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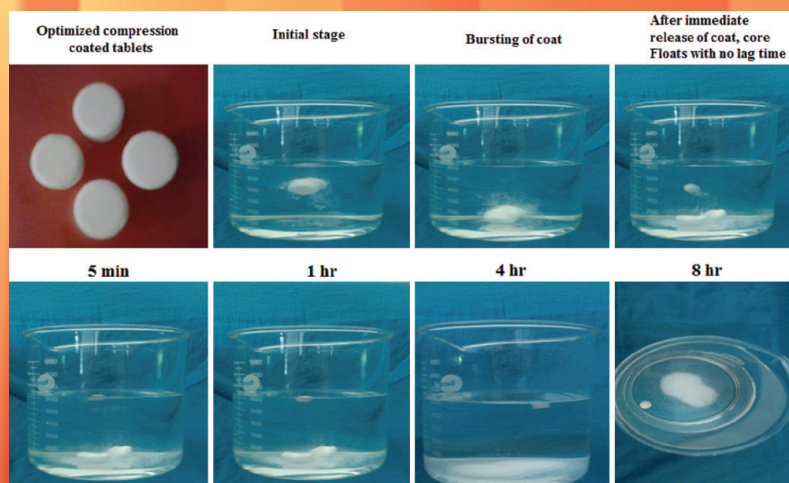


Figure showing the images of compression coated formulation

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Fast disintegrating crystalline solid dispersions of simvastatin for incorporation into orodispersible tablets

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Abstract

Aim: Spray dried solid dispersion (SDP) of crystalline simvastatin (SIM) in a fast disintegrating matrix of superdisintegrants was studied as a method to enhance SIM dispersibility, rheology, compactibility and compressibility for incorporation into orodispersible tablets (ODTs). **Materials and Methods:** The superdisintegrants investigated were croscopovidone (CP), sodium starch glycollate (SSG) and calcium silicate (CS) were spray dried with simvastatin to form SDPs. **Results:** The SDPs were characterized and the median particle size of SDPs was similar or greater than the SIM, contributing to good rheology of SDPs, while the low bulk density of SDPs indicated a high compactibility. Interestingly electron micrographs for SDPs showed a CP or CS carrier coating of the SIM crystals, contributing to its rheology. Thermal analysis and X-ray diffraction confirmed that SIM was crystalline in the SDPs and no interaction between SIM and any of the carrier(s) was shown by Fourier transform-infra red. Drug content analysis showed a SIM content of 90-95% in SDPs containing CP or CS, while a higher SIM content of 143% was found in SDP containing SSG. When formulated as ODTs, blend containing SIM SDPs in CP showed ease of tableting, regardless of the turret speed. In comparison, tablet blend consisting of a physical mix (PM) of SIM and CP could only be tableted at the lower turret speed of 7 rpm. ODTs formulated using SIM SDPs in CP showed a higher extent of dissolution, compared to the ODTs containing corresponding PM or the commercially available SIM Zocor® tablets (ANOVA, $P < 0.05$). **Conclusion:** SDP using disintegrants as carriers may offer an alternative formulation approach for ODTs of poorly soluble drugs.

Key words: Crystallinity, orodispersible tablets, simvastatin, solid dispersion, spray drying, superdisintegrants

INTRODUCTION

Simvastatin (SIM), a cholesterol lowering drug, is a lipophilic drug with a log P value of 4 with aqueous solubility of $\sim 30 \mu\text{g/ml}$.^[1,2] It is categorized as a class II drug according to the biopharmaceutics classification system because it has a low solubility and high permeability. As for compounds with low aqueous solubility, SIM exhibits low and variable bioavailability associated with dissolution rate-limited absorption after oral administration.^[1,3,4]

SIM is one of many pharmaceutical actives which have solubility limitation. It is estimated that ~ 40 -50% of drugs

current or in development have poor solubility and numerous formulation strategies have been developed and used over the years. A commonly used approach is to formulate solid dispersions (SDPs) of the poorly soluble drug using a carrier such as polyvinylpyrrolidone in which the drug is molecularly dispersed.^[5,6] Other strategies include particle size reduction,^[7] although size reduction methods can cause solid state modifications, complexation with cyclodextrins,^[8] formation of amorphous forms by spray drying.^[9,10]

Attempts to increase the solubility of SIM by formulating amorphous SDPs of SIM with hydrophilic polymers such as PVP or HPMC by spray drying, using organic solvents resulted in an increase in solubility and dissolution rate of SIM.^[9,11] A major disadvantage of amorphous materials however is their instability and reversion to crystallinity and to prevent conversion to the crystalline form, demands strict storage conditions of temperature and humidity.

Orodispersible tablets (ODTs) have gained popularity amongst the wide population, including the pediatrics, geriatrics and patients suffering from dysphagia and emesis.^[12] According to the Food and Drug Administration^[13] ODTs should have an *in vitro* DT of 30 s or less. Poorly soluble drugs may however increase the disintegrating time of ODT as due to their hydrophobicity, they can reduce the wetting and water uptake ability of ODTs.^[14,15] This can be overcome by adding wetting agents and/or surfactants

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to the blend to encourage wetting. However, addition of surfactant/wetting agent may result in processing difficulties such as sticking during tableting as most of the surfactants are in liquid or wax form or have low melting point.

A possible way of enhancing the disintegration time (DT) of ODTs containing poorly soluble drugs by formulating the poorly soluble crystalline drugs in a hydrophilic disintegrating matrix as a spray dried (SD) SDP for subsequent tableting as ODTs. Such a rapid disintegrating SDP of the drug will provide an intimate mix of the drug and disintegrant which will enhance wetting, disintegration and dissolution of the drug. In addition as SD product is often associated with enhanced rheology, this should allow for a direct compression material for ease and consistency of further processing into ODTs.^[16] Superdisintegrants such as croscopovidone (CP) (Kollidon® CL), croscarmellose sodium (Ac-Di-Sol) and sodium starch glycolate (SSG) (Explotab® or Primogel®) have been shown to enhance dissolution of itraconazole (log *P* = 5.66) and nifedipine (log *P* = 2.5) attributed to amorphous formation of the drug during formation of SDPs by wet massing or solvent deposition.^[17,18] Amorphous drugs however are associated with reversion to original crystal, crystal growth or phase separation which is accompanied by a decrease in solubility and dissolution.^[19]

During the formation of SDPs, active pharmaceutical ingredients (APIs) can also undergo phase transformations into other metastable polymorphic form with different physicochemical properties. SIM is reported to occur in three different crystalline forms; conventionally available and most stable form I, orthorhombic which is stable from -1.15°C to the fusion temperature (138.85-142.85°C), form II, orthorhombic stable in the range -41.15°C- -1.15°C and form III, assigned as monoclinic and stable below -41.15°C.^[20] At room temperature (RT) however there polymorphs should not be present and are not expected to form from spray drying at high temperature of ≥90°C.

The aim of this study was to maintain the drug in its crystalline form for retention of its stability during product shelf life, while providing a disintegrating matrix to facilitate its dissolution and hence absorption. We formulated crystalline SIM as a SD SDP using the hydrophilic superdisintegrant carriers; CP (Kollidon® CL-SF), SSG (Explotab®) and calcium silicate (CS) and were subsequently mixed with the direct compression sugar, mannitol and tableted as ODTs. An aqueous dispersion was used to minimize drug solubilization and hence conversion of the drug to amorphous form and forming a crystalline SDP [Figure 1]. The superdisintegrants selected were previously shown by us to promote wetting and water uptake into ODTs.^[15]

MATERIALS AND METHODS

Materials

SIM was bought from Leo Chemical, Mongkok, Kowloon, Hong Kong, China, Mannitol 200 (Pardeck®) was a gift from Merck

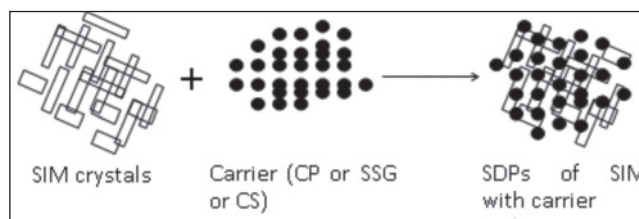


Figure 1: Schematic representation of the structure of rapidly disintegrating solid dispersion

KGaA, Norman Lauder, Dublin, CP (Kollidon® CL-SF) was a gift from BASF, Cheshire, UK, SSG (Explotab®) was a gift from JRS Pharma, Germany, CS (RxCIPIENTS™ FM1000) was a gift from Huber Engineered, Finland, magnesium stearate was a gift from JMB, UK. Zocor® tablets were bought from United Drug (Dublin, Ireland).

Preparation of SD SDPs

SDPs were prepared by a conventional spray drying technique using a Buchi Mini Spray Dryer B290 (Switzerland) operated in an open loop. SIM alone or in combination with the carriers, CP or SSG or CS was formulated as an aqueous dispersion (feed dispersion) containing 7.5% w/v of total solids at drug to carrier weight ratios 1:1. The feed dispersions (100 ml) at a feed flow rate of 4.0 ml/min were sprayed in the spray drying chamber using compressed air flowing at 414 NL/h. The inlet drying temperature of 90°C was used with air aspirator setting of 40 m³/h. The spray drying outlet temperature was monitored and was found to be in the range 29-44°C.

The resultant SDPs were recovered, weighed and the percentage product yield was calculated using the below equation 1.

$$\text{Percentage Yield} = \left(\frac{\text{weight of solid dispersions}}{\text{weight of drug + carrier}} \right) \times 100$$

Particle size analysis

The particle size of SIM API, carriers, aqueous dispersions of SIM API and SIM in combination with various carriers and SDPs was measured in triplicates by laser diffraction analysis using a Mastersizer 2000 (Malvern Instruments, U.K.). For measurements in the dry state, dry dispersion attachment (Scirocco™) was used, whereas when in aqueous dispersion, the wet dispersion cell of the Mastersizer 2000 (Hydro 2000SM; Malvern Instruments, Malvern, Worcestershire, UK) was used.^[21] The particle size median diameter (D50%) and size distribution (Span) are reported.

Morphology

The surface morphology of SIM, carriers and SIM SDPs were examined using a Variable Pressure Field Emission Scanning Electron Microscope (Hitachi S-4300 USA). Samples were prepared as previously described by Ramtoola *et al.*,^[21] the gold coated specimen was then photographed at an appropriate magnification of ×200 to 25 kx.

Rheology

Carrs compressibility index (CI) value was used as an indicator of the rheological property of SIM API and SIM SDPs. CI was derived from the bulk and tapped density values using equation 2. The bulk and the tapped density (1000 taps) of each sample was determined in triplicates as described in the British Pharmacopoeia (BP)^[22] using a tapped density volumeter (Copley Instruments, Nottingham, UK). The CI was interpreted by the generally accepted scale of flowability outlined in the BP 2008.

$$CI = 100 \times \frac{\rho_{\text{tapped}} - \rho_{\text{bulk}}}{\rho_{\text{tapped}}}$$

Where ρ_{tapped} and ρ_{bulk} are tapped and bulk densities, respectively.

Solid state analysis

Differential scanning calorimetry (DSC)

DSC was conducted using a DSC Q100 V9.0 Build 275 (TA Instruments, New Castle, Delaware, USA). The analysis was performed under a purge of dry nitrogen (50 ml/min). Aliquots of SIM or SDPs or physical mix (PM) of SIM and carrier, were accurately weighed (1-5 mg) and sealed in aluminum pans. Samples were heated by a ramp method to a temperature of 200°C at a heating rate of 10°C/min. An empty aluminum pan was utilized as the reference. Calibration and validation of the instrument was performed with an indium reference standard prior to the start of the study.

Hot stage microscopy (HSM)

HSM was carried out using an Olympus BX51 (Olympus Optical Co. Ltd., Tokyo, Japan) polarizing optical microscope equipped with a Linkam LTS350 hot stage (Linkam Scientific Instruments Ltd., Surrey England) and Linkam TMS94 programmable temperature controller. SIM API or SDP were placed on a glass slide and gradually heated at 5°C/min until 200°C. Photographs were taken at RT and near the melting point of SIM, using Olympus C-7070 Digital Camera (7.1 megapixel, 4× optical zoom).

X-ray powder diffractometry (XRPD)

The XRPD patterns of SIM, SDPs and PM of SIM and carriers were obtained using a Bruker D8 Discover instrument. Each sample was placed and flattened with a glass slide to obtain a good surface texture and inserted in the cavity of an aluminum sample holder. The sample holder and detector were moved in a circular path during measurement of the powder pattern, to determine the angles of scattered radiation and to reduce preferred sample orientation. The samples were irradiated with monochromatized Ni filtered CuK α anode radiation (01542 nm). Samples were analyzed using a step width of 0.02° and 2 θ between 2° and 40° 2 θ , at ambient temperature.

Fourier transform-infra red (FT-IR)

FT-IR spectra were obtained using a Bruker Tensor 27 FT-IR spectrometer (Bruker Optics, Ettlingen, Germany) equipped with deuterated triglycine sulfate detector. A background scan was performed prior to analysis. The spectra were an average

of 16 scans at a resolution of 4/cm over the frequency range of 4000-400/cm. KBr discs containing SIM, SDPs or PM of SIM and carrier were prepared using a manually operated hydraulic press (Specac, Kent, UK). Analysis of the spectra was performed using the OPUS Data Collection Program (V 1.1). The samples for infrared analysis and the KBr were dried for at least an hour prior to analysis in a drying oven (Specacabinet, Kent, UK) at 32°C \pm 0.5°C.

Formulation and characterization of ODTs

ODTs containing 20 mg SIM/tablet were formulated by weighing and blending the drug, SIM or SIM SDPs equivalent to a dose of 20 mg/unit tablet of 300 mg with Mannitol 200, CP, Raspberry flavor and Mint flavor using a plastic resealable polythene bag [Table 1]. Magnesium stearate was then added and blended for a further 5 min in a plastic resealable polythene bag. The blend was used to prepare ODTs weighing 300 mg by compression on an 8 station rotary tablet press fitted with 13 mm flat beveled edge toolings (Riva Piccola, Hampshire, UK). ODTs were characterized for uniformity of weight, hardness, tensile strength (TS), friability, porosity, DT using BP methods and as described by us previously.^[15,23]

Analysis of SIM content

The SIM content of SDPs and tablets was determined using the high performance liquid chromatography (HPLC) analysis as described in the USP^[24] under the section, “USP monographs: SIM tablets.”

An appropriate quantity of the SIM SDP equivalent to 1-2 mg of SIM was accurately weighed or in case of ODT small volume of water was added and swirled to disintegrate and then suitably diluted using the HPLC sample diluting solution (1:4 of water pH 4.0 and acetonitrile) to obtain a concentration of about 0.1-0.2 mg/ml of SIM. The solution was filtered and analyzed for drug content using HPLC analysis using a Perkin Elmer Series 200 Model S200 A/S and a 250 mm \times 4.6 mm, Gemini 5 μ C18 column, at 45°C. The mobile phase used consisted of acetonitrile and buffer pH 4.5 solution at 65:35 v/v. A flow rate of 1.5 ml/min was used and analysis was carried out by ultraviolet (UV) spectrophotometer at 238 nm. A total volume of 20 μ l of the extracted SIM sample was injected by autosampler and the assayed content of the drug was calculated using the calibration equation generated from the standards prepared within the concentration range of 0.0156-0.25 mg/ml.

Table 1: Formulation composition of ODTs

Formulation	ODT001 (% w/w)	ODT002 (% w/w)
Solid dispersion (SIM: Kollidon® CL-SF)	13.34	—
SIM	—	6.67
Parateck® Mannitol 200	84.56	86.23
Kollidon® CL-SF	—	5.00
Magnesium stearate	0.50	0.50
Raspberry	0.80	0.80
Mint	0.80	0.80
Total blend (% w/w)	100.00	100.00

ODTs: Orodispersible tablets, SIM: Simvastatin

Drug release from ODTs

SIM release from the ODTs was determined in the dissolution apparatus 2 and the procedure outlined in the BP 2008^[22] under the monograph of SIM tablets was used. The dissolution medium used was 900 ml of 0.01 M sodium dihydrogen orthophosphate containing 0.5% w/v of sodium dodecyl sulfate and adjusted to pH 7.0 with 1M sodium hydroxide. The paddle was set to rotate at 50 rpm. Samples (20 ml) were withdrawn at various time points of 5, 10, 20, 30 and 60 min, filtered using 0.45 µm filter and 10 ml of the filtrate added to 0.1 g pre-washed manganese (IV) oxide and the absorbance was measured at 247 nm and 257 nm by UV visible (UV-vis) spectrophotometer (Libra S22 UV-vis Spectrophotometer, Biochrom, UK). The total content of SIM in the medium was calculated using the differences in absorbance at 247 nm and at 257 nm and using the absorbance values from SIM standards. Withdrawn samples were replaced using fresh dissolution medium. Results are presented as the cumulative amount of drug release.

Statistical analysis

The results obtained are expressed as a mean \pm standard deviation calculated using Microsoft excel (Redmond, WA, USA) software. Statistical analysis was performed using SPSS version 15.0 for windows (SPSS, Inc., Chicago, IL, USA). *Post hoc* analysis was performed using Tukey. $P < 0.05$ was considered to be statistically significant.

RESULTS AND DISCUSSION

Characterization of SIM SDPs

The particle size of SIM API, carriers and corresponding aqueous dispersions is illustrated in Table 2. The median particle size (D50%) of SIM API was small at 7.39 µm and was similar to the D50% of CP and CS at 4.06 and 11.73 µm respectively. SSG showed a D50% of 42.66 µm. The size distribution across all samples was narrow as indicated by the span value of 1.20-2.32. When dispersed in water, SIM API showed about 2-fold increase in D50% to 16.08 µm [Table 2]. A similar, 2-3-fold increase in median particle size was observed when SIM was dispersed with the carriers, CP or SSG or CS, in an aqueous medium.

Aqueous dispersion of SIM API showed highest very high span value of 8.67, indicating aggregates/clumping of SIM crystals as expected from its hydrophobicity. The addition of any hydrophilic carriers to the aqueous dispersion of SIM resulted in lower span values probably related to the dispersing effect of hydrophilic carriers on SIM. In general, narrow size distribution of the API contributes to a homogenous drug distribution during formulation hence resulting in the formulation with uniform drug content.^[25]

The D50% of SD SIM was found to be similar to SIM API at \sim 7 µm. The D50% of SDPs was in the range 5.76-12.09 µm, similar to the D50% of SIM and/or the carriers [Table 3]. The D50% of SDP with SSG was found to be similar to SIM API or SD SIM despite the significant difference ($P < 0.005$) between the D50% of respective aqueous feed dispersions [Tables 2 and 3].

Table 2: Particle size analysis of drug/carriers only and corresponding aqueous dispersions of SIM only and in combination with carrier

API/ carrier	D50% (µm)	Span	Aqueous dispersions	D50% (µm)	Span
SIM	7.39±0.03	1.71±0.01	SIM only	16.08±1.78	8.67±1.65
CP	11.73±0.03	2.32±0.04	SIM+CP	25.15±0.39	2.43±0.05
SSG	42.66±0.41	1.20±0.01	SIM+SSG	104.2±3.94	2.79±0.42
CS	4.06±0.16	1.89±0.04	SIM+CS	12.75±0.41	2.53±0.04

SIM: Simvastatin, CP: Crospovidone, SSG: Sodium starch glycolate, CS: Calcium silicate, API: Active pharmaceutical ingredient

Table 3: Characteristics of solid SD SIM and SIM SDPs

Drug/SDP	D50% (µm)	Span	Assayed SIM content (%)	SDP yield (%)
SIM (SD)	7.19±0.07	1.72±0.15	N/A	60.40
SDP CP	12.09±0.55	1.68±0.03	45.36±0.11	21.07
SDP SSG	7.45±0.19	1.89±0.10	71.59±4.79	21.87
SDP CS	5.76±0.42	2.09±0.08	47.89±3.11	27.73

SIM: Simvastatin, SD: Spray dried, SDP: Solid dispersion, CP: Crospovidone, SSG: Sodium starch glycolate, CS: Calcium silicate

The SIM content of SDPs containing CP or CS was found to be 45.36% and 47.89%, respectively, i.e., close to the 1:1 starting ratio of the drug to carrier [Table 3]. For SDP formulated with SSG, the SIM content was higher at 71.59%, at nearly a 3:1 ratio of the drug to carrier, indicating loss of the carrier [Table 3]. The high SIM content in SDP containing SSG can also be related to the loss of the swelled SSG during spray drying, possibly through settling of the swelled SSG in the feed solution and resulting in a SIM rich feed suspension. A similar observation was reported by Gonnissen *et al.*,^[16] when spray drying aqueous suspensions containing SSG. The authors reported that swelled SSG could have led to the formation of comparatively coarser gel-like droplets during spray drying, leading to its preferential deposition on the spray dryer chamber walls.

Product recovery of SD SIM was high at 60.40% [Table 3], while for SDPs was 3-fold lower at 21.07-27.73%, probably related to the higher viscosity of aqueous dispersions and hence larger residual feed dispersions from the aqueous dispersions.

Morphology of SIM SDPs

Scanning electron microscopy (SEM) showed SIM API to be elongated crystals [Figure 2a], which was in agreement with the observations of Jun *et al.*^[26] SD SIM also showed similar crystals although these appear to be shorter as a result of fragmentation probably due to exposure to the shear forces encountered during spray drying [Figure 2b]. The morphology of the carriers ranged from irregular, crumpled to nearly smooth surface microparticulate morphology for the SSG as expected for starch granules [Figure 2c, e and g]. Corresponding SDPs of carriers and SIM showed morphology similar to the carrier and interestingly a carrier coated SIM crystals for SDPs with CP and CS was observed [Figure 2d and h]. For SSG, the

SDP showed the presence of unchanged SIM crystals and SSG granules [Figure 2f]. This morphology for SSG and SIM suggests a non-homogenous mixture which indicates that non-homogenous dispersions of SSG and SIM resulting in settling of the larger swollen SSG particles from the aqueous feed dispersions resulting in the higher SIM content observed for this SDP [Table 3].

Rheology of SIM SDPs

From the data in Table 4, SDP of SIM with CP or CS showed excellent rheological property, greatly improved compared to that of SIM API. This could be due to the coating of the API by CP and CS [Figure 2d and h]. A free-flowing rheology of the product is a critical parameter for formulation of uniform weight tablets particularly at high tableting speeds.^[27] The Carr's index and rheology of SDP containing SSG was similar to that of SIM API. This was related to the non-homogeneity and higher SIM content of this SDP [Tables 3, 4 and Figure 2f]. The lowest bulk density of the SDP containing CP suggests that particles could fit more compactly,^[28] while the SDP consisting of CS were found to show highest density amongst all SDP and SIM API, probably related to its small D50% of 5.76 μm .

Solid state analysis of SDPs

DSC

DSC thermograms (T_g) of SIM API and SD SIM were found to be similar, a sharp endotherm at 140.01°C [Figure 3a (a and c)],

close to the literature value of 139.5°C,^[26] corresponding to the melting point of the crystalline SIM. On cooling and reheating, SIM API or SIM SD showed a glass transition at 34.70°C corresponding to the T_g of the drug and was similar to the literature value of 35°C [Figure 3A (b and d)].^[9] Spray drying aqueous dispersions of SIM API therefore did not result in changes to its crystalline form.

DSC T_g of the single component of the superdisintegrant carrier CP or SSG exhibited a broad endotherm typical of amorphous substances [Figure 3b (a) and c (a)].^[29] On the other hand, DSC T_g for CS, over the temperature range scanned, did not reveal any event [Figure 3d (a)] as was reported by Sharma *et al.*^[30] This phenomenon was related to its relatively high melting point of 1700°C (Huber Engineered materials).

The DSC T_gs of the physical mixtures (PM) of SIM with CP or SSG showed two endothermic events attributed to each single component [Figure 3b (c) and c (c)]. For PM CS and SIM, one event corresponding to the melting point of SIM API was obtained as was expected since CS did not show any thermal event over the temperature range of the thermal analysis [Figure 3d (c)]. Therefore, it suggests that SIM and CP or SSG or CS when physically mixed forms a heterogeneous mix, with no interaction or changes in crystallinity of SIM.

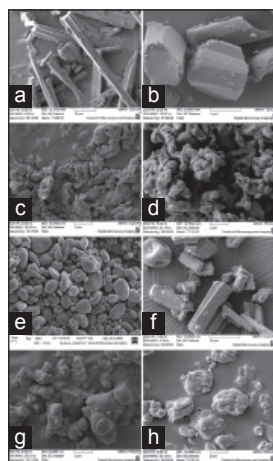


Figure 2: Scanning electron microscopy images of (a) simvastatin (SIM) active pharmaceutical ingredient, (b) spray dried SIM, (c) crospovidone (CP), (d) solid dispersion (SDP) of SIM with CP, (e) sodium starch glycolate (SSG), (f) SDP of SIM with SSG, (g) calcium silicate (CS), (h) SDP of SIM with CS

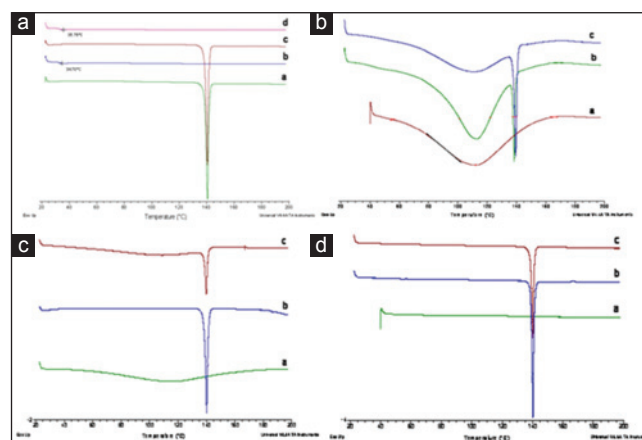


Figure 3: Differential scanning calorimetry thermogram of simvastatin (SIM) (a): (a) active pharmaceutical ingredient (API) (b) API (rerun after cooling) (c) spray dried (SD) (d) SD (rerun after cooling), (b): (a) crospovidone (CP) (b) solid dispersion SIM:CP (c) physical mix (PM) SIM:CP, (c): (a) sodium starch glycolate (SSG), (b) SD SIM:SSG (c) PM SIM:SSG, (d): (a) calcium silicate (CS), (b) SD SIM:CS (c) PM SIM:CS

Table 4: Density and rheological property of SIM and its SDP

Carrier/SDP	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Flowability ^a
SIM	0.2169±0.02	0.2629±0.02	17.50	Fair
SDP CP	0.1172±0.00	0.1230±0.00	4.72	Excellent
SDP SSG	0.1598±0.01	0.1976±0.01	19.13	Fair
SDP CS	0.2500±0.00	0.2778±0.00	10.01	Excellent

^aCarr's index flowability – ≤10%: Excellent, 11–15%: Good, 16–20%: Fair, 21–25%: Poor, fluid, 26–31%: Poor, cohesive, 32–73%: Very poor, >38%: Extremely poor.

SIM: Simvastatin, SDP: Solid dispersion, CP: Crospovidone, SSG: Sodium starch glycolate, CS: Calcium silicate

T_{gs} of SD SDP of SIM with CP and CS [Figure 3b (b) and d (b)] were similar to the T_{gs} of their corresponding PM confirming crystallinity of SIM and no interaction with SIM and the carrier used. On the other hand, SD SDP of SIM with SSG [Figure 3c (b)] showed one endothermic event corresponding to the crystalline SIM in its original polymorphic form. The absence of an endothermic peak corresponding to the SSG component was related to the loss of SSG during spray drying resulting in SIM rich SDP and the heterogenous SDP formed as shown in Figure 2f.

HSM

HSM was performed to visualize SDP morphology, morphological changes of the SDP on heating and to support the DSC analysis. HSM images for the SIM API in Figure 4a and SD SIM in Figure 4c showed SIM crystals at RT which are similar in morphology to that observed by SEM [Figure 2a]. At the higher temperature of 130-133°C, the crystals showed onset of melting [Figure 4b and d], which was consistent with that observed by DSC [Figure 3a (a and c)]. HSM images of the SDP of SIM in CP or CS [Figures 4e and i] demonstrated the presence of small sized crystals of SIM at RT as aggregates due to the carrier coating of SIM as was observed by SEM [Figure 2d and h]. As the temperature increased to 130-133°C, the crystals started to melt [Figure 4f and j] confirming the presence of crystalline SIM in the SDP. SDP with SSG [Figure 4g] showed crystalline

SIM as smaller crystals, similar to SD SIM, as observed by SEM [Figure 2f], which melted at the higher temperature of 130-133°C [Figure 4h].

X-ray powder diffraction (XRPD)

XRPD of SIM API and its corresponding PM and SDP with each of the 3 carriers showed the presence of numerous distinct peaks at different diffraction angles of 2 θ , corresponding to those of crystalline SIM [Figure 5], similar to XRD diffraction pattern of SIM reported in the literature.^[26,31] This confirms the presence of crystalline SIM in the SDP.

FT-IR

FT-IR spectrum of the SIM API and each of the 3 carriers, CP, CS and SSG showed characteristic peaks [Figure 6] as reported in the literature.^[9,26,31-35] The spectrum of the PM and SDP of SIM in CP or SSG or CS was found to be a superimposition of the respective individual pure components and did not indicate any interactions occurring between the SIM and carriers. This therefore supports that SIM is present in its original stable crystalline form in these SDPs.^[36]

Formulation and characterization of ODTs

Based on the SDP data observed, SDP with CP showed highest size of 12.09 μ m contributing to the lowest Carr's index and best rheological properties and hence SDP containing CP was used to formulate ODTs and was compared with ODTs prepared using

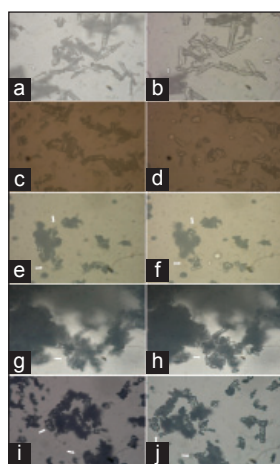


Figure 4: Hot stage microscopy pictures at room temperature (a, c, e, g) and at 130-133°C (b, d, f, h) for simvastatin active pharmaceutical ingredient (a, b), spray dried simvastatin (c, d), solid dispersion of simvastatin in (e, f) croscopidone, (g, h) sodium starch glycollate and (i, j) calcium silicate

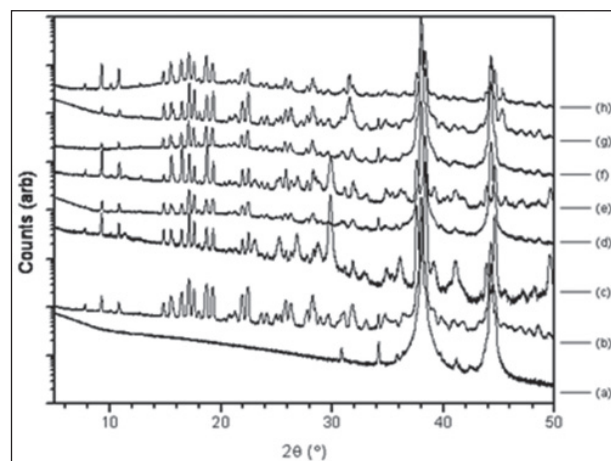


Figure 5: X-ray powder diffraction patterns of (a) background measurement, (b) simvastatin (SIM), physical mix of SIM with (c) calcium silicate (CS), (d) croscopidone (CP), (e) sodium starch glycollate (SSG), solid dispersion of SIM in (f) CS, (g) CP, (h) SSG

Table 5: Characteristics of ODTs prepared using SDP containing CP and a blend of SIM with CP

SIM	Turret speed (rpm)	Weight (mg)	Hardness (N)	TS ¹ N/mm ²	Friability (%)	Porosity (%)	DT (s)	Drug content (%)
SDP SIM:CP	7	304.80±1.22	51.86±3.89	0.1014	0.16	20.88	19.17±6.08	92.91±2.13
	49	296.23±8.46	35.48±9.83	0.0693	0.24	23.48	15.17±3.49	98.95±6.76
Blend SIM:CP	7	303.93±2.66	55.91±4.48	0.1092	0.19	21.85	13.33±3.67	95.55±3.41
	49	283.47±15.6	32.03±9.05	0.0628	Failed	26.02	*	*

*ODTs formed were soft and breaking as they were being compressed, therefore ODTs produced were not sufficient to perform all the characterization tests. SIM: Simvastatin, ODTs: Orodispersible tablets, SDP: Solid dispersion, CP: Croscopidone, DT: Disintegration time, TS: Tensile strength

a blend of SIM with CP. It can be observed from the Table 5 that the characteristics of the ODT containing a blend of SIM with CP, such as weight variation, hardness, TS and friability were similar to that of ODTs containing SDP with CP at the lower turret speed of 7 rpm. No significant difference was found between the DT and assayed drug content of ODTs prepared using SDP containing CP and ODTs prepared using a blend of SIM with CP ($P > 0.05$). Compressibility of a material is measured by its ability to be reduced in volume as a result of an applied pressure.^[37] Hence lower the porosity of the tablets higher is the compressibility of the material. The porosity of ODTs containing SIM SDPs was lower than the tablets containing SIM API indicating the higher compressibility of SIM SDPs compared to SIM API.

Interestingly, at the higher turret speed of 49 rpm, the blend containing SDP of SIM with CP resulted in ODTs with lower weight variation, probably related to a consistent flow properties and hence consistent die filling. In comparison, ODTs prepared from the blend of SIM with CP showed higher weight variation. SD materials are known to have improved flow and compressibility, hence such materials are easier to scale up and tablet at higher speeds. The ODTs containing SDP of SIM with CP also showed lower porosity, higher hardness and TS and were not friable [Table 5]. In contrast ODTs containing the blend of SIM with CP showed poor compressibility reflected by the higher porosity values of these ODTs as well as poor mechanical strengths as shown by their high friability and breaking. Sufficient ODTs could not be produced from this batch to allow all the characterization tests to be carried out.

ODTs containing the SDP of SIM with CP showed a higher dissolution compared to the ODTs containing a blend of SIM with CP and the commercial innovator product, Zocor® (ANOVA, $P < 0.05$) [Figure 7]. Both ODTs showed a much higher release

of SIM of 102.04 ± 2.50 and $94.48 \pm 1.63\%$, respectively at the earlier time point of 5 min compared to $19.27\% \pm 5.32\%$ SIM released from the Zocor® tablets. The lower amount of SIM released from Zocor® can be attributed to its higher DT of 9.08 min as it is a conventional oral tablet compared to the rapid DT of the ODTs at <20 s.

Higher SIM dissolution from ODTs containing ODTs prepared using SDP containing CP compared with ODTs prepared using a blend of SIM with CP ($P < 0.05$) could be related to the intimate mix of disintegrant carrier and SIM in the SDP that may facilitate disintegration to primary SIM particles.

CONCLUSIONS

SDPs of SIM with hydrophilic superdisintegrant carriers CP and CS showed narrow size distribution, excellent rheology and $>90\%$ SIM recovery. Moreover, SIM in the SDP was retained in its original stable crystalline form. No interaction, amorphous formation, polymorphic transition or degradation of SIM following formulation as SDPs in each of the disintegrant carrier used was observed. SDPs with CP showed high compactability and compressibility which are critical parameters for ease of tableting. Tablet blend consisting SDPs with CP showed ease of tableting which was maintained at high tablet turret speed of 49 rpm. In comparison, tablet blend consisting of SIM and CP could only be tableted at the lower speed of 7 rpm.

ODTs formulated using SIM SDP with CP showed a higher extent of dissolution compared to the ODTs containing SIM and CP or the commercially available SIM Zocor® tablets. This was related to the facilitated disintegration of SIM to primary drug particles as a result of the intimate mix of CP and SIM in the SDP. SDPs of hydrophobic crystalline drugs in a hydrophilic superdisintegrant carrier may provide a flowable, compressible, stable and easily scalable direct compression matrix, offering an alternative formulation approach for ODTs of poorly soluble drugs.

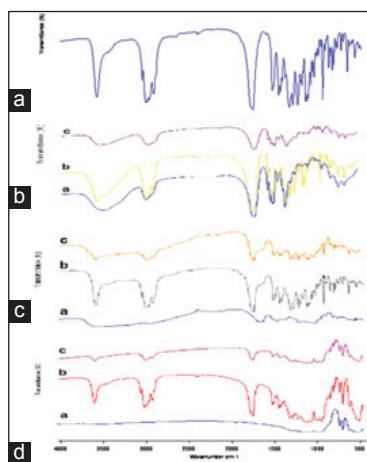


Figure 6: Fourier transform-infra red spectra of (a) simvastatin (SIM) active pharmaceutical ingredient, (b) (a) crospovidone (CP), (b) solid dispersion (SDP) of SIM: CP, (c) physical mix (PM) of SIM:CP, (c) (a) sodium starch glycolate (SSG), (b) SDP of SIM:SSG, (c) PM of SIM:SSG, (d) (a) calcium silicate (CS), (b) SDP of SIM: CS, (c) PM of SIM:CS

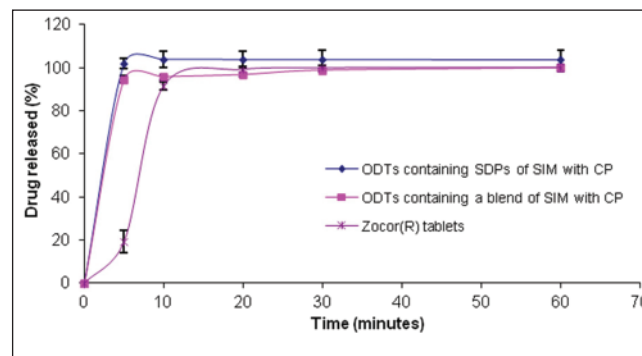


Figure 7: Drug release profile from orodispersible tablets prepared using a blend of simvastatin and crospovidone, its corresponding solid dispersions and Zocor® tablets

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