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Application of melt granulation technology to enhance stability of a moisture sensitive immediate-release drug product

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ABSTRACT

The preparation of tablets by the melt granulation process was investigated to enhance chemical stability of a highly water-soluble drug substance, dipeptidylpeptidase IV (DPP-IV) inhibitor (Compound **I**), that is susceptible to degradation in presence of moisture. Melt granulation with a lipophilic binder (hydrogenated castor oil; Cutina HR®) improved the stability of the drug, while still maintaining immediate-release characteristics of the drug product. The drug to binder ratio was shown to impact the degradation behavior of the drug product. With higher binder levels, the sensitivity of the drug to degradation under humidity conditions decreased. It is postulated that the lipophilic binder coated drug particles at the surface protecting them from the influence of moisture. The granules had good flow properties and good compressibility and tablets prepared from them exhibited low weight variation and low friability.

1. Introduction

Many moisture sensitive therapeutic compounds are difficult to formulate into commercially deliverable compositions because of their incompatibility with excipients that contain high intrinsic moisture and/or have a high propensity for moisture uptake during long-term accelerated stress stability conditions (Serajuddin, 1999). Pharmaceutical excipients used for solid formulation for moisture sensitive drugs influence the degradation rate of active pharmaceutical ingredients (Du and Hoag, 2001). The physical and chemical properties of pharmaceutical solids, such as powder flow, compaction, dissolution, stability upon storage, processing into formulations and final product packaging, are critically dependent on the moisture content (Kontny and Zografi, 1995). This article describes how the melt granulation technology was used to enhanced stability of a dipeptidylpeptidase IV inhibitor, Compound **I**, by minimizing the contact with water as well as by modulating moisture sorption and desorption properties of the drug substace in the product.

Melt granulation is a size enlargement process in which the addition of a binder that melts or softens at relatively low temperatures is used to achieve agglomeration of solid particles in the formulation (Evrard et al., 1999). The process utilizes materials that are effective as granulating agents when they are in the softened or molten state. Cooling of the agglomerated powder and the resultant solidification of the molten materials complete the granulation process. Thomsen et al. (1994) proposed that materials melting in the range of 45–100 °C are suitable binders for melt granulation. The method is gaining increased popularity as an alternative to conventional granulation methods, such as wet granulation, roller compaction, fluid-bed granulation, etc., and there are numerous reports in the literature on the application of melt granulation in drug product development as well as on different granulating agents used and various techniques applied during the process (Kidokoro et al., 2002, 2003; Passerini et al., 2002; Perissutti et al., 2003; Royce et al., 1996; Tan et al., 2006; Vilhelmsen and Schaefer, 2005; Vilhelmsen et al., 2005; Walker et al., 2005; Young et al., 2002) Furthermore, by selecting suitable binders, the melt granulation may be used to prepare controlled release granules (Grassi et al., 2003; Hamdani et al., 2002; Maejima et al., 1998; Theis and Kleinebudde, 1999; Zhang and Schwartz, 2003; Voinovich et al., 2000). Many different hydrophobic excipients (e.g., stearic acid, mono-, di- and tri-glycerides, glyceryl behenate, hydrogenated castor oil, etc.) have been employed in preparing controlled release granules. The melt granulation process has also been applied to enhance compressibility pharmaceutical excipients, such as lactose and microcrystalline cellulose, for their enhanced tabletting properties (Gohel and Jogani, 2003)). The method may also find

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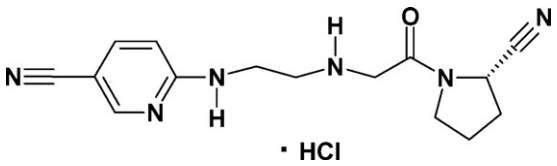

Fig. 1. Compound **I** ([S]-1-[2-(5-cyano-2-pyridinylamino)ethylamino]acetyl-2-pyrolidine carbonitrile monohydrochloride).

application in the continuous processing of solid dosage forms (Keleb et al., 2002). However, there are no reports in the literature where the melt granulation was used to enhance stability of drug substances in dosage forms, especially of moisture sensitive compounds.

The aim of this study was to evaluate melt granulation and the influence of a lipophilic binder to improve the stability of a moisture sensitive drug for an immediate-release dosage form. The following factors have been investigated: drug to binder ratio, binder type, and comparison to dry granulation process. The effects of binders on processing properties, degradation levels, dissolution, and tablet properties were also determined.

2. Materials and methods

2.1. Materials

The drug substance, [S]-1-[2-(5-cyano-2-pyridinylamino)ethylamino]acetyl-2-pyrolidine carbonitrile monohydrochloride (Compound **I**) was synthesized by Novartis Pharma AG, Basel, Switzerland. The structure of the compound is given in Fig. 1. Hydrogenated castor oil (Cutina® HR, Henkel International, Dusseldorf, Germany) and stearic acid, NF (J.T. Baker Inc., Phillipsburg, NJ) were used as low-melting lipophilic binders. Hydrogenated castor oil was also used as the lubricant. Lactose spray dried, NF (Fast Flo®, Foremost Ingredient Group, Baraboo, WI) was used as a diluent and crospovidone XL (Polyplasdone®, International Specialty Products, Wayne, NJ) as a disintegrant. Talc USP (Mallinckrodt, Phillipsburg, NJ) was used as an anti-adherent in the dry granulation formulation. Microcrystalline cellulose (Avicel® PH-101, FMC Corporation, Philadelphia, PA), which has high intrinsic moisture level, was used externally to challenge the formulations.

2.2. Characterization of drug substance

The morphology of Compound **I** was examined by the scanning electron microscopy (SEM) at 2000× magnification using a Joel 6301-FXV (JEOL USA, Inc., Peabody, MA) scanning electron microscope. The crystallinity of the drug substance was determined by X-ray diffraction performed on a Scintag diffractometer, model XDS2000 (Scintag Inc., Cupertino, CA).

2.3. Characterization of melt granulation

The morphology of the melt granules was also examined using SEM at 2000× magnification. The melting behavior of the lipophilic binder was estimated by TA4200 2910 differential scanning calorimeter (DSC) (TA Instruments, New Castle, Delaware). The samples were heated at the rate of 10 °C/min to temperatures above the melting temperature of the melt component and/or drug substance and then cooled at 5 °C/min to 20 °C. Heating the samples to a temperature at least 10 °C higher than the melting point and then rapidly cooling and solidifying avoided the effects of previous thermal history (Schaefer et al., 1993).

Table 1
Composition of 5-mg tablet of Compound **I** prepared by melt granulation using Cutina HR.

Ingredients	Amount/tablet, mg	% per unit
Compound **I**[a]	5.6	3.7
Cutina HR[b]	20.0	13.3
Spray-dried lactose	114.4	76.3
Crospovidone XL	7.0	4.7
Cutina HR[c]	3.0	2.0
Total core weight	150.0	100

[a] 1.12 mg of HCl salt is equivalent to 1.0 mg of the free base.
[b] Melt granulation component.
[c] Lubricant component.

2.4. Characterization of tablets

The tablet friability test was performed using a Distek DF-3 friabilator (North Brunswick, NJ) with 20 tablets at 100 drops and the tablet disintegration was performed using a USP apparatus with 1000 ml of deionized water at 37 °C. The moisture content of tablets was measured by Karl Fischer titration using Metrohm 701 KF Titrino (Metrohm Ltd., Switzerland) titrator equipped with a Kinematica Polytron PT 2100 homogenizer (Kinematica AG, Switzerland) and Hydranal Composite-5 as titrant. Assay and chemical degradation were determined by using gradient HPLC with UV detection at 254 nm and using external standard calibration method. The dissolution testing of tablets was performed over 30 min using the USP 24 Dissolution Apparatus 2 with 0.01N HCl, 500 ml, at a paddle speed at 50 RPM.

2.5. Formulations

Hydrogenated castor oil (Cutina HR) or stearic acid was used as the melt granulating material at various levels. In one series of experiments, the concentration of the drug substance to melt component ratio was varied from 1:0.5 to 1:4 to evaluate the effect of lipophilic binder on degradation. The spray-dried lactose comprised the bulk of the formulation while the crospovidone XL was used as the disintegrant and Cutina HR was used as the lubricant in all formulations. One representative formulation containing Cutina HR as the melt component is presented in Table 1. For comparison, a dry granulation formulation without the melt component was also developed and is shown in Table 2. In this formulation, talc was added as an anti-adherent.

2.6. Melt granulation

Granules were prepared in a 10-l laboratory scale top-driven high shear mixer (Collette Gral, Denmark) equipped with a water and steam jacket. Both the drug substance and the lipophilic binder (Cutina HR) were passed though a No. 25-mesh screen prior to charging the mixer. Mixer loading for the granulations was 1 kg or approximately 67% of the mixer volume. The materials were mixed for 5 min at the setting 1 with no heat and the

Table 2
Dry granulation formulation for 5 mg tablets of Compound **I**.

Ingredients	Amount/tablet, mg	% per unit
Compound **I**[a]	5.6	3.7
Spray-dried lactose	129.4	86.3
Crospovidone XL	7.0	4.7
Talc, USP	5.0	3.3
Cutina HR	3.0	2.0
Total core weight	150.0	100

[a] 1.12 mg of HCl salt is equivalent to 1.0 mg of the free base.

chopper off. Cutina HR has a softening temperature around 65 °C and a melting range of 85–87 °C. Differential scanning calorimetry (DSC) was utilized to investigate interactions between the components.

Granulations were prepared by raising the jacket temperature to approximately 85 °C. The applied heat and the heat of friction generated during mixing caused the softening or melting of the binder to form agglomerates with the drug substance. Since the binder was added in powder form to the starting materials at ambient temperature followed by heating above the melting point of the binder, the temperature of the mixture was increased by the heating jacket (Kinget and Kemel, 1985) along with the heat of friction (McTaggart et al., 1984; Flanders et al., 1987). Therefore, the impeller and chopper speeds were set on low. The choice of a low impeller speed was supported by the preliminary experiments conducted in the 1-quart KG-5 high shear mixer and literature references, which indicated that smaller granules could be generated at lower impeller speeds with little or no lumping due in part to the homogeneous distribution of binder during granulation (McTaggart et al., 1984; Schaefer et al., 1990). The product temperature is likely to affect the agglomeration process because both the density and the viscosity of the molten binder is dependent on temperature (Schaefer et al., 1990).

The product temperature was monitored with a hand-held Raytec® IR temperature sensor (Raytec Americas, Missouri City, TX) through a port hole in the mixer lid instead of opening the lid in order to minimize cooling of the mass. The power consumption was monitored by using a high shear mixer retrofitted with strain gauges in impeller shaft and a Metropolitan® MGM mixer granulator module system (Metropolitan Computing Corporation, East Hanover, NJ). The granulation endpoint was determined when the rising power consumption and torque values peaked. Mixing was interrupted during the granulation process to scrape the bowl and inspect granules. Adhesion of the granules to the sides of the mixing bowl, which is common for hydrophobic melt granulations (McTaggart et al., 1984; Schaefer et al., 1993), was observed in all batches. Immediately after the granulation endpoint was reached, the mixer was stopped and cold water was allowed to circulate through the jacket. Since the fast cooling of melt granules was reported to have a negative effect on drug release (Flanders et al., 1987), the contents of the mixing bowl were discharged and the warm granules were cooled at room temperature by spreading them out on trays before milling. Granules were milled through a No. 35 mesh screen using an oscillator mill (Frewitt Ltd., Fribourg, Germany). The milled granules were blended with the external phase using a diffusion blender (Patterson-Kelley, East Stroudsburg, PA) for 200 rotations and 50 additional rotations for lubrication. The blend was subsequently tabletted using a rotary tablet press (Oystar Manesty, Knowsley, UK).

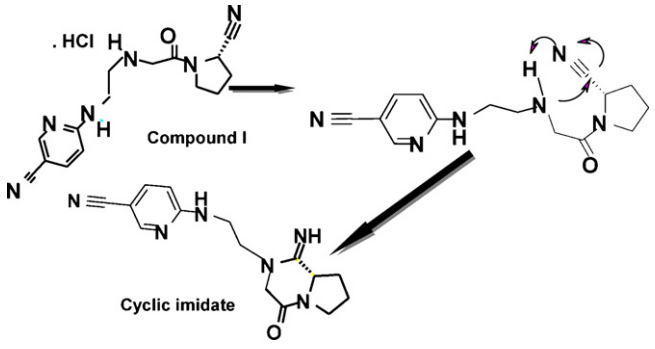

Fig. 2. Degradation pathway of Compound **I** forming cyclic imidate as the major product.

2.7. Dry granulation

Compound **I** dry granulation formulation was prepared by a conventional dry blending process. The materials were blended using a diffusion blender with the same amount of blend rotations as the melt granulation formulation and subsequently tabletted using a Manesty Beta rotary tablet press. In this formulation, spray-dried lactose was used as the main diluent and crospovidone XL was added as the disintegrant. Talc and Cutina HR were, respectively, used as anti-adherent and lubricant.

3. Results and discussion

3.1. Drug substance properties

The drug substance exists as a hemihydrate crystalline monohydrochloride salt (theoretical water content of 2.4%) which is slightly hygroscopic at ≤75% relative humidity (RH) under ambient room temperature (25 °C). At >75% RH, the drug substance absorbs significant amounts of moisture with subsequent deliquescence. It was used as a fine powder composed of thin plates with a very low bulk density of 0.1 g/cc and poor flow characteristics. The compound has a high aqueous solubility of >100 mg/ml in water at 25 °C and a log *P* value of −1.8 between octanol and water at 25 °C. The drug substance undergoes degradation in presence of water. Also, excipients that contain high or appreciable equilibrium moisture content (>5%) at 25 °C and 75% RH adversely impact the stability of the compound. A 4-week drug-excipient compatibility screening study by storing binary mixtures at 25 °C/60% RH and 40 °C/75% RH showed that some degree of stability was obtained only with a limited number of standard excipients (lactose, crospovidone, talc, hydrogenated castor oil, stearic acid, and titanium dioxide).

Compound **I** was found to be unstable in solution with 52.2% degradation after 3 days at 50 °C in pH 1 buffer. The solution stability decreases with increasing pH. Under both acidic and basic conditions, the major degradation product was the cyclic imidate (CI) and the main degradation pathway was hydrolysis. The degradation pathway is illustrated in Fig. 2. It was also the primary degradation pathway in solid state in presence of moisture.

3.2. Melt granule properties

A number of papers have been published showing that the process variables (impeller speed, mixing time, and jacket temperature) and the amount of binder have major influences on characteristics of the granules obtained by melt granulation (Passerini et al., 2002; Perissutti et al., 2003; Schaefer et al., 1990; Vilhelmsen and Schaefer, 2005; Vilhelmsen et al., 2005).

The DSC heating scans of Cutina HR, the cycled Cutina HR and a mixture of Cutina HR with the drug substance are shown in Fig. 3. As can be seen, Cutina HR has a complex melting behavior as it melts over a relatively wide range of temperature showing at least three endothermic peaks at approximately 60, 79 and 86 °C, respectively. In comparison, the cycled Cutina HR material shows a slight difference in the scan as the material begins to soften and/or partially melt. The differences might be due to solid–solid transformations during heating and subsequent cooling of the Cutina HR. The DSC scan of the mixture show that the melting point of Cutina (~86 °C) and the drug substance (~167 °C) do not interfere with each other.

The influence of melting and rheological properties of the binder on the granulation process in high shear mixers can be understood better by considering the granule formation as well as the impeller motor power; the later permits better control of the granule size and of the granulation endpoint during the granulation process (Evrard

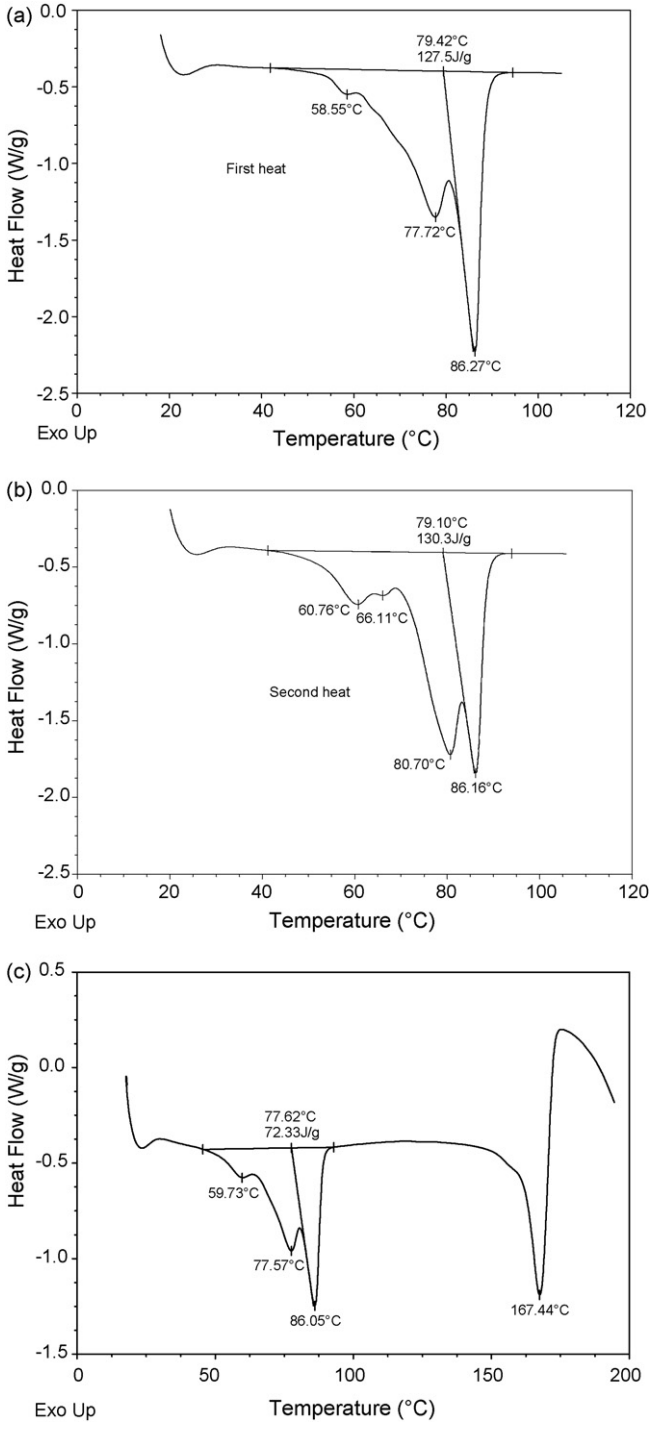

Fig. 3. DSC heating scans obtained from (a) Cutina HR (first heating), (b) cycled Cutina HR (second heating) and (c) mixture of drug substance and Cutina HR.

et al., 1999). Other investigators also found that the main factors influencing granule properties were the amount and viscosity of the molten binder, the particle size of the starting material, the speed of the impeller and the addition of a sieving procedure prior to cooling of the granules (Kinget and Kemel, 1985; Passerini et al., 2002; Seo and Shaefer, 2001; Vilhelmsen et al., 2005; Vilhelmsen and Schaefer, 2005).

The melt granulation process was evaluated by the time taken to achieve granulation, the temperature at which granulation occurred, the torque that was generated, the granule size determined by sieve analysis by crushing the cooled granulate through

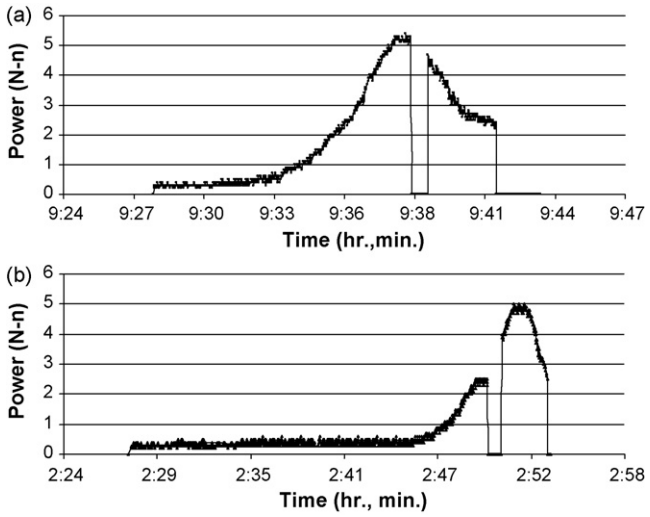

Fig. 4. Power consumption curves for melt granulation endpoint for (a) 1:4 and (b) 1:1 ratios of drug substance to lipophilic binder (Cutina HR).

a 500 micron screen and the dissolution properties of the end product. The effect of lipophilic binder concentration on end point detection, process time and power consumption can be seen in Fig. 4. As the lipophilic binder begins to soften, the power consumption or torque curve begins to increase until it peaks indicating the endpoint of the granulation. The power consumption curves also show the interruption during the granulation process to scrape the bowl and inspect granules approximately 2 min before the granulation endpoint. An increase in drug substance to binder concentration from 1:4 ratio (Fig. 4a) to 1:1 ratio (Fig. 4b) increased the granulation time from approximately 14 to 26 min.

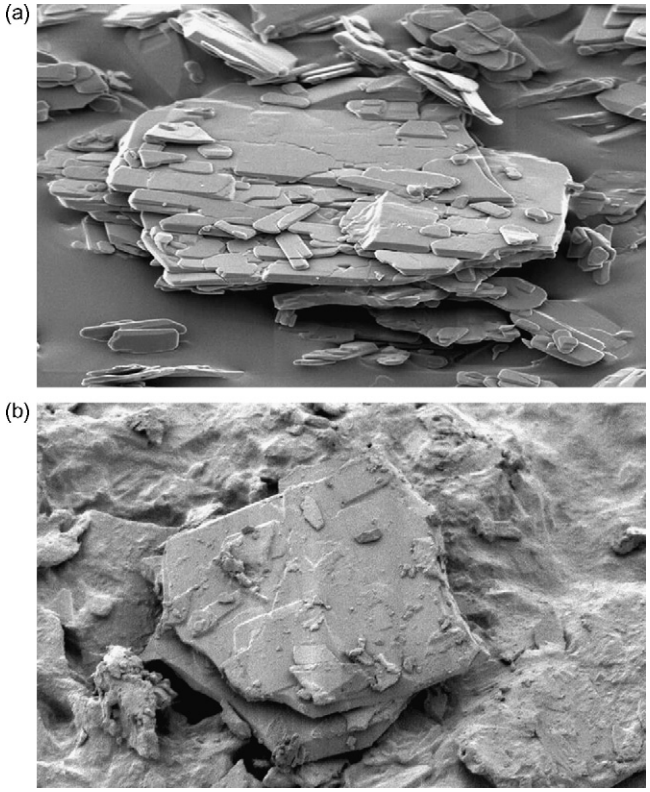

Fig. 5. Scanning electron microscopy images of (a) drug substance crystal and (b) melt granules. The magnification is 2000×.

Table 3
Comparison of melt granulation process (1:4 drug to binder ratio) to dry granulation for 5-mg tablets packaged in HDPE bottles with induction seals.

Granulation process	Time	Storage condition	Cyclic imidate (CI) (%)
Cutina HR MG	Initial		0.09
	1 month	25 °C/60% RH	0.12
	1 month	40 °C/75% RH	0.31
Stearic acid MG	Initial		0.09
	1 month	25 °C/60% RH	0.13
	1 month	40 °C/75% RH	0.34
Dry granulation	Initial		0.12
	1 month	25 °C/60% RH	0.18
	1 month	40 °C/75% RH	0.81

Table 4
Evaluation of various binder levels.

Ratio of DS: Cutina:Avicel	Time	Storage condition	CI (%)
Formulation 1	Initial		0.06
1:0:1 (dry blend)	4 weeks	40 °C/75%RH	3.04
Formulation 2	Initial		0.07
1:0.5:1	4 weeks	40 °C/75%RH	1.80
Formulation 3	Initial		0.07
1:1:1	4 weeks	40 °C/75%RH	1.56
Formulation 4	Initial		0.07
1:2:1	4 weeks	40 °C/75%RH	1.45
Formulation 5	Initial		0.07
1:4:1	4 weeks	40 °C/75%RH	1.13

The morphology of Compound **I** and the melt granules was examined using SEM. The morphology of the samples are shown in Fig. 5, where Fig. 5a shows that the drug substance exists as thin plates of single crystals and Fig. 5b shows melt granules at a drug substance to melt component 1:0.5 ratio. It is still possible to see the single crystal within the melt granulation suggesting only a light coating of the lipophilic binder, thus, protecting the particle from moisture while still maintaining the high solubility and immediate-release characteristics of the crystal.

The active substance and binder ratios of 1:1 and 1:4 were also evaluated. With higher binder levels, the sensitivity of the drug to degradation further decreased. The powder agglomeration promoted by the low temperature melting point binder also improved the poor flow properties of the drug.

To assess whether the goal of improving the stability of the moisture sensitive drug substance was reached, degradation levels of 5-mg tablets prepared by melt granulation using Cutina HR and stearic acid were compared to those prepared by dry granulation (Table 3). To reduce the dilution of drug substance with excipients, and thereby minimize the degradation, a tablet weight of 150 mg was selected. The initial water content in the drug substance was 0.1% (w/w) for all batches as determined by the Karl–Fischer analysis. When compared to melt granulation (1:4 ratio of drug substance to melt component formulation), the cyclic imidate (CI) level of the dry granulation was clearly the highest at 0.81% compared to 0.31% of the Cutina HR melt granulation when stored for 1 month at 40 °C/75% RH. The formulation containing strearic acid as the melt component was comparable to the Cutina HR melt granulation formulation with a 0.34% CI level.

Table 6
Physical properties of the immediate-release drug product.

Parameter	Cutina HR MG	Stearic acid MG	Dry granulation
Tablet size (mm)	7	7	7
Hardness (Kp)	3.5	4.0	6.4
Thickness (mm)	4.04	4.09	3.72
Friability, % (100 drops-20 units)	0.33	0.30	0.33
Disintegration time (min:s)	2:30	1:30	2:30
Bulk density (g/cc)	0.43	0.45	NT
Tap density (g/cc)	0.58	0.55	NT

To further evaluate the hypothesis that coating of drug particles by the binder was responsible for stabilization of the drug in tablets, formulations containing different drug substance to binder ratios were studied. As early compatability results showed that the drug substance is incompatible with excipients with high equilibrium moisture content, microcrystalline cellulose (~5% intrinsic moisture) was also added to challenge the melt granulation formulations. Formulations containing drug:binder:microcrystallinecellulose (Avicel) ratios of 1:0:1–1:4:1 were placed in stability chambers at 40°/75%RH for 4 weeks in HDPE bottles with induction seal (Table 4). The stability data show a 3-fold reduction in the degradation level (CI) when the binder concentration is increased to the 1:4 ratio.

Long-term stability studies for the selected formulation containing a 1:1 drug substance:Cutina ratio is illustrated in Table 5. The results indicate that degradation levels (specification < 2%) and dissolution release were at acceptable levels up to 4 months at 40°/75%RH stored in HDPE bottles with induction seal. Futhermore, no significant increase in moisture level, as determiend by Karl–Fischer moisture analysis, was observed in the drug product after being stored for 4 months at 40°/75%RH condition. The low moisture uptake was also evident with select samples stored with 1 g of desiccant in each bottle. The desiccant did not provide any significant reduction in degradation levels or moisture levels when stored for 6 months at the 25°/60%RH condition which may be attributed due to low moisture uptake of the hydrophobic coating.

Even for a high solubility compound such as Compound **I**, the addition of a hydrophobic excipient might adversely impact the immediate-release characteristics of the final drug product. In

Table 5
Long-term stability for formulation containing 1:1 drug substance: Cutina ratio.

Conditions	Time	Moisture (KF%)	Assay (%)	Degradation (% CI)	Dissolution in 30 min	
					% Mean	% Min–Max
Initial	0	3.2	100.2	0.11	100.9	99.5–102.7
25 °C/60%RH	4W	3.7	100.4	0.14		
	6M	3.9	101.2	0.33	100.5	99.9–101.7
25 °C/60%RH (with desiccant)	4W	3.4	100.4	0.11		
	6M	3.4	101.1	0.30	99.6	98.3–101.0
30 °C/60%RH	4W	3.6	99.4	0.18		
	6M	4.0	100.3	0.61	100.9	99.4–102.0
40 °C/75%RH	4W	3.5	99.1	0.48	99.0	98.4–99.9
	4M	4.2	98.8	1.44		

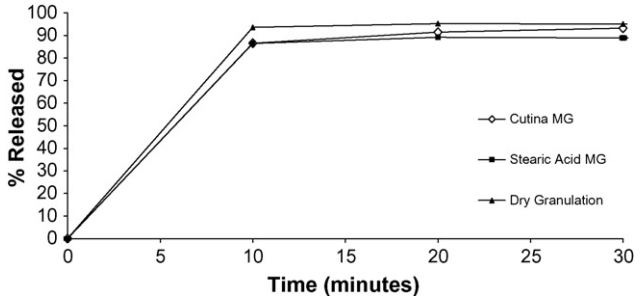

Fig. 6. Dissolution profiles of melt granulation formulations and dry granulation formulation.

order to assess if the goal of immediate-release dissolution rate of melt granulation was reached, in vitro dissolution profiles of melt granulation formulations were compared to dry granulation formulation (Fig. 6). The profiles show that release of the melt granulation formulations is comparable to that of the dry granulation formulation.

A comparison of the physical properties of tablets prepared by melt granulation and dry granulation processes is shown in Table 6. The disintegration times for lipophilic binder formulations and dry granulation formulation are similar. Although the dry granulation produced harder tablets, the tablet friability was comparable to that of tablets prepared by the melt granulation process at corresponding compression forces. The powder agglomeration promoted by the low temperature melting point binder also improved the poor physical properties. The melt granules had good flow characteristics and increased bulk density. Tablets prepared by the melt granules exhibited low weight variation, good compressibility and low tablet friability.

4. Conclusion

The effectivness of the melt granulation of a highly soluble moisture sensitive compound (Compound **I**) with lipophilic binders in stabilizing the compound from hydrolysis was demonstrated in this study. Melt granulation with lipophilic binders (hydrogenated castor oil or stearic acid) improved the stability the drug, while maintaining the immediate-release characteristics of the drug product. The drug to binder ratio was shown to impact the degradation behavior of the drug in the final drug product. With higher binder levels the sensitivity of the drug to degradation in presence of moisture decreased. The powder agglomeration promoted by the low temperature melting point binder also improved the poor physical properties of the drug substance. The melt granulation of moisture sensitive, high solubility compounds using hydrophobic binders can thus be utilized to enhance the stability of drug products.

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