talc, a cheap, inert material in terms of physico-chemical properties and physiology. It has historically been extensively utilized in a variety of solid dosage forms as a diluent, lubricant, and glidant [56]. One of the more inventive uses of talc is in the form of talc granules, which were first used as placebo beads in studies by Lin and Peck. There, talc was granulated in a fluidized bed processor using PVP as a binder, yet the granules' strength was subpar. Pellets were investigated as a coating substrate and WSA of talc was performed in order to address the issue of low strength and give sphericity to granules [57]. In this procedure, DCM was utilized as a bridge liquid to bring together all of the talc particles, PEG was employed to help disperse the internal phase, and HPMC was used to provide the agglomerates strength and sphericity. It was found that the talc pellets performed just as well as sugar spheres in terms of coating and exhibited acceptable micromeritic, mechanical, and compressional qualities. While talc pellets' strength was found to be lower than that of sugar pearls, friability experiments verified that it was still satisfactory, indicating that it could endure the intense force of attrition during coating operations.Once more, the release of enteric coated talc pellets containing diclofenac sodium was comparable to that of pellets containing sugar [58]. Therefore, a detailed examination into the talc pellets produced by WSA as an inert substrate for coating is necessary. Ibuprofen-and bromhexine hydrochloride-talc pellets were created as a result of the successful exploration of talc's potential as a diluent in CCA. Depending on the amount of drug matrixed and the size of the agglomerates, the drug-loaded spherical agglomerates in both types of pellets had adequate sphericity and strength and released the medication in 10 to 30 minutes[59].

5. SEMI SYNTHETIC EXCIPIENTS

5.1 Cellulose Derivatives

As a pelletization aid, many semi-synthetic polymers have been reported, such as hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC) [60]. Their characteristics as a pellet excipient vary as their viscosity classes do. It has been stated that isopropyl alcohol, rather than water, is utilized as a wetting solvent during the pelletization process because of its soluble nature. But isopropyl alcohol has a negative impact on the pellet's mechanical strength. The HPMC-based pellets were the more suitable of the two in terms of sphericity, strength, and smoothness of the surface. However, since no medicines were used during the tests, more thorough research is required. Few studies have looked into the unique use of HPMC as a CCA method pelletization help. In ibuprofen-talc agglomerates, Pawar et al. have added up to 16.16% w/w of HPMC, whereas in bromhexine hydrochloride-talc agglomerates, 4% w/w has been added [61]. HPMC was responsible for giving the agglomerates sphericity and strength in both instances. In a different investigation, Indapamide-talc agglomerates were given

mechanical strength by adding 3.6% wt/wt of ethyl cellulose (EC) as a pelletization aid. Sphericity was negatively impacted, even while strength improved [62]. Drug release from HPMC-based pellets occurs via the gel that forms, whereas erosion occurs from HEC and EC. Based on the function of semi-synthetic celluloses, it may be inferred that they are excellent binders that provide the pellets strength. It is impossible to ignore their potential contribution to spheronization[63].

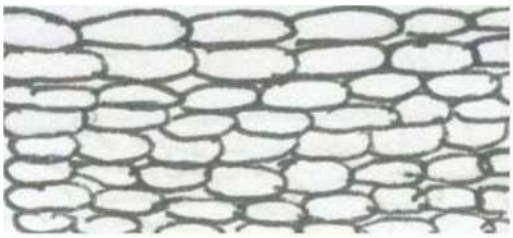

Figure 2. a picture showing compressed, distorted talc agglomerates.

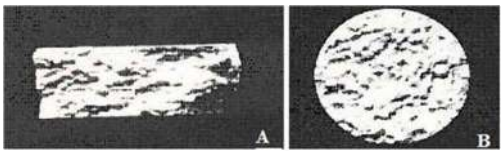

Figure 2. Breakage of the compact (40 X magnification). (A) Diametrial and (B) Axial. Fatty Acid Esters of Poly Ethylene Glycol.

These are known by the popular term Gelucires, and their melting points and HLB values vary . Gelucire 50/02 has been the subject of recent research as a carrier for melt solidification for ES pellet production. Pure diffusion regulated the release of drugs from these pellets, whereas extrusion-spheronization-prepared pellets released theophylline relatively slowly in comparison to hydrophilic gelucire 55/18. Nifedipine was used in a different investigation to pelletize a blend of hydrophilic Gelucire 50/13 and hydrophobic Glyceryl palmito stearate (GPS) at varying concentrations. It was discovered that the drug released in a regulated manner and showed fickian diffusion [64].

6. SYNTHETIC POLYMERS

6.1 Crospovidone

It is a synthetic N-vinyl-2-pyrrolidone cross-linked homopolymer that is insoluble in water. Cross-linked polyvinyl pyrrolidone, also known as crospovidone, has been suggested by Liew et al. as a pelletization aid for the ES process [65]. There are various grades of crospovidone with varying particle sizes available from manufacturer to manufacturer. While Polyplasdone® XL-10 and Polyplasdone® INF-10 are finer grades, Polyplasdone® XL is a coarser grade. When lactose was utilized to test these three grades of crospovidone as a pelletization aid, it was found that while the coarse grade could not be employed, the smaller grades could be used to produce pellets. Verheyen et al. (2008) recently verified that crospovidone's tiny particle grade is suitable for use as a pelletization aid [66]. 70% (w/w) of medications, including hydrochlorothiazide and paracetamol, could be added to the pellets; however, pellets with extremely high drug loading could not be made. Every pellet disintegrated in less than 40 seconds, with the exception of those that contained 70% weight-to-weight paracetamol. The dissolving times of all the pellets were fast (paracetamol < 20 min and hydrochlorothiazide < 45 min). With the exception of pellets containing 50% hydrochlorothiazide (1%), and 70% paracetamol (1.4%), the friability of the pellets

containing polyvinyl pyrrolidone was determined to be less than 1%. According to a another study, crospovidone did not effectively hasten the breakdown of propyphenazone in pellets made by ES [67]. Theophylline's dissolution from pellets made in a rotary processor, however, was considerably sped up by the addition of croscarmellose sodium. If combined with other co-pelletization aids, this safe excipient—which is routinely and safely used in dosage forms—may be a viable pelletization aid [68].

6.2 Carbopol

It is a derivative of cross-linked acrylic acid with water-swellability, pH sensitivity, and ionizability.A recent evaluation examined the effects of several process variables on theophylline pellets with high levels of MCC and carbopol 934. Carbopol: Blends having a high percentage of MCC wetted with water alone displayed a different rheological behavior than blends wetted with a CaCl2 solution. The carbopol:MCC ratio was shown to have an impact on the mean pellet diameter. Using Na-benzoyl-L-arginine ethyl ester as a model medication, sustained release freeze-dried pellets containing carbopol 934P and avicel PH-101 were produced in a different study [69]. Safak PakerLeggs et al. have shown that the drug form—free base or the hydrochloride and maleate salt form in the formulations—determines the release of propranolol pellets containing carbopol. It was determined that, although polymer relaxation had a greater impact with the free base form, both fickian diffusion and polymer relaxation contributed to the release mechanism in each instance. Carbopol has a high degree of stickiness and swelling, which makes it difficult to process when pelletized alone[70].

6.3 Polyethylene-glycols and Oxides

Recently, pellet manufacturing has made use of PEG and polyethylene oxide (PEO). PEG results in a decrease in the force of cohesion between particles by reducing the interfacial tension. Smaller spherical agglomerates are produced as a result. PEG experiences plastic deformation because of its soft, plastic character, which improves the agglomerates' compressibility throughout the compression process [71]. PEO is an additional ethylene glycol polymer with a high molecular weight and good water solubility. It has been suggested as a spheronization help lately. It gives the wetted mass enough plasticity. It has been shown that adding low molecular weight methoxypolyethylene glycol enhances the lubricating qualities of wetted bulk. Because the polymers in this situation are soluble, there was an immediate drug release seen. PEG and PEO can be used n conjunction with other pellet aids to increase the flexibility of wetted material, but they cannot be utilized exclusively for pelletization [72].

CONCLUSION

Pellets have emerged as a favored alternative to traditional tablets and capsules in pharmaceutical applications, offering advantages in drug distribution and reducing physiological variability. Their uniformity, flowability, and reduced susceptibility to gastric conditions make them ideal for consistent drug release. Various pelletization methods, such as

extrusion-spheronization, solution layering, and advanced techniques like cryopelletization and melt pelletization, have been developed to cater to different drug formulations and delivery requirements. The use of natural, semi-synthetic, and synthetic excipients further enhances the versatility and effectiveness of pellets in drug delivery systems. Overall, the evolution of pelletization techniques and excipient choices underscores their importance in modern pharmaceutical development, ensuring better patient outcomes through improved drug delivery.

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