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RESEARCH ARTICLE

Formulation and process design for a solid dosage form containing a spray-dried amorphous dispersion of ibipinabant

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Abstract

Amorphous forms of poorly soluble drugs are more frequently being incorporated into solid dispersions for administration and extensive research has led to a reasonable understanding of how these dispersions, although still kinetically unstable, improve stability relative to the pure amorphous form. There remains however a paucity of literature describing the effects on such solid dispersions of subsequent processing into solid dosage forms such as tablets. This paper addresses this area by looking at the effects of the addition of common excipients and different manufacturing routes on the stability of a spray-dried dispersion (SDD) of the cannabinoid CB-1 antagonist, ibipinabant. A marked difference in physical stability of tablets was seen with the different fillers with microcrystalline cellulose (MCC) giving the best stability profile. It was found that minimising the number of compression steps led to improved formulation stability with a direct compression process giving the best results. Increased levels of crystallinity were seen in coated tablets most likely due to the exposure of the amorphous matrix to moisture and heat during the coating process. DSIMS analysis of the SDD particles indicated increased levels of polymer on the surface.

Keywords: Amorphous, spray-dried dispersion, crystallinity, physical stability, direct compression, roller compaction, tablet, coating, excipients, lactose, mannitol, microcrystalline cellulose

Introduction

This paper describes the formulation and process development of an amorphous form of a poorly-soluble drug compound which focussed on maximising its physical stability. Use of the high-energy amorphous form is one strategy which has been widely explored to reduce the variability and improve the bioavailability of poorly-soluble drugs. These tend to have higher rates of dissolution and kinetic solubilities compared to the corresponding crystalline form, due to the absence of an organised crystal lattice which requires energy to overcome and bring the drug into solution.[1] However, such amorphous forms have the disadvantage of presenting a risk of conversion to the more stable crystalline form over time.[2] Such crystallisation can have serious adverse effects on critical quality attributes of the final drug product, in particular its dissolution, leading to reduced bioavailability in the patient. Therefore, amorphous forms are usually presented as solid dispersions to stabilise them.[3]

The area of physical stability of amorphous solid dispersions is complicated and even their method of preparation can have a large influence.[4] There has been extensive investigation of this area which has led to a reasonable understanding of such systems.[5–8] However, such solid dispersions are not, in themselves, suitable for large-scale commercial manufacture and typically require combination with excipients followed by compression into a tablet. Therefore, although the solid dispersion may stabilise the amorphous form, careful formulation design and process control is needed to prevent thermodynamic instability during processing and subsequent storage. Such instability can arise from interactions between excipients and the amorphous dispersion. In addition, compression, heat and exposure to

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moisture, which can occur at different stages on the way to a coated solid dosage form, are all known risk factors for promoting physical phase transformations.[9,10] Such factors have been less widely investigated and are the central focus of this paper.

The compound used in this study, ibipinabant (BMS-646256), is a selective cannabinoid receptor-1 (CB-1) antagonist explored for the treatment of obesity and diabetes. It is a BCS class II compound with a partition coefficient (log $P_{O/W}$) of 5.01. Aqueous solubility is very poor with levels of less than 0.05 μg/mL detected at 25°C after 24 h of equilibration (below the quantitation limit of the HPLC assay). The molecule behaves as a neutral species with no experimental pKa values in the pH range 3–11. Due to the non-ionisable nature of the compound, salt formation was not possible and solubility did not vary with pH. To maximise bioavailability, the active pharmaceutical ingredient (API) was micronised but *in vivo* studies indicated that exposure was still relatively low. A solid dispersion of ibipinabant was considered as an alternative approach to improve bioavailability.[11]

Many different stabilising polymers have been used to prepare solid dispersions containing amorphous drug. One of the most widely used materials has been polyvinylpyrrolidone (PVP)[12–19] which in addition to being a hydrophilic polymer also acts as a crystallisation inhibitor; most likely because of its ability to interact with drug molecules limiting their degree of molecular mobility whilst also increasing the overall glass transition temperature (Tg) of the solid dispersion.[20] Surfactants, such as sodium lauryl sulphate (SLS) have also been incorporated into solid dispersions in order to improve wettability and dispersion thus increasing dissolution rate.[20–22] It has also been reported that SLS, along with the water-soluble PVP, can improve drug solubility by preventing uncontrolled crystallisation of the API during the tablet dissolution process.[23] In the case of this particular solid dispersion, SLS was found to lead to a significant increase in dissolution rate.

For ibipinabant, a solution of the API in dichloromethane and ethanol was spray-dried with PVP and SLS to produce an amorphous spray-dried dispersion (SDD). The Tg for the solid dispersion was 132°C compared to 70°C for the pure amorphous drug. Stability study testing on the SDD indicated that it was stable for up to 13 weeks under a variety of common accelerated stability conditions (5°C and 50°C closed, 25°C/60% relative humidity (RH) open and closed). This study aimed to monitor the corresponding physical stability of the SDD when incorporated into a tablet formulation. In this instance, detection of the amorphous component was complicated by the low level of drug (1%) and the presence of other components in the tablet formulation. This study utilised a sensitive Raman analytical method in combination with a discriminating dissolution test to follow the physical stability (amorphous nature) of drug in the presence of excipients in the low-dose formulation.[24]

Practical considerations during the drug development process mean that many decisions have to be made with limited API availability. This study adopted a staged approach to design an optimised formulation utilising material-sparing techniques wherever possible. A previous study had shown that using a combination of microcrystalline cellulose (MCC): lactose as filler in the amorphous tablet led to increases in observed crystallinity during storage at standard stability conditions.[24] The first stage of the current investigation aimed to aid rational formulation selection by assessing the impact of individual fillers on physical stability. In addition to MCC and lactose, mannitol was also included as, in addition to its good compaction properties, it is non-hygroscopic which could be a potential advantage in formulating an amorphous SDD where moisture could lead to stability issues. Finally, the optimum routes of manufacture capable of best retaining the amorphous nature of the formulations were chosen and the influence of ancillary processing and storage conditions on the final solid dosage form determined.

Experimental

Materials

The crystalline form of the drug substance, ibipinabant, 3 - (4 - cholorphenyl) - N- [(4 -chlorophenyl)sulfonyl] - 4,5 - dihydro - N'methyl - 4 - phenyl - 1H - pyrazole - 1 - carboximidamide, was synthesised at Solvay Pharmaceuticals (Weesp, Netherlands). It is a crystalline solid having a melting point of 159°C and a molecular weight of 487.1 (Figure 1).[25] MCC (Avicel®), lactose monohydrate, PVP (Povidone, PVP K-30), croscarmellose sodium (AcDiSol®), magnesium stearate, SLS and silicon dioxide (Syloid 244®) were of compendial grade and were obtained through Bristol-Myers Squibb's Material Management Group. Mannitol (Pearlitol SD 200®) was purchased from Roquette (Lestrem, France). Opadry II (85F Series) and Opadry AMB (aqueous moisture barrier) were supplied by Colorcon (Dartford, UK). Ibipinabant amorphous SDD was manufactured at Bristol–Myers Squibb using a similar process to that previously reported[26,27] and consisted of 20%

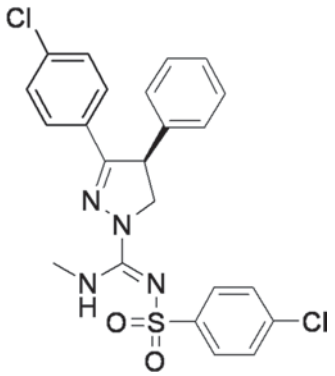

Figure 1. Structure of ibipinabant (SLV-319/BMS-646256).

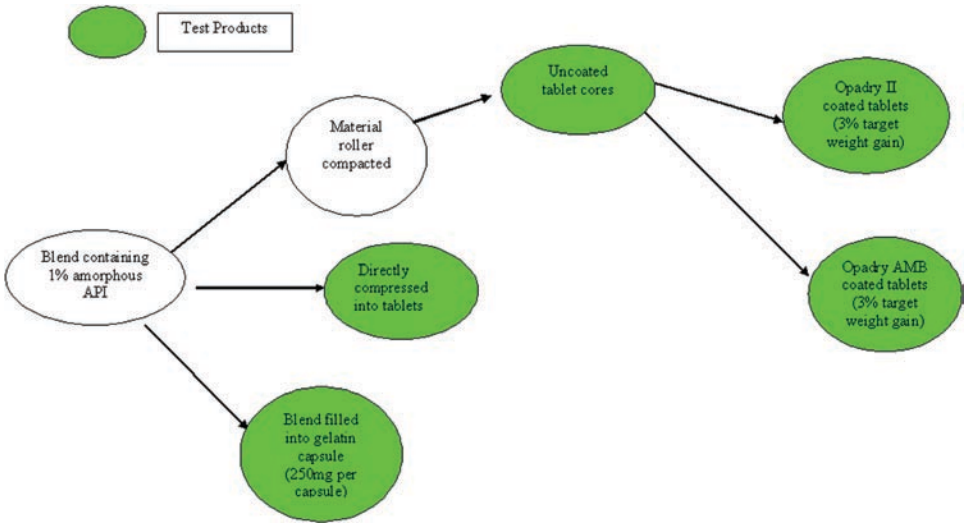

Figure 2. Study plan for processing conditions stability study. (See colour version of this figure online at www.informahealthcare.com/phd)

ibipinabant, 5% SLS and 75% PVP K-30. All drug product lots were manufactured using the same batch of SDD which had a measured particle size (D50) of 6μm. Solvents used were of analytical grade.

Quantitation of crystalline content in amorphous SDD

A quantitative Raman method was developed to detect crystalline content within the amorphous SDD, formulated blends and final solid dosage form. Using multivariate methods this technique could detect crystallinity at levels of ~5% in tablets containing only 1% of API.[24] An FTIR spectrometer (Nicolet Nexus 870, Thermo Fisher) attached with an FT-Raman module was used to collect Raman spectra via Omnic software. Analysis was carried out at room temperature with an air-cooled diode pumped Nd:YAG laser (1064 nm) as the excitation source, CaF_2 beam splitter and indium-gallium arsenide (InGaAs) detector. The laser power was focused on the sample with a power of about 500 mW. Calibration samples (100 mg) were measured in 5-mm diameter NMR tubes. Tablet samples were measured by placing them directly facing the Raman laser. Duplicate measurements were taken in each case. For each spectrum, 256 scans were performed at a resolution of 4 cm^{-1} over the spectral range of 3700–100 cm^{-1} in a 180° scattering configuration in order to provide Raman spectra with a high S/N ratio in combination with well-resolved Raman signals. Sulphur was used as the reference standard to monitor wavenumber accuracy.

Dissolution method

A discriminating dissolution method was developed that demonstrated fast, complete dissolution from an amorphous dosage form but showed slow, incomplete dissolution in the presence of crystalline API.[24] A USP II (paddle) dissolution method at a paddle speed of 65 rpm was used for dissolution testing of formulated prototype capsules and tablets containing amorphous ibipinabant SDD. Tablets were tested using a six station USP II (paddle) dissolution apparatus (Vankel) operating at 65 rpm. Each vessel contained 500 or 1000 mL of the desired medium (pH 6.8 phosphate buffer, 0.075% SLS) maintained at 37°C. The amount of dissolved drug in the dissolution medium was determined by UV spectrometry (Agilent 8543 using Chemstation software) with a flow-through cuvette at a wavelength of 313 nm. The absorbance values of aliquots of the dissolution medium were collected at 5, 10, 20, 30, 45, 60, 90, 120 min. Lack of interference from excipients was confirmed by UV scanning the placebo tablet. Standard calibration curves in the linear BMS-646256 concentration ranges were used to quantify the relative amounts of dissolved drug using the system's internal calculation program (calculated % dissolved). Six tablets were tested.

Formulation stability studies

An initial study investigated the effect of different excipients on tablet stability. Three different filler materials were examined: lactose, MCC and mannitol. The formulation was prepared using a roller compaction process with final tablets having a drug loading of 1% corresponding to 5% w/w SDD per tablet. Tablets also contained filler (85.5% w/w), croscarmellose sodium (5% w/w), SLS (2% w/w), silicon dioxide (2% w/w) and magnesium stearate (0.5% w/w). Tablets were compressed within a hardness range of 10–18 SCU. Dissolution and Raman testing were performed following storage of tablets in closed high-density polyethylene (HDPE) bottles for 3 months at 2–8°C, 25°C/60% RH and 40°C/75% RH. Storage at open conditions was also carried out at 25°C/60% RH.

A further study evaluated selected unit process operations on the stability of the MCC-based formulation only. The influence of compression steps during manufacture was examined by comparing tablets prepared from roller-compacted granules (two compression steps), tablets prepared from a direct compression blend (one compression step) and blend filled directly

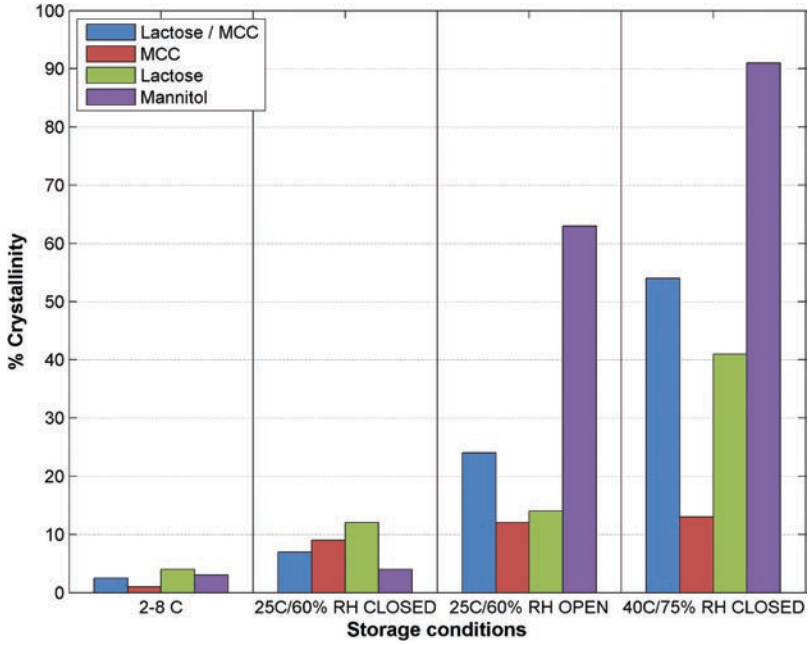

Figure 3. Summary of Raman results for formulations containing different excipients following storage under controlled conditions for 3 months. (See colour version of this figure online at www.informahealthcare.com/phd)

Table 1. Composition of amorphous SDI of ibipinabant tablet

Component	Level (%)
API/PVP/SLS (20:75:5)	5.0
MCC	85.5
Croscarmellose Sodium	5.0
SLS	2.0
Silicon Dioxide	2.0
Magnesium Stearate	0.5

into capsules without compression. The effect of different coating materials was assessed by comparing uncoated tablets to those coated to 3% target weight gain. In addition to an Opadry II coating formulation, Opadry AMB was also evaluated. Opadry AMB was developed for the coating of oral solid-dosage forms that need to be protected from moisture.[28] Analysis was carried out using Raman and dissolution testing following storage of tablets for three months at 30°C/65% RH open and 40°C/75% RH closed. A summary of the study design can be found in Figure 2.

DSIMS analysis

Dynamic secondary ion mass spectrometry (DSIMS) depth profiles were obtained using a method previously described.[29] Prior to analysis, the powder sample was mounted on to the sample holder as a flat bed, pressed into double-sided conducting adhesive tape and given a thin sputter-coating of gold to minimise electrostatic charging during analysis. The depth scales on profiles were estimated, based on a sputter rate calculation. The measure of drug concentration was assessed by comparing the relative secondary ion ratios, allowing differentiation between the different species in the particles.

Results

Filler stability study

Different excipients had a marked effect on the formulation stability (Figure 3). In general, formulations were comparable when stored under more moderate conditions (2–8°C and 25°C/60% RH closed) with low levels of crystallinity seen after three months storage. However, under more challenging conditions, clear differences were visible. In general, the detection of crystalline material increased under storage conditions of higher temperature and humidity with substantial amounts present in all dosage forms analysed after three months at 40°C/75% RH. This is a well known phenomenon as molecular mobility increases with increasing temperature and also in the presence of moisture due to a plasticising effect, increasing the potential for crystallisation.[30–32] In the case of solid dispersions containing PVP an additional factor leading to reduced stability at higher humidity conditions could be due to moisture-induced drug-polymer immiscibility.[33] It is recognised that when formulated into drug product, interaction between water-soluble excipents and PVP at higher RHs could lead to dissolution of excipients and enhanced moisture sorption, and this would be reflected in subtle changes in the moisture uptake profile, which may not be detected using the standard ICH condition used in this study. This will be followed up in future studies.

The increase in crystalline content had a noticeable effect on formulation performance with a good correlation seen between dissolution and Raman results (Figure 4). The fastest and most complete dissolution profiles were seen for tablets with low crystallinity detected by Raman. Slow and incomplete profiles, indicative of the conversion of API from an amorphous to a crystalline

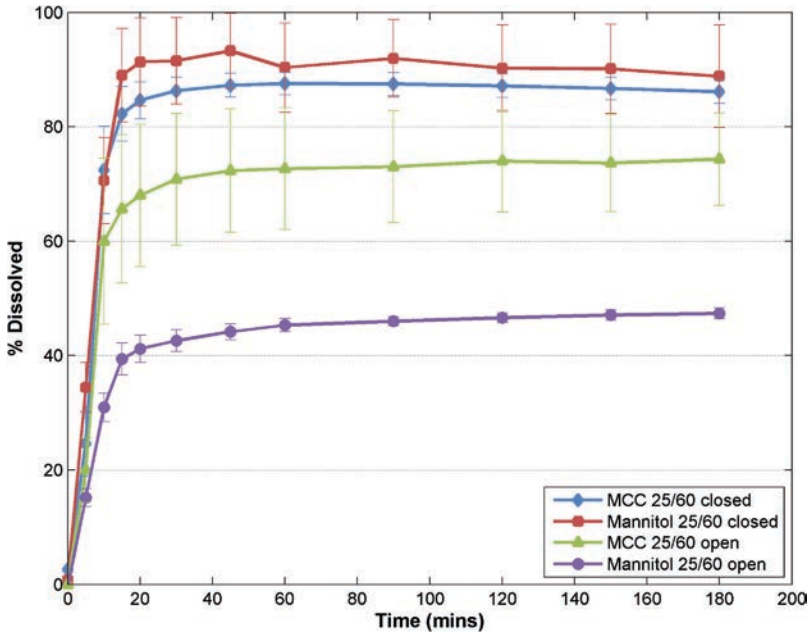

Figure 4. Dissolution results for MCC and mannitol based formulations showing differing profiles (corresponding to differences in crystalline formation) following storage for 3 months at 25°C/60%RH open or closed. (See colour version of this figure online at www.informahealthcare.com/phd)

form, were seen under more stressful storage conditions with samples stored at 40°C/75% RH showing the slowest drug release profiles.

A more surprising finding was the fact that large differences in stability were seen depending on which filler was included in the formulation. Greater physical stability was observed for formulations containing MCC compared to other materials. For example, at the 40°C/75% RH closed condition, greater than 90% crystallinity was detected with the mannitol formulation, compared to just over 10% with the MCC formulation. Such a finding is important when considering the choice of filler within a formulation as in the case of a low-dose formulation, such materials can compose 80–90% of the total tablet weight. Such filler excipients are often regarded as inert materials and if they show no sign of chemical incompatibilities are considered suitable for use. The results from this study show that in the case of formulations containing SDD, there is an increased stability risk and greater care must be taken when choosing all formulation components.

Excipients have been shown in the literature to have effects on polymorphic transformations during wet granulation[34,35] so the potential for excipient-induced physical instability does exist. It has been observed that the negative effects of excipients on stability is exacerbated in formulations with a high excipient: active ratio, as is the case here.[36] With regard to the differences between the various fillers there are a number of factors which could be making a contribution. Mannitol is more crystalline in nature than MCC.[37] It is therefore possible that it could promote the crystallisation process by facilitating the nucleation and propagation crystal growth stages. Indeed, other researchers have used crystalline excipients such as lactose to mitigate unwanted milling-induced amorphisation of a crystalline active, salbutamol.[38]

Another explanation for the differences seen could be due to differences in compaction properties of the different excipients. As MCC is more compressible than lactose or mannitol, it is possible that the higher compression energies introduced into the mannitol system, in order to produce a compact of required hardness, could have promoted crystallisation and physical instability. A related factor is that excipients such as lactose and mannitol deform by brittle fracture whereas MCC compacts primarily by plastic deformation. Therefore, the latter could offer greater mechanical protection from fracture or surface perturbations to the SDD particles, and this protection could limit the tendency to nucleation.[39]

DSIMS analysis was carried out to characterise the relative amounts of the three SDD components close to the particle surface. Comparison of the relative secondary ion ratios, in this case C3N (drug)/CNO (from PVP) indicated increased levels of PVP and relative drug depletion on the surface (Figure 5). This could be evidence of a protective PVP-rich layer which, when breached, could promote physical instability. The beneficial impact of excipients which provide a cushioning action in preventing polymorphic transformations has previously been described in the case of the conversion of amorphous celecoxib to crystalline following tablet compression.[40] Limited stabilisation was noted when carrageenan, a viscoelastic polymer, was physically incorporated into the tablet blend with a greater improvement seen when carrageenan was incorporated into the SDD itself. This latter strategy led to improved physical stability for the amorphous formulation most likely due to its cushioning effect.

Process conditions stability study

Based on these results, a formulation containing MCC as sole filler was selected for further evaluation in a follow-up study (Table 1). This evaluated the effect of processing conditions on physical stability; in particular the theory that compression and other physical manipulation steps during processing can cause physical instability in SDD particles. Analysis showed that formulations manufactured using simpler manufacturing routes i.e. blend in capsule, direct compression, showed lower levels of crystalline conversion compared to tablets prepared using roller-compacted blend (Figure 6). It is possible that the extra compaction and milling step involved in roller compaction could lead to increased mechanical fracture of the SDD particles. Physicochemical transformation of pharmaceutical agents following the administration of mechanical energy is a well-known phenomenon.[41] However, most research has concentrated on the effect of milling on causing unwanted drug phase transitions.[42] However, the phenomenon of compaction force causing such phenomena has also been described.[31]

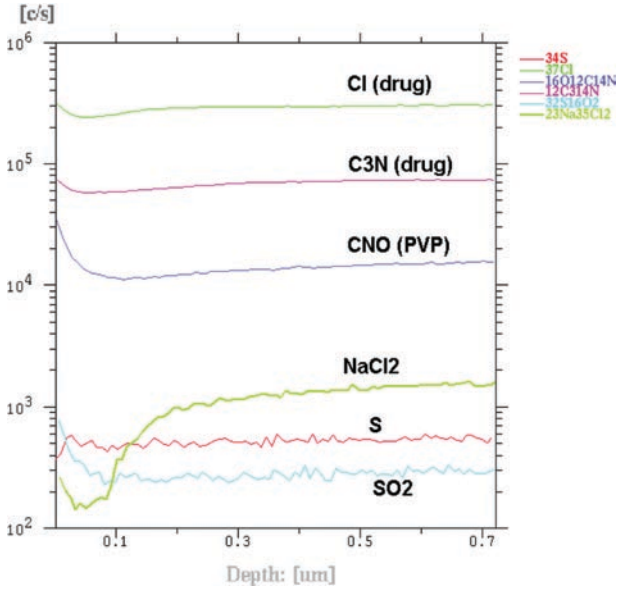

Figure 5. Results from DSIMS depth profiling of the SDD particle. (See colour version of this figure online at www.informahealthcare.com/phd)

Increased levels of crystallinity were seen in coated tablets (Figure 6). Use of a moisture-barrier coating formulation (Opadry AMB) did not result in a noticeable performance improvement. Coating is a necessary step for many potent pharmaceutical dosage forms in order to ensure patient and operator safety. In the case of amorphous dosage forms, care will need to be taken because the coating process may result in the "seeding" of crystals particularly near the tablet surface either through interaction with excipients in the coating formulation or due to the exposure of the amorphous matrix to heat and moisture during the coating process. Once seeded, this can promote instability in the whole tablet. Alternatives could include consideration of organic coating which typically requires lower temperatures with no water being present. Compression and electrostatic coating techniques could also be options.[43,44] The stability of the dosage form was not influenced by temperature (up to 40°C) but available atmospheric moisture influenced observed physical stability. The formulation prepared by direct compression showed undetectable levels of crystalline formation after three months storage at 40°C/75%RH. A combination of packaging which protects from moisture along with careful selection of excipients and processing route can therefore assist in delivering a stable amorphous dosage form.

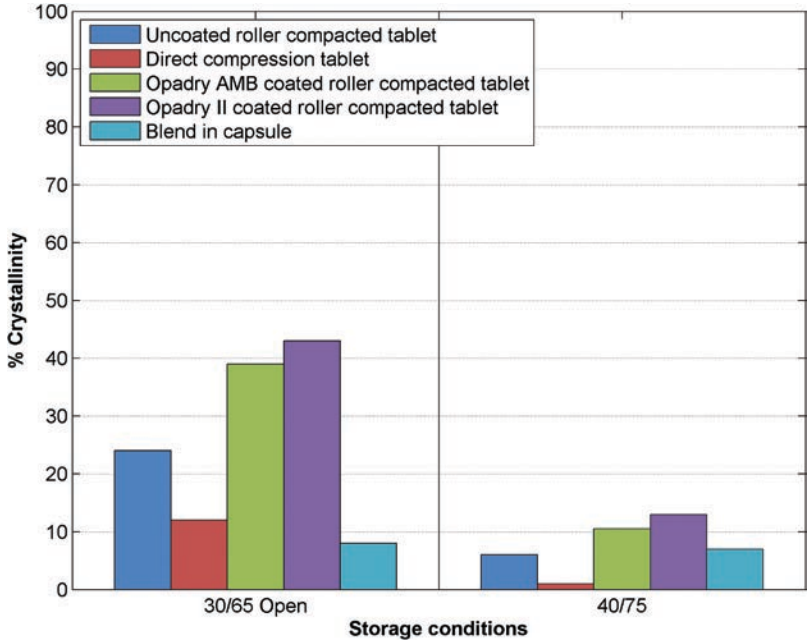

Figure 6. Selected Raman results from formulations manufactured using different processing conditions and stored under controlled conditions for 3 months. (See colour version of this figure online at www.informahealthcare.com/phd)

Conclusions

Quantitative Raman spectroscopy, in combination with a discriminating dissolution method, allowed for rapid and accurate discrimination of the effects of changing excipients and process conditions on the physical stability of low-dose amorphous ibipinabant formulations. Using these techniques, it was found that such variables have a marked influence on the observed final physical stability for an amorphous product. MCC was found to provide distinct benefits over other filler excipients possibly due to its compaction mechanism providing a cushioning effect preventing damage to the SDD particles. Compression, milling and tabletting during the dry granulation process also had a noticeable effect on stability. Direct compression best preserved the amorphous nature. Exposure to moisture, either during storage or as part of the coating process was another risk factor for the generation of unwanted crystalline material.

It can be concluded that the formulation of amorphous SDD requires great care as physical instability can be promoted with the inappropriate choice of excipient or processing route. Studies which give increased mechanistic understanding provide for better informed decisions. This paper has shown that, in the case of this particular compound, there is a scientific (as well as economic rationale) for adopting a direct compression approach for formulations containing amorphous SDD.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Hancock BC, Parks M. What is the true solubility advantage for amorphous pharmaceuticals? Pharm Res 2000;17:397–404.
2. Bhugra C, Pikal MJ. Role of thermodynamic, molecular, and kinetic factors in crystallization from the amorphous state. J Pharm Sci 2008;97:1329–1349.
3. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000;50:47–60.
4. Surana R, Pyne A, Suryanarayanan R. Effect of preparation method on physical properties of amorphous trehalose. Pharm Res 2004;21:1167–1176.
5. Moore MD, Wildfong PLD. Aqueous solubility enhancement through engineering of binary solid composites: Pharmaceutical applications. J Pharm Innovat 2009;4:36–49.
6. Friesen DT, Shanker R, Crew M, Smithey DT, Curatolo WJ, Nightingale JA. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview. Mol Pharm 2008;5:1003–1019.
7. Marsac PJ, Li T, Taylor LS. Estimation of drug-polymer miscibility and solubility in amorphous solid dispersions using experimentally determined interaction parameters. Pharm Res 2009;26:139–151.
8. Marsac PJ, Rumondor AC, Nivens DE, Kestur US, Stanciu L, Taylor LS. Effect of temperature and moisture on the miscibility of amorphous dispersions of felodipine and poly(vinyl pyrrolidone). J Pharm Sci 2010;99:169–185.
9. Chan HK, Grant DJW. Influence of compaction on the intrinsic dissolution rate of modified acetaminophen and adipic acid crystals. Int J Pharm 1989;57:117–124.
10. Morris KR, Griesser UJ, Eckhardt CJ, Stowell JG. Theoretical approaches to physical transformations of active pharmaceutical ingredients during manufacturing processes. Adv Drug Deliv Rev 2001;48:91–114.
11. Ranzani LS, J. F, Galimany F, Santanach A, Gomez-Gomar AM, G. C, Galimany F, Gryczke A. Enhanced in vivo absorption of CB-1 antagonist in rats via solid solutions prepared by hot-melt extrusion. Drug Dev Ind Pharm 2011:DOI: 10.3109/03639045.03632010.03535822.
12. Thybo P, Pedersen BL, Hovgaard L, Holm R, Mullertz A. Characterization and physical stability of spray dried solid dispersions of probucol and PVP-K30. Pharm Dev Technol 2008;13:375–386.
13. Shah J, Vasanti S, Anroop B, Vyas H. Enhancement of dissolution rate of valdecoxib by solid dispersions technique with PVP K 30 & PEG 4000: Preparation and in vitro evaluation. J Incl Phenom Macro 2009;63:69–75.
14. Fini A, Cavallari C, Ospitali F. Raman and thermal analysis of indomethacin/PVP solid dispersion enteric microparticles. Eur J Pharm Biopharm 2008;70:409–420.
15. Thybo P, Kristensen J, Hovgaard L. Characterization and physical stability of tolfenamic acid-PVP K30 solid dispersions. Pharm Dev Technol 2007;12:43–53.
16. Damian F, Blaton N, Desseyn H, Clou K, Augustijns P, Naesens L et al.Solid state properties of pure UC-781 and solid dispersions with polyvinylpyrrolidone (PVP K30). J Pharm Pharmacol 2001;53:1109–1116.
17. Tantishaiyakul V, Kaewnopparat N, Ingkatawornwong S. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone. Int J Pharm 1999;181:143–151.
18. Taylor LS, Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm Res 1997;14:1691–1698.
19. Tantishaiyakul V, Kaewnopparat N, Ingkatawornwong S. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone K-30. Int J Pharm 1996;143:59–66.
20. Kaushal AM, Gupta P, Bansal AK. Amorphous drug delivery systems: molecular aspects, design, and performance. Crit Rev Ther Drug Carrier Syst 2004;21:133–193.
21. Ghebremeskel AN, Vemavarapu C, Lodaya M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: stability testing of selected solid dispersions. Pharm Res 2006;23:1928–1936.
22. Ghebremeskel AN, Vemavarapu C, Lodaya M. Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: selection of polymer-surfactant combinations using solubility parameters and testing the processability. Int J Pharm 2007;328:119–129.
23. de Waard H, Hinrichs WL, Visser MR, Bologna C, Frijlink HW. Unexpected differences in dissolution behavior of tablets prepared from solid dispersions with a surfactant physically mixed or incorporated. Int J Pharm 2008;349:66–73.
24. Sinclair W, Leane M, Clarke G, Dennis A, Tobyn M, Timmins P 2011. Physical Stability and Recrystallization Kinetics of Amorphous Ibipinabant Drug Product by FT-Raman Spectroscopy. J Pharm Sci:In Press. DOI: 10.1002/jps.22658.

25. Lange JH, Coolen HK, van Stuivenberg HH, Dijksman JA, Herremans AH, Ronken E et al. Synthesis, biological properties, and molecular modeling investigations of novel 3,4-diarylpyrazolines as potent and selective CB(1) cannabinoid receptor antagonists. J Med Chem 2004;47:627–643.
26. Fakes MG, Vakkalagadda BJ, Qian F, Desikan S, Gandhi RB, Lai C et al. Enhancement of oral bioavailability of an HIV-attachment inhibitor by nanosizing and amorphous formulation approaches. Int J Pharm 2009;370:167–174.
27. Tobyn M, Brown J, Dennis AB, Fakes M, Gao Q, Gamble J et al. Amorphous drug-PVP dispersions: application of theoretical, thermal and spectroscopic analytical techniques to the study of a molecule with intermolecular bonds in both the crystalline and pure amorphous state. J Pharm Sci 2009;98:3456–3468.
28. Jordan MP. 1999. Moisture barrier film coating composition, method, and coated form. In Office USP, editor, ed., US: BPSI Holdings, Inc. US Patent No 5, 885, 617.
29. Fowler CE, Gracia L, Edwards MI, Brown A, Rees GD. Fluoride penetration from toothpastes into incipient enamel erosive lesions investigated using dynamic secondary ion mass spectrometry. J Clin Dent 2009;20:186–191.
30. Hancock BC, Zografi G. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. Pharm Res 1994;11:471–477.
31. Xie Y, Tao W, Morrison H, Chiu R, Jona J, Fang J et al. Quantitative determination of solid-state forms of a pharmaceutical development compound in drug substance and tablets. Int J Pharm 2008;362:29–36.
32. Weuts I, Kempen D, Verreck G, Decorte A, Heymans K, Peeters J et al. Study of the physicochemical properties and stability of solid dispersions of loperamide and PEG6000 prepared by spray drying. Eur J Pharm Biopharm 2005;59:119–126.
33. Rumondor AC, Stanford LA, Taylor LS. Effects of polymer type and storage relative humidity on the kinetics of felodipine crystallization from amorphous solid dispersions. Pharm Res 2009;26:2599–2606.
34. Airaksinen S, Karjalainen M, Kivikero N, Westermarck S, Shevchenko A, Rantanen J. Excipient selection can significantly affect solid-state phase transformation in formula wet granulation. AAPS PharmSciTech 2005; 6:E311–322.
35. Airaksinen S, Luukkonen P, Jørgensen A, Karjalainen M, Rantanen J, Yliruusi J. Effects of excipients on hydrate formation in wet masses containing theophylline. J Pharm Sci 2003;92: 516–528.
36. Ku MS, Dulin W. A biopharmaceutical classification-based Right-First-Time formulation approach to reduce human pharmacokinetic variability and project cycle time from First-In-Human to clinical Proof-Of-Concept. Pharm Dev Technol 2010; 1–18. DOI: 10.3109/10837450.2010.535826.
37. Hulse WL, Forbes RT, Bonner MC, Getrost M. The characterization and comparison of spray-dried mannitol samples. Drug Dev Ind Pharm 2009;35:712–718.
38. Balani PN, Ng WK, Tan RB, Chan SY. Influence of excipients in comilling on mitigating milling-induced amorphization or structural disorder of crystalline pharmaceutical actives. J Pharm Sci 2010;99:2462–2474.
39. Schmidt AG, Wartewig S, Picker KM. Potential of carrageenans to protect drugs from polymorphic transformation. Eur J Pharm Biopharm 2003;56:101–110.
40. Dhumal RS, Shimpi SL, Paradkar AR. Development of spray-dried co-precipitate of amorphous celecoxib containing storage and compression stabilizers. Acta Pharm 2007;57:287–300.
41. Colombo I, Grassi G, Grassi M. Drug mechanochemical activation. J Pharm Sci 2009;98:3961–3986.
42. Descamps M, Willart JF, Dudognon E, Caron V. Transformation of pharmaceutical compounds upon milling and comilling: the role of T(g). J Pharm Sci 2007;96:1398–1407.
43. Randolph Sanders J, Mason PJ, Whiteman M. Digital Fabrication 2005 - Final Program and Proceedings, Baltimore, MD, 2005, pp. 148–152.
44. Lin KH, Lin SY, Li MJ. Compression forces and amount of outer coating layer affecting the time-controlled disintegration of the compression-coated tablets prepared by direct compression with micronized ethylcellulose. J Pharm Sci 2001;90: 2005–2009.