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Investigating the Use of Polymeric Binders in Twin Screw Melt Granulation Process for Improving Compactibility of Drugs

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ABSTRACT

Traditionally, the melt granulation for pharmaceutical products was performed at low temperature (<90°C) with high-shear granulators using low-melting waxy binders, and tablets produced using such granules were not amenable to large-scale manufacturing. The situation has changed in recent years by the use of twin screw extruder where the processing temperature could be increased to as high as 180°C and polymers with high T_g could be used as binders. In this study, different polymeric binders were screened for their suitability in improving compactibility of 2 drugs, metformin hydrochloride and acetaminophen, by twin screw melt granulation. Processing temperatures for the 2 drugs were set at 180°C and 130°C, respectively. Screw configuration, screw speed, and feed rate were optimized such that all polymeric binders used produced granules. Several hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, and methacrylate-based polymers, including Klucel® EXF, Eudragit® EPO, and Soluplus®, demonstrated good tablet tensile strength (>2 MPa) when granules were produced using only 10% wt/wt polymer concentration. Certain polymers provided acceptable compactibility even at 5% wt/wt. Thus, twin screw melt granulation process may be used with different polymers at a wide range of temperature. Due to low excipient concentration, this granulation method is especially suitable for high-dose tablets.

Introduction

In tableting, active pharmaceutical ingredients (APIs) and excipients are agglomerated into granules to improve flow, content uniformity, and tableting properties of powders.[1] The successful granulation of an API is, however, a complex procedure dependent on interplay of granulation methods and properties of materials used. The conventional methods used for granulation are divided into wet and dry methods, depending on whether water or solvent is used for granulation or not. In both processes, it is necessary to incorporate binders into formulations to hold fine particles together. However, the efficiency of binders with respect to their ability to form granules, the granule strength, and the compactibility of granules formed may depend on many factors, including the method of granulation and inherent physicochemical properties of binders. The properties of drug substances or API also play critical roles in the granulation process and subsequent compression of granules into tablets. For example, if the API is poorly compactible, the granulation process and the binder should be selected such that the compactibility of the material is improved and tablets with optimal pharmaceutical properties can be prepared.

Despite the critical roles of binders in granulation and tableting, they are often selected arbitrarily, and some binders may gain popularity over time for a specific granulation method. For instance, polyvinylpyrrolidone (PVP) with some variation in its grades is usually the binder of choice for wet granulation.[2] Such an arbitrary selection of binders, however, restricts the use and experimentation with other available binders that may provide better performance for a certain formulation. Thus, for any granulation method, it is desirable to screen a variety of binders and select the ones that may provide the best results in terms of granule strength, yield, and tableting properties.

Even after careful selection of binders, the addition of binders alone to the API does not lead to granules having optimal tableting properties, such as powder flow, granule strength, compactibility, friability, disintegration time, and so on. Particularly, large amounts of other functional excipients, such as microcrystalline cellulose, dicalcium phosphate, anhydrous lactose, lactose monohydrate, and

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so on, are often added to overcome undesirable tableting properties of API and obtain adequate granule porosity and strength, improve flow, and increase compactibility.[3] It is very common to have >50% of the total tablet weight that is composed of binders and such other excipients. This becomes problematic in formulating high-dose tablets, because the tablet weight and size may increase drastically due to the presence of high amounts of excipients, thereby reducing aesthetic appeal, ease of swallowing, and batch productivity of tablets.

Newer granulation methods may help in eliminating the need for large amounts of binders and excipients in a tablet. One such method is twin screw melt granulation. Lakshman et al.[4] reported the use of twin screw melt extruder to granulate a high-dose and poorly compactible drug, metformin hydrochloride, by using <10% hydroxypropyl cellulose (HPC) as the polymeric binder. No other intragranular excipients were used, and yet the compactibility of metformin hydrochloride improved such that the granules could be compressed successfully into tablets even without any extragranular excipients, except for 1% magnesium stearate as a lubricant. In another study, Vasanthavada et al.[5] melt granulated imatinib mesylate successfully with only 5%-10% wt/wt polymers by using twin screw extruder to develop high-dose and modified release tablets. Thus, it is possible to granulate API by using twin screw extruders without much excipient. These studies were, however, limited to only 1 or 2 selected binders, and it is, therefore, essential that a comparative study of a wide range of polymeric binders is conducted to determine their suitability for melt granulation and ability to improve compactibility of drug substances.

Properties of polymeric binders as they relate to compressibility,[6] density of binder,[7] drug-binder interaction,[8] and so on in solid dosage forms were studied extensively in case of wet granulation. In this method, the solvent plays a major role in the incorporation of binders and the resulting properties of granules. However, because there is no solvent involved in melt granulation and properties of polymeric binders are largely dependent on processing temperature, thermomechanical properties of polymers become more relevant to granulation. The polymeric binders that may be used in the melt granulation method could have different glass transition temperatures and, therefore, variable melt viscosity at processing temperature. Also, there could be a possibility of partial miscibilization of drug with the melted polymer that may influence the viscosity of the polymer and the drug-polymer interaction at the specific processing temperature.[9]

A series of papers published in the literature describe the results of a detailed investigation on thermomechanical properties of cellulosic,[10,11] PVP-based,[12] and methacrylate[13] polymers during melt extrusion. The studies relate to the development of solid dispersions for poorly water-soluble drugs by melt extrusion. However, the preparation of solid dispersion by melt extrusion is quite different from melt granulation using twin screw extruder. In general, solid dispersions utilize more than 60% polymer, the API is miscibilized in the polymer at high temperature, and the molten material is extruded from the twin screw extruder as strands that solidifies at room temperature. On the other hand, in case of melt granulation, only about 10% polymer is mixed with the API and the mixture is extruded through a melt extruder at a temperature above the glass transition temperature (T_g) of the polymer but below the melting temperature of API. At the granulation temperature, the drug substance remains as dry powder while the polymer converts into the rubbery state, and granules are produced by the high shear energy imparted by the extruder to such a drug-polymer mixture. To our knowledge, a complete screening of polymeric binders for twin screw melt granulation has not been reported in the literature. Therefore, our objective in this study was to investigate the suitability of various polymeric binders at low concentration ($\leq$10% wt/wt) for twin screw melt granulation of poorly compactible drugs.

As mentioned above, the processing temperature during melt granulation is above the T_g of polymeric binders but below the melting point of API for the powders to remain solid. In this investigation, the 2 poorly compactible drugs, metformin hydrochloride and acetaminophen, with over a 50°C difference in melting points were selected. It was expected that the processing temperatures of acetaminophen and metformin hydrochloride having melting points of 169°C and 222°C, respectively, would be different and, under those conditions, the same polymers might behave differently. Thus, the use of these model drugs would provide an opportunity to comprehensively study the effect of processing temperature and polymer properties on melt granulation. In addition, blends of drug and polymer were also roller compacted and the granules produced were compared with those granulated by twin screw melt extruder. Roller compaction has lesser number of unit operations than wet granulation and, in recent years, it has become more popular than wet granulation.[14] For this reason, a comparison between twin screw melt granulation and roller compaction may provide a better insight into whether these 2 dry granulation methods have any advantage over one another.

Materials and Methods

Materials

Metformin hydrochloride USP was obtained from Harman Finochem Ltd. (Maharashtra, India), and acetaminophen was purchased from Sigma-Aldrich (St. Louis, MO). Table 1 lists all polymers used in this study along with their chemical names, trade names, manufacturers, glass transition temperatures, melting points in case of crystalline polymers, and onsets of possible thermal degradation. It should be noted that the detailed analysis of the stability of different polymers at high temperatures applicable to melt extrusion has not been reported in the literature. In several studies,[10-13] the onset of weight loss during thermogravimetric (TG) analysis was considered as the onset of potential degradation of the polymer. The same was also used in Table 1, which shows that onsets of possible degradation of all PVP, HPC, hydroxypropyl methylcellulose (HPMC) and acrylate-based polymers, except for Kollidon® 30 and Eudragit® L100-55, are much higher than the highest processing temperature of 180°C used in the present investigation. Although the onset temperatures for Kollidon 30 and Eudragit L100-55 were slightly lower (171°C and 176°C, respectively), a close examination of the TG scans indicated that any weight loss and, therefore, the possibility of degradation at 180°C was very small. HPC is a semicrystalline material exhibiting complex thermal and thermomechanical events with T_g at ~19°C and a possible melt at ~200°C.[15] Poloxamers and polyethylene oxide used were crystalline. Melting temperatures of these materials were reported in Handbook of Pharmaceutical Excipients,[16] and their degradation temperatures[17-19] were also reported to be higher than the melt granulation temperatures used in the present investigation. All polymers were donated by their respective manufacturers.

Methods

Powder Blending

Metformin hydrochloride by itself has a low moisture sorption capability[20] and is a free flowing powder. However, due to its high water solubility, it is prone to make solid bridges between particles even in the presence of small amount of moisture, resulting in powder lumps or solid blocks over time. It is essential to mill or