

Preparation, characterization and in vitro evaluation of tablets containing microwave-assisted solid dispersions of apremilast

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Abstract

Background. Solid dispersions are among the techniques successfully employed to enhance the dissolution of poorly water-soluble drugs. Microwave (MW)-assisted evaporative crystallization has been used to prepare solid dispersions of drugs and polymers.

Objectives. The aim of the study was to investigate the solubility of apremilast (APM) in water by exploring the effect of MW-assisted solid dispersion technology.

Material and methods. In the present study, solid dispersions of APM, a poorly water-soluble drug, were prepared. The solid dispersions were prepared using the conventional method (CM) and the MW-based solvent evaporation technique. Microwave energy was used to enhance the solubility and dissolution rate of APM. The physical mixture and solid dispersions were characterized using Fourier-transform infrared spectroscopy (FTIR), X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM). Apremilast tablets containing MW-assisted solid dispersions were prepared by the direct compression technique and compared with the marketed formulation (Aprezo tablets).

Results. The results obtained confirmed the conversion of crystalline APM to an amorphous form. The XRPD pattern of the MW-assisted formulation at a 2:1 ratio suggests the amorphous structure of APM within the formulation. Based on solubility studies results, Syloid[®] 244FP was selected as the best carrier. The dissolution study results suggested that the APM tablet prepared using MW-assisted solid dispersions at a 2:1 carrier/drug ratio improved the APM dissolution rate compared to the marketed formulation.

Conclusions. Based on the results, it can be concluded that the MW-assisted solid dispersion technique may be an effective approach to enhancing the dissolution profile of other poorly water-soluble drugs.

Key words: microwave, solubility, apremilast, solid dispersions

Introduction

A drug being developed into an oral formulation requires sufficient solubility in the dissolution medium in order to obtain optimal dissolution rates. The Biopharmaceutics Classification System (BCS) recognizes the importance of the rate of dissolution and aqueous solubility as key factors in the determination of the oral absorption of drugs.

Solid dispersions are among the techniques successfully employed to enhance the dissolution of poorly water-soluble drugs.^{1–9} Traditionally, solid dispersions are prepared by the melting, melting-solvent or solvent methods. Newer methods for the manufacture of solid dispersions include hot spin mixing,¹⁰ supercritical fluid technology and hot-melt extrusion (HME).^{11,12} Researchers are also investigating the potential of microwaves (MWs) to enhance solubility and bioavailability of poorly soluble drugs using the formation of solid dispersions and nanocomposite materials. In a recent study, MW-assisted evaporative crystallization was used to prepare solid dispersions of drugs and polymers.¹³

Microwaves are part of the electromagnetic spectrum, the frequency range of which is 0.3–300 GHz. The migration of MW within materials causes molecular oscillation, which leads to the generation of heat.^{14,15} The MW approach to heating is different from conventional heating, in which heat transfer takes place from the surface to the inner core. In the MW approach, heat is generated in the material and then passes to the entire volume, with a constant heating rate leading to uniform and deep heating of materials.^{14,16} Microwave technology is rapid, cost-effective, energy-saving, and environmentally safe. The crystalline drug is generally converted into an amorphous form, which means the approach can be used for the improvement of the dissolution profiles of BCS class II and IV drugs.^{14,17}

Apremilast (APM) is a novel, orally available small molecule inhibitor of type 4 cyclic nucleotide phosphodiesterase (PDE4). It is indicated in the treatment of active psoriatic arthritis in adults and moderate to severe plaque psoriasis.^{18–21} It is practically insoluble in aqueous buffers, irrespective of pH range; it is soluble in acetone, acetonitrile, methyl ethyl ketone, methylene chloride, and tetrahydrofuran. The BCS classifies APM as having low solubility and low permeability (i.e., BCS class 4). Very poor solubility of APM in water influences the dissolution of the drug in aqueous media. Its oral bioavailability has been reported to be 20–33%.^{22,23} In order to achieve an acceptable dissolution profile, crystal forms of APM or reduction of the APM particle size have been studied to improve its dissolution.^{24,25}

Considering the various attempts at improving solubility of APM with different approaches, the objective of present study was to increase the solubility of APM in water by exploring the effect of MW-assisted solid dispersion technology.

Materials and methods

Apremilast was provided for the study by Glenmark Pharmaceuticals Ltd. (Nashik, India); APM tablets (Aprezo, the reference tablet) were purchased from the same company. Syloid[®] 244FP and Syloid[®] XDP 3150 were purchased from Grace GmbH & Co. KG (Worms, Germany). Polyethylene glycol (PEG) 6000, polyvinylpyrrolidone (PVP), β -cyclodextrin, lactose monohydrate, ethyl cellulose, and magnesium stearate were obtained from Research Lab Fine Chem Industries (Mumbai, India). Idacol Erythrosine Food Red-4 coloring agent was obtained from Roha Dyechem Pvt. Ltd. (Mumbai, India). All other reagents were of analytical grade.

Determination of apremilast solubility in various buffers

Saturation solubility studies of APM in water, pH 1.2 acidic buffer, pH 2, pH 4, pH 6.8, and pH 7.4 phosphate buffers, as well as pH 6.8 phosphate buffer with 0.15% sodium lauryl sulfate (SLS) were conducted, using a magnetic stirrer (REMI Instruments Ltd., Mumbai, India). All media were prepared in individual flasks, and an excess amount of APM (\approx 50 mg) was weighed and transferred into the flasks. The flasks were placed on a magnetic stirrer at a speed of 200 rpm for 24 h at 37°C. After 24 h, the solution was centrifuged at 2000 rpm for 15 min. The supernatants were diluted with the respective media. Absorbance was measured at 230 nm using a Shimadzu V-630UV Visible Spectrophotometer (Shimadzu Corp., Kyoto, Japan) and solubility was calculated.^{6,26}

Preparation of physical mixtures of carriers and apremilast

Apremilast and carriers (Syloid[®] 244FP (S244), Syloid[®] XDP 3150 (S3150), PEG 6000, PVP, and β -cyclodextrin) were each passed through a No. 100 sieve and physical mixtures (PMs) were prepared by mixing pre-weighed amounts of APM with each carrier at a 1:1 ratio.

Preliminary trials for the preparation of solid dispersions by the conventional method

We prepared solid dispersions of APM with the 5 selected carriers – S244, S3150, PEG 6000, PVP, and β -cyclodextrin – at a carrier/drug ratio of 1:1. The solid dispersions of APM with S244, S3150 and β -cyclodextrin were prepared using the solvent evaporation method: APM (250 mg) was dissolved in 3 mL of ethanol; after complete dissolution, the solution was transferred into a round-bottom flask with a polymer carrier. The solvent was evaporated at 45°C and dried in a Hei-VAP Value HB/G5 rotary evaporator (Heidolph Instruments GmbH & CO. KG, Schwabach, Germany) for 2 h, and the residues were passed through a No. 85 sieve.

To prepare solid dispersions of APM in PEG 6000 and PVP, APM (250 mg) was dissolved in 3 mL of ethanol; after complete dissolution, the solutions were transferred to beakers holding the polymeric carriers PEG 6000 and PVP. The solvent was evaporated at 45°C and the resulting residues were dried in a hot air oven for 1 h and stored in a desiccator. Subsequently, the residues were ground in a mortar and passed through a No. 85 sieve.

On the basis of solubility studies, solid dispersions of APM with S244 at ratios of 2:1 and 3:1 were also prepared. All the solid dispersions were stored in vials at room temperature until further use. These batches were identified with the symbol CM.^{27,28}

The preparation of solid dispersions by the microwave-assisted solvent evaporation method

For the microwaving process, we used a CATA 2R MW oven (Catalyst Systems, Pune, India), containing an in-built mode stirrer to ensure even MW distribution. Accurately weighed 0.5 g amounts of physically mixed S244 with APM at ratios of 1:1, 2:1 and 3:1 were dissolved in 3 mL of ethanol. After complete dissolution, the solutions were transferred to silica crucibles. The crucibles were kept in a MW oven at 560 W for 3 min, until the solvent completely evaporated.^{13,29,30} The prepared solid dispersions were passed through a No. 85 sieve and stored in vials at room temperature until further use. These formulations were identified with the symbol MW.

Characterization of the solid dispersions

Drug content

The drug content of all the prepared solid dispersions was calculated. For each solid dispersion, an accurately weighed amount of solid dispersion containing 30 mg of APM was transferred to a 100 mL volumetric flask, diluted to 100 mL with methanol and sonicated for 30 min for complete solubilization of the drug. The mixture was filtered using Whatman grade 41 filter paper and the absorbance was measured at 230 nm. The drug content was calculated using a Shimadzu V-1800 UV spectrophotometer (Shimadzu Corp., Kyoto, Japan).^{14,25}

Phase solubility studies

The phase solubility studies were performed according to the method described by Higuchi and Connors.³¹ Physical mixtures and solid dispersions containing different carrier/APM ratios were prepared and added to glass vials containing 10 mL each of different media. Each vial was shaken in a mechanical shaker for 12 h to obtain equilibrium solubility, and the solution was allowed to equilibrate for 24 h. Each solution was further

centrifuged at 2000 rpm for 10 min in an ultra-centrifuge and filtered through Whatman grade 41 filter paper. An aliquot was suitably diluted with distilled water and analyzed using the Shimadzu V-1800 UV spectrophotometer at 230 nm.³²

Fourier-transform infrared study

The Fourier-transform infrared spectra (FTIR) of APM, the PM of APM with S244 and solid dispersion (Batch 7, MW 2:1) were recorded over a range of 4000–400 cm⁻¹ to study the principal peaks with an Affinity-1 FTIR spectrophotometer (Shimadzu Corp.) using the potassiumbromide (KBr) disc method.

X-ray powder diffraction analysis of apremilast

The X-ray powder diffraction (XRPD) spectra of APM, S244, the PM of APM with S244 and all the solid dispersions were recorded using a Smart Lab high power powder X-ray diffractometer (Rigaku Corp., Tokyo, Japan) with Cu as a target filter, a voltage/current of 40 kV/40 mA and a scan speed of 4°/min. The samples were analyzed at a 2θ angle range from 10° to 89°. The step time was 0.5 s and the acquisition time was 1 h.^{33,34}

Differential scanning calorimetry analysis

Thermograms of APM, S244, the PM of APM with S244 and all the solid dispersions were recorded by using a Shimadzu DSC-60 differential scanning calorimeter (Shimadzu Corp.). An empty aluminum pan was used as a reference. The differential scanning calorimetry (DSC) measurements were performed at a heating rate of 10°C/min from 30°C to 300°C.^{29,35}

Surface morphology

The surface morphology of APM, the PM of APM with S244 and solid dispersion (Batch 7, MW 2:1) was studied using a Supra 5 scanning electron microscope (SEM) (Carl Zeiss AG, Oberkochen, Germany) with an accelerating voltage of 10 kV.

Preparation of apremilast tablets using the direct compression technique

All the ingredients as shown in Table 1 were individually passed through a No. 60 sieve. A solid dispersion containing 30 mg of APM and microcrystalline cellulose were mixed to obtain a uniform mixture. The other ingredients were weighed, mixed and tablets were pressed using an 11 mm concave round punch on a Rimek compression machine (Karnavati Engineering Ltd., Ahmedabad, India). The post-compression parameters of the uncoated tablets were evaluated before they were coated.³⁶

Table 1. Composition of apremilast (APM) tablets prepared by direct compression method

Ingredients	mg/tablet
S244 + APM MW (2:1)	90.00
Lactose monohydrate	140.00
Croscarmellose sodium	16.30
Microcrystalline cellulose	41.50
Magnesium stearate	2.20
Total weight	290.00

Preparation of coating solution for film coating

Ethyl cellulose (1% w/w) was weighed accurately and added to approx. 5 mL of acetone in a beaker with continuous stirring using the handshake method. Idacol Erythrosine Food Red-4 coloring agent (Roha Dyechem Pvt. Ltd., Mumbai, India) was then added. The stirring was continued for 15 min.

Film coating of tablets

The compressed tablets were coated in a conventional coating pan (Avon Engineering Work, Mumbai, India) with an inlet air temperature of 50–55°C, a tablet bed temperature of 35–40°C and exhaust air temperature of 35–42°C. The pan speed, spray air pressure and solution spray rate were 25–30 rpm, 3 kg/cm² and 20 mL/min, respectively. The tablets were dried for 15 min at 45°C. The coating increased weight of the core tablets by 4%.

Dissolution studies

The dissolution rates of the APM tablets and Aprezo (the reference tablet) were studied using a USP XXIII Dissolution Test Apparatus (Labindia Instruments, Mumbai, India) at 50 rpm in 900 mL of phosphate buffer (pH 6.8) with 0.15% SLS. The temperature of the dissolution medium was maintained at 37 ± 0.5°C. Aliquots (5 mL) were withdrawn at 5-, 10-, 20-, 30-, 40-, 50-, and 60-minute intervals and filtered. The absorbance of the filtered sample solution was measured using the Shimadzu V-1800 UV spectrophotometer at 230 nm, and concentration of APM was determined from the standard calibration curve.

Results and discussion

Solubility studies

Our study showed that APM has poor solubility in all buffers. The highest solubility (24.74 ± 0.857 µg/mL) was observed in phosphate buffer (pH 6.8) with 0.15% SLS (Table 2). The FDA has also suggested phosphate buffer (pH 6.8) with 0.15% SLS as a dissolution medium for APM tablets.³⁷

Table 2. Results of solubility study of apremilast (APM) in different media

Dissolution media	Solubility [µg/mL]
Water	5.4 ± 0.298
pH 1.2, acidic buffer	5.2 ± 0.118
pH 2, phosphate buffer	9.96 ± 0.827
pH 4, phosphate buffer	14.96 ± 1.065
pH 6.8, phosphate buffer	16.22 ± 0.640
pH 6.8, phosphate buffer with 0.15% SLS	24.74 ± 0.857
pH 7.4, phosphate buffer	22.84 ± 0.331

Data presents mean ± standard deviation (SD), n = 3.

All the carriers used in the preliminary trials showed an increase in the solubility of APM in both PMs and solid dispersions (Tables 3 and 4). Several studies on solid dispersions have been published, confirming the advantageous properties of solid dispersions in increasing the solubility and dissolution rate of poorly water-soluble drugs. Solid dispersions tend to reduce particle size, possibly to a molecular level, and change the crystalline state of drugs, thereby promoting their solubility.^{38,39} The results of phase solubility studies indicate that the solubility of APM was maximally enhanced when S244 was used as the carrier for preparing solid dispersions utilizing the conventional method (CM). This is because the increase in surface area, along with the potential existence of the drug in pores in an amorphous (rather than crystalline) form, can aid in enhancing solubility. When MW heating is used for solvent evaporation, a 3 mL solution completely evaporates within 3 min. Thus, the time consumed by MW-assisted solvent evaporation was significantly shorter than in the conventional method.

Further, when a solid dispersion is prepared using the MW-assisted solvent evaporation method, it is possible that APM molecules are transported into the pores by capillary action and stored in the pores in a partially crystalline and partially amorphous form. Earlier findings suggest that particle size decreased to the submicron range when using the MW-assisted technique, thus improving dissolution rate.¹³ However, at a low carrier/drug ratio (1:1), surface adsorption of APM was noted. These results were also supported by the DSC thermogram. When the carrier/drug ratio is increased to 2:1, APM is more confined to the pores and can exist in an amorphous or a semi-crystalline state.

Table 3. Results of phase solubility studies of physical mixtures (PMs)

Physical mixtures	Solubility [µg/mL]
S244 + APM (1:1)	28 ± 0.221
Syloid XDP 3150 + APM (1:1)	22 ± 0.123
PVP + APM (1:1)	18 ± 0.344
PEG 6000 + APM (1:1)	19 ± 0.243
β-cyclodextrin + APM (1:1)	20 ± 0.354

Data presents mean ± standard deviation (SD), n = 3.

Table 4. Results of drug content and solubility studies of solid dispersion

Batch code	Solid dispersion	Drug content [%]	Solubility [$\mu\text{g/mL}$]
APM 1	S244 + APM (CM 1:1)	97.24 \pm 3.24	28 \pm 0.154
APM 2	Syloid XDP 3150 + APM (CM 1:1)	96.88 \pm 2.84	23 \pm 0.231
APM 3	PVP+ APM (CM 1:1)	99.12 \pm 5.31	24 \pm 0.269
APM 4	PEG 6000 + APM (CM 1:1)	97.37 \pm 2.57	23 \pm 0.347
APM 5	β -cyclodextrin + APM (CM 1:1)	96.56 \pm 3.62	21 \pm 0.215
APM 6	S244 + APM (MW 1:1)	98.23 \pm 3.64	30 \pm 0.364
APM 7	S244 + APM (MW 2:1)	100.32 \pm 2.81	33 \pm 0.385
APM 8	S244 + APM (MW 3:1)	98.41 \pm 4.11	33 \pm 0.316

Data presents mean \pm standard deviation (SD), $n = 3$

A similar reduction in crystallinity was observed as the carrier/drug ratio is increased to 3:1.

On the basis of our solubility studies, S244 was selected as the best carrier for the further studies.

Fourier-transform infrared study

The FTIR spectrum of APM (Fig. 1) shows the characteristic strong N–H stretching peak for APM at 3364 cm^{-1} . The FTIR spectrum of APM also shows the characteristic peak at 1764 cm^{-1} due to amide carbonyl (C=O), along with the peaks between 2837 cm^{-1} and 3081 cm^{-1} for aliphatic and aromatic benzene ring C–H stretching. The peak for amide N–H bending was observed at 1597 cm^{-1} and the peak for C–O stretching was observed at 1164 cm^{-1} . The FTIR spectrum of S244 showed a stronger intensity band from 900 cm^{-1} to 1300 cm^{-1} due to Si–O stretching of the silanol group. The FTIR spectra for the PM of APM with S244 and for solid dispersion (Batch 7, MW 2:1) show the combined individual characteristic peaks for APM and S244. The individual peaks for APM are more intense in the PM as compared to the solid dispersion. This suggests that in the PM, the physical interaction of APM with S244

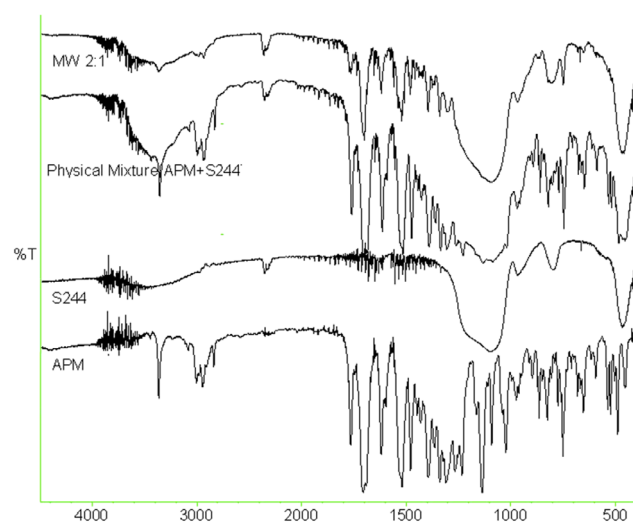


Fig. 1. Fourier transform infrared (FTIR) spectra of solid dispersion (MW 2:1), the physical mixture (PM) of S244 and apremilast (APM), S244 alone and APM alone

is weak; possibly APM is only physically interacting with the outer surface of the silica particles. In the solid dispersion, the individual peaks for APM are weak, which suggests that MW irradiation results in pronounced physical interaction between APM at the deeper sites of the S244 pores. The FTIR spectrum also clearly suggests that in both the PM and the solid dispersion, APM was physically adsorbed rather than undergoing any chemical interaction on the surface of the porous silica particles of S244.

Differential scanning calorimetry and X-ray diffraction

Differential scanning calorimetry and XRPD were employed to investigate the crystal lattice of pure APM and APM solid dispersions with S244. Figure 2 depicts the DSC thermograms for S244, a PM of APM and S244, solid dispersions of S244 and APM obtained using the CM and the MW-assisted solvent evaporation method. Apremilast was characterized by a single sharp melting endothermic peak at 157.56°C . The peak onset temperature and heat of fusion (ΔH_f) were 155.01°C and 111.0595 Jg^{-1} , respectively. This characteristic peak appeared in the PMs and in the CM batches at carrier/drug ratios of both 1:1 and 2:1, with slight variations in terms of the melting peak depression and broadening, indicating the transition from

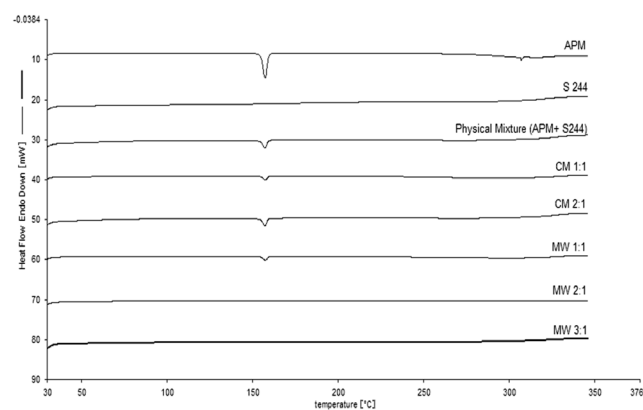


Fig. 2. Differential scanning calorimetry (DSC) thermograms of apremilast (APM), S244, the physical mixture (PM) of S244 and APM, solid dispersion (CM 1:1, CM 2:1), solid dispersion (MW 1:1, MW 2:1, and MW 3:1)

a crystalline to a semi-crystalline state. In the MW solid dispersion of APM with S244 at a carrier/drug ratio of 1:1, a melting peak of less intensity was detected. At this ratio, the pore volume of S244 was insufficient for hosting extra APM molecules, and the residual APM instead remained on the external surface of S244. However, the melting peak was completely absent in the 2:1 and 3:1 MW solid dispersions, confirming the amorphous state of APM within these formulations.

Figure 3 displays the XRPD patterns of APM, S244 and the MW solid dispersions with ratios of 1:1 and 2:1. The characteristic diffraction peaks observed at 10.09°, 11.87°, 13.53°, 16.34°, 26.09°, and 26.92° correspond to the powder diffraction pattern for pure APM, while the absence of diffraction peaks in the solid dispersions confirms their amorphous structure. The crystalline state of APM in the physical mixture of S244 and APM is evident from the characteristic diffraction peaks. The less intense diffraction peaks in the MW solid dispersion at a ratio of 1:1 indicates the partially crystalline state of APM deposited between the pore walls as a result of the blockage of pores with viscous molten APM. However, the XRPD pattern in the MW solid dispersion at a ratio of 2:1 suggests the amorphous structure of APM within the formulation.

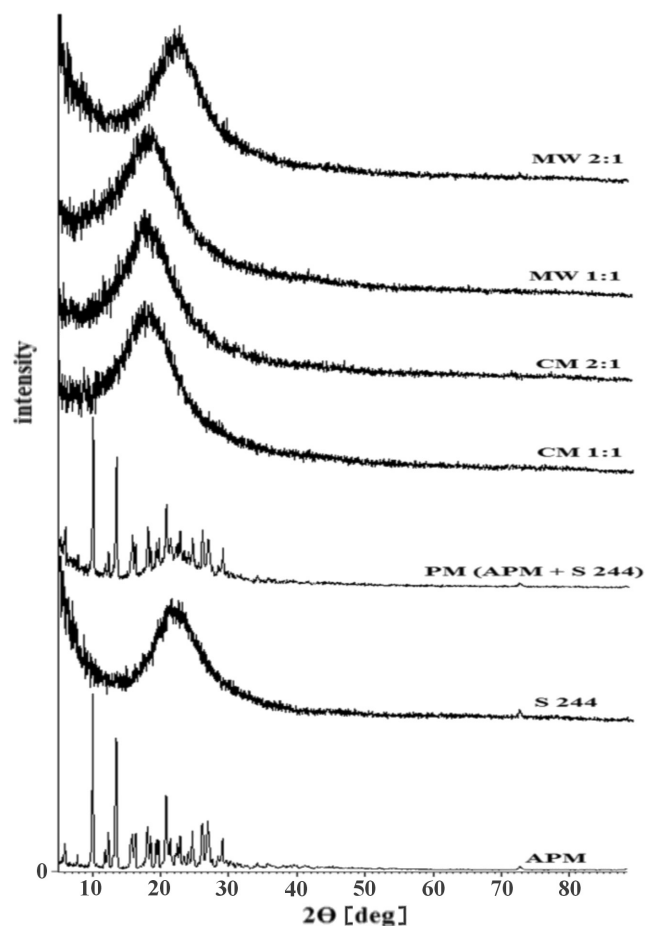


Fig. 3. X-ray powder diffraction (XRPD) patterns of solid dispersion (MW 2:1, MW 1:1), solid dispersion (CM 1:1), the physical mixture (PM) of S244 and apremilast (APM), S244, and APM

It also confirms that the APM was confined within the pores of S244. These XRPD results are compatible with the DSC observations discussed above. S244 is a non-ordered porous silicon dioxide with a neutral pH and has randomly oriented pores with an average pore diameter of 19 nm.⁴⁰ The single-crystal structure of APM has been reported for its ethanol hemisolvate solvomorph.²⁴ This single-crystal structure is most stable experimentally determined conformation of APM, and this conformation was therefore used to measure the size and shape of APM. Another reason for using the single-crystal structure is that very small changes in the conformation of a molecule or changes in the hydrogen bonds around the molecule can have major effects on its size, shape, surface area and volume.

As shown in Fig. 4, the most widely spaced atoms in APM are 14.7 Å apart. The unit cell dimensions required to fit the conformer of APM are 1.29 × 1.29 × 1.47 nm, calculated using Discovery Studio (Biovia, San Diego, USA) with the PyMOL interface (Schrödinger LLC, New York, USA). This suggests that the size of APM is below 1.9 nm, whereas the pore size of S244 is in the range of 19–20 nm. Therefore, the restricted pore size of S244 may have inhibited the crystallization of APM inside the pores. In summary, the transformation of APM from crystalline to amorphous form is highly dependent on the selection of an optimum carrier/drug ratio and on the formulation method.

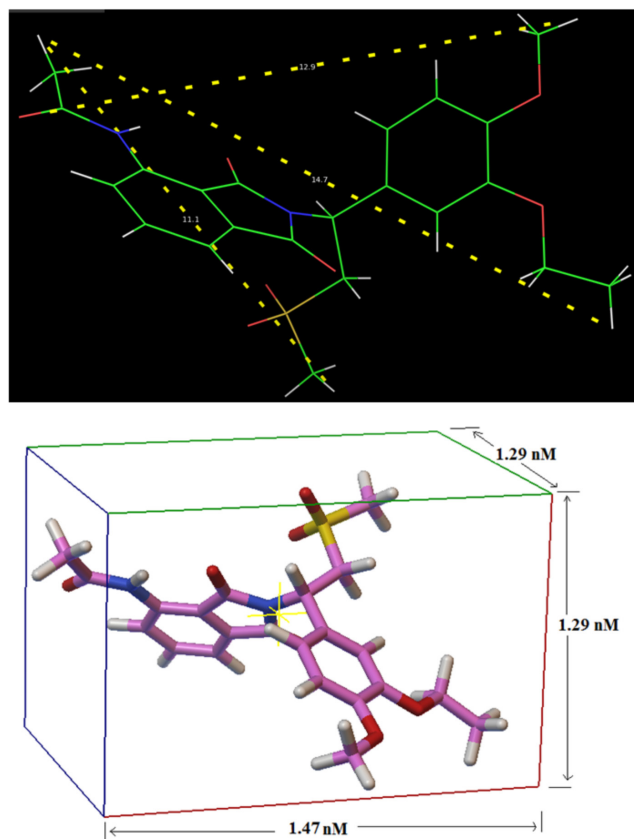


Fig. 4. Representation of a 3-dimensional apremilast (APM) molecule with inter-atomic distances shown

Surface morphology

Scanning electron microscopy images of APM, the physical mixture of APM and S244 and the MW solid dispersion of S244 and APM (2:1) are presented in Fig. 5. The SEM images of pure APM showed irregularly shaped crystals of the drug with large particles, showing its existence in the crystalline form. When APM was converted into solid dispersions, the morphology changed to an amorphous state with a fine particle size.

Preparation of apremilast tablets

Based on the results of our solubility studies, DSC thermograms and X-ray powder diffraction patterns, the best solid dispersion was found to be Batch 7 (MW 2:1). This was used to prepare tablets. The post-compression parameters of the uncoated tablets are presented in Table 5.

Dissolution studies

From the dissolution profiles, it is evident that the APM tablets prepared with the MW-assisted solid dispersion at a 2:1 ratio had a significantly better APM dissolution rate as compared to the marketed formulation (Aprezo tablets) (Fig. 6). Factors such as the lack of a crystalline form, the increased surface area of the drug, and the hydrophilic surface of S244 helped improve the dissolution of APM. When this formulation comes into contact with the dissolution media, a rapid release of APM in the form of fine particles occurs, possibly because of desorption of APM by the influx of the dissolution media inside the pores of S244.²⁸ These results are in agreement with the findings of earlier researchers,³⁹ who used MW-induced solid dispersions to improve the solubility of APM.

Conclusions

In summary, solid dispersions of APM, a poorly water-soluble drug, with Syloid 244FP as a carrier were prepared by CM and MW-assisted method. The latter was found to be a suitable and less time-consuming method. The prepared solid dispersions were evaluated for physicochemical parameters. The study shows that the dissolution rate of APM can be improved using Syloid 244FP as a carrier. The transformation of APM from crystalline to amorphous form is highly dependent on the selection of an optimum carrier/drug ratio and formulation method. The tablet formulation of solid dispersion (Batch 7, MW 2:1) (S244 with APM, MW 2:1) showed a higher dissolution rate when compared with the reference tablets.

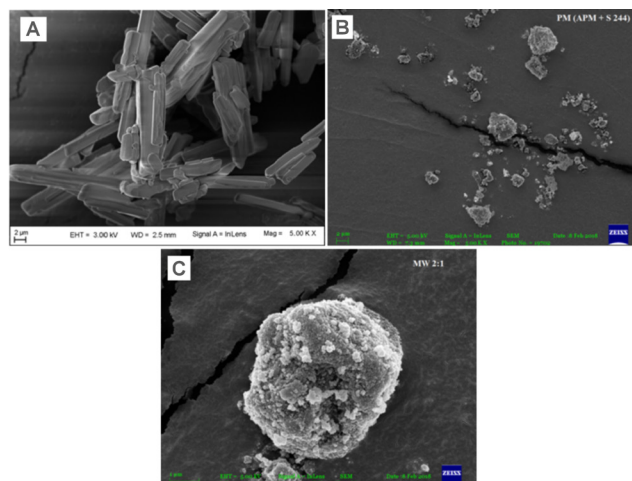


Fig. 5. A – scanning electron micrographs of pure apremilast (APM), B – the physical mixture (PM) of S244 and APM, C – solid dispersion (batch 7, MW 2:1). Scales are given on the individual micrographs

Table 5. Results of uncoated Apremilast (APM) tablet

Average weight [mg]	Friability [%]	Disintegration time [s]	Hardness [kg/cm ²]
290	0.63 ± 0.05	66 ± 1.52	7.5 ± 0.5

Data are presented as mean ± standard deviation (SD), n = 3.

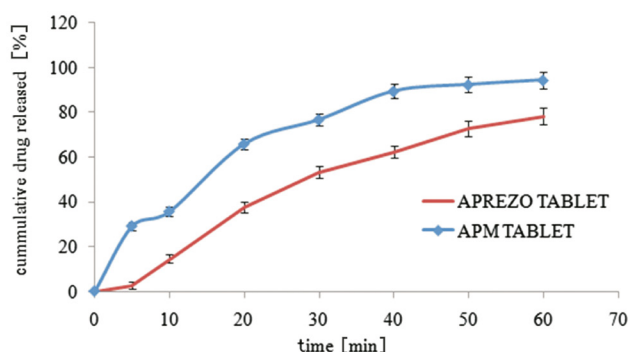


Fig. 6. Comparative dissolution profiles of prepared apremilast (APM) tablets and the marketed formulation (Aprezo tablets). Data are presented as means ± standard deviation (SD), n = 3

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