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Development of Mefenamic Acid-Soluplus ® amorphous dispersions via hot melt extrusion and *in silico* prediction of oral absorption

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ABSTRACT

The objective of this study was to increase the solubility of Mefenamic Acid (MA), a BCS class II drug by formulating amorphous solid dispersions via Holt-Melt Extrusion. The extrudates were prepared at different drug to polymer ratios and characterised by standard analytical techniques. Dissolution studies were performed in Phosphate buffer saline (PBS) pH 7.4 medium. Stability of the different ratios of MA: Soluplus (1:1, 1:4 and 4:1) was studied at room temperature for 12 months. Computer simulation using GastroPlus™ was run to depict the gastrointestinal absorption of MA in humans. DSC thermograms and the diffractograms of the solid dispersions confirmed amorphous nature. Dissolution studies showed enhanced dissolution rate of MA from the solid dispersions. Stability studies indicated 1:4 (MA: Soluplus®) dispersion as the most stable dispersion. GastroPlus™ simulation using *in vitro* data showed improvement in the PK parameters of the solid dispersión in comparison with pure MA.

Keywords: Hot-melt extrusion, Metanamic Acid, Soluplus, solubilisation, solid dispersion

INTRODUCTION

Mefenamic Acid (MA) [(2-(2,3-dimethylphenyl) aminobenzoic acid] is a widely prescribed non-steroidal anti-inflammatory drug (NSAID) for relief of pain primarily dysmenorrhoea and rheumatoid arthritis[1,2]. Poor solubility affects the

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rate of absorption of MA from the gastrointestinal tract [3,4]. Oral administration is associated with side effects in the gastrointestinal tract as perforation of the stomach, small and large intestine, ulceration and bleeding that may be fatal[4].

There are multiple delivery strategies for oral administration of poorly soluble drugs and some of them have been explored for the oral delivery of MA[5-7]. The use of amorphous form has the potential to increase oral absorption and is usually considered when drug cannot be suitably solubilised. Melt extrusion is one such means of obtaining amorphous forms. Specifically, amorphous solid dispersions (ASDs) are advantageous as they have high free energy and kinetic solubility due to structural changes that modify chemical and physical properties, such as endothermic end exothermic values, the lack of melting point observed in ASDs, and the lack of symmetry at conformational, translational and orientational structures.

Most of the published research data for solid dispersion of MA are based on carriers like PVP, polyoxyethylene, eudragit EPO, Pluronic F127® polyethylene glycol 4000 and Gelucire 50/13[8-15].

Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®), is an attractive carrier for solid dispersion due to numerous advantages. As it has a low Tg, 70°C, it is suitable for poorly soluble drugs with high melting point and ensures that the API is thermally stable during the process. Being hydrophilic and non-ionic, solubility is unaltered along the GI tract. Apart from enhancing solubility, Soluplus® stabilizes the solid dispersion[16-19].

Hot melt extrusion (HME) is a documented process for the manufacturing of solid dispersions. Compared to other techniques for preparing solid dispersions, HME is a reliable and robust process, far less complex, cost efficient and avoids the use of organic solvents[20,21].

There are no reports on the use of Soluplus® with HME technology in preparation of solid dispersion of MA. MA is a challenging drug to process via HME owing to its high melting point indicating high crystallinity. Hence the present study was taken to explore HME with Soluplus® as a carrier, to generate solid dispersion of MA. To ensure that MA is indeed in its amorphous form, the performance of DSC, FTIR and XRD analysis were carried out and to confirm stability XRD was studied after 12 months. The novelty of this paper lies in the use of co rotating twin screw extruder for preparing solid dispersion of MA and *in silico* tool to predict the enhanced oral bioavailability with the obtained in vitro results. GastroPlus™ simulation software was used to predict the oral absorption of the solid dispersion. The *in vitro* data was used as the input function into a simulation software.

METHODOLOGY

Materials

Mefenamic acid was purchased from Yarrow Chem Products, Mumbai, India. Soluplus® (M_w = 118,000 g/mol, density = 1.08 g/cm^3) was a gift from BASF. All other chemicals and reagents were of analytical grade and used in the study without further purification.

Calculation of solubility parameter

To predict possibility of glass solution formation on melt extrusión, Hansen solubility parameter of MA and Soluplus® was calculated. In the present study prediction was based on comparison of solubility parameters of drug and excipient. The solubility parameters were obtained from literature.

Thermal analysis of the physical mixtures

The thermal properties of the physical mixtures were determined using a DSC (DSC-50, Shimadzu, Japan). Physical mixtures (100 mg) consisting of one (crystalline) drug and one polymer in concentrations ranging from 60 – 90% drug (w/w) were prepared by gentle mixing using a mortar and pestle. Samples of 4 – 6 mg were analyzed by DSC at a heating rate of 10 °C/min from ambient temperature to 20 °C above the Tm of the pure crystalline drug. The calibration of the baseline was done using empty aluminium pans as a reference, and temperature/ enthalpy using indium.

Preparation of hot-melt extrudates

HME operation was carried out by twin screw extruder (STEER-Omicron 10P, India). Soluplus® was blended with MA until it was mixed evenly and introduced manually into the extruder barrel. Three different extrudates were prepared, drug to polymer ratios, at 1:4, 1:1 and 4:1. The extrusion process was performed at various barrel temperatures 110°C, 130°C and 130°C while screw speed was fixed at 150 rpm. The external to internal screw diameter (Do/Di) ratio of the HME apparatus was 1.71. The samples were milled using mortar and pestle and meshed through a 60 mesh and stored in a desiccator until use.

Physical characterisation

Differential Scanning Calorimetry (DSC)

The DSC thermograms of the extrudates were recorded on a DSC (DSC-50, Shimadzu, Japan). The samples were weighed into aluminium pans, sealed and heated under nitrogen flow at a scanning rate of 10 °C min-1 to obtain a temperature range from 25 °C to 300 °C. The calibration of the baseline was done

using empty aluminium pans as a reference, and temperature/ enthalpy using indium.

Fourier Transform Infrared Spectroscopy (FTIR)

The FT-IR spectra (Shimadzu - FTIR 8300) were recorded based on the KBr pellet technique for the extrudates the drug and the polymer in the wavelength region of 400-4000 cm^{-2}.

X-Ray Diffraction (XRD)

The X-ray diffraction pattern of extrudates the drug and the polymer was recorded using benchtop X-ray Diffractometer (Rigaku MiniFlex 600, Japan) at an angle range of 10 to 80° at the rate of 2°/min. The experiment was carried out at room temperature.

Scanning electron microscope (SEM) analysis

The surface size, shape and structure of the pure drug and extrudates were evaluated using a JEOL JSM-7600 F, SEM. The samples to be examined were mounted on the SEM sample slab using a double-sided adhesive tape and were coated with gold (200 °A) under reduced pressure (0.001 torr) for 5 min to increase the conductivity using an ion sputtering device and viewed.

Solubility determination

MA and the extrudates were placed in a 2 ml Eppendorf tube with water and PBS until saturation and left for two days in the rotospin (Tarsons). The samples were filtered, and absorbance measured with the UV-Spectrophotometer[22].

Drug content

The drug content of the different extrudates were performed by weighing 10 mg of the different extrudates in 100ml methanol volumetric flask, sonication for 20 minutes and measurement of absorbance with UV-Spectrophotometer[23].

***In vitro* drug release studies**

Dissolution study was performed with TDT-08L Dissolution Tester USP Apparatus II (Electrolab) by placing 50 mg equivalent of drug content of the different extrudates in in 900ml of PBS pH 7.4 at 37°C and 75 rpm. Samples were taken at 15, 30, 45, 60, 90 and 120 minutes and media replaced immediately. Absorbance of samples was measured using the UV-Spectrophotometer[22].

***In silico* simulation of oral absorption**

An absorption model was built using the GastroPlus™ simulation software

(version 9.0, Simulations Plus Inc, Lancaster, CA, USA). Input parameters like drug solubility, pKa, effective permeability were determined *in silico* using the ADMET predictor module of GastroPlus™. The default human fasted physiological model in GastroPlus™ (Opt logD SA/v6.1) was used for simulations. Metabolism of MA is predominantly mediated via CYP enzymes particularly CYP2C9 in addition to CYP1A2. The GastroPlus™ default Km and Vmax values based on the Metabolism and Transporter module were utilised. Human PK parameters were estimated by fitting the 250mg capsule oral data from humans to a one compartment model in PKPlus[22]. The generated mean PK parameters were exported to the Pharmacokinetics tab to enable software prediction. Simulations were conducted using the dissolution data of solid dispersions.

Physical stability studies upon storage

Physical stability studies were conducted for 12 months at 30°C/75%RH. The prepared solid dispersions were stored in air tight containers. The stored samples were investigated for the recrystallisation tendency by XRPD after 12 months.

RESULTS AND DISCUSSION

Solubility parameter

The solubility parameter of MA and Soluplus® were obtained from literature. Based on the group contribution method, individual solubility parameter values (δ) for MA[25] and Soluplus®[17] are 21 MPa $^{1\backslash 2}$ and 23.77 MPa $^{1\backslash 2}$ respectively.

The use of solubility parameter in predicting miscibility between drugs and polymers is based on the standard solution theory "likes dissolves likes" whereby if two solvents have similar solubility parameters, they can be mixed to form a uniform solution with any ratios. Likewise, if drugs and polymers are predicted with close solubility parameters, a miscible drug-polymer solid dispersion could be prepared. It has been proposed empirically that compounds with a $\Delta\delta$ < 7.0 MPa$^{0.5}$ were likely to be miscible while compounds with a $\Delta\delta$ > 7.0 MPa$^{0.5}$ were expected to be immiscible[26,27]. The solubility parameter difference between Soluplus® and MA is 2.77, which is below 7.0 MPa$^{0.5}$

The small difference between the calculated solubility parameters of MA and Soluplus® indicates that MA is likely to be miscible with Soluplus®**.** The comparison of solubility parameters can be a rapid way to predict miscibility between drugs and polymers.

Thermal analysis of the physical mixtures

The DSC thermograms of the physical mixtures of MA: Soluplus® is displayed in figure1. The DSC thermogram of pure crystalline MA displayed a single endothermic melting event at 231 °C, with a melting enthalpy (ΔHm) of approximately 187.51 J/g, Physical and thermodynamic values measured for the physical mixtures are presented in Table 1. Drastic change in Cp value from pure drug to the polymer mixture could be due to slow transition of the phase of the drug which is significant.

Accordingly, it can be predicted that at 80%+20% (MA: Soluplus®) could be optimum as enthalpy change over at this composition. Based on these observations the ratios 1:4, 1:1 and 4:1 were selected for preparing solid dispersions.

Table 1. Thermodynamic values of the MA and physical mixtures measured by DSC

MEFENAMIC ACID %	PEAK Tm (°C)	ONSET (°C	ENDSET (°C)	ΔHm (J·g-1)	ΔCp (J·g-1·K-1)
100	231.92	230.17	236.09	-187.51J/g	0.37
90	230.47	226.08	233.37	-47.74J/g	0.09
80	229.64	224.15	232.75	-28.64J/g	0.05
70	230.28	225.31	232.31	-13.79J/g	0.027

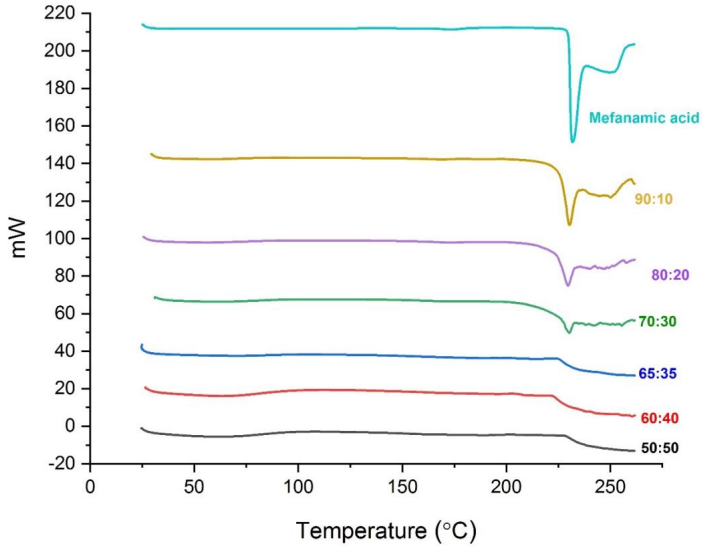

Figure 1. Thermograms of the MA-Soluplus physical mixtures (% w/w)

Preparation of Hot melt extrudates

Three different extrudates were prepared with drug to polymer ratios, at 1:4, 1:1 and 4:1. The melting point (Tm) of MA is 230°C The thermal decomposition kinetics of MA is reported in literature[28]. Positive value of the Gibbs free energy obtained from the study showed that the decomposition reaction of MA is nonspontaneous. Since the carrier Soluplus® has excellent plasticizing effect, the operation was possible at lower processing makes Soluplus® a good candidate for extrusión.

DSC

The DSC thermograms of pure MA and exrudates are displayed in figure 2. However, in the thermogram of solid dispersion (extrudates) the peaks of crystalline MA completely disappeared. This indicates crystalline MA was transformed into amorphous state by HME. Amorphisation was possible due to molecular interaction with carrier.

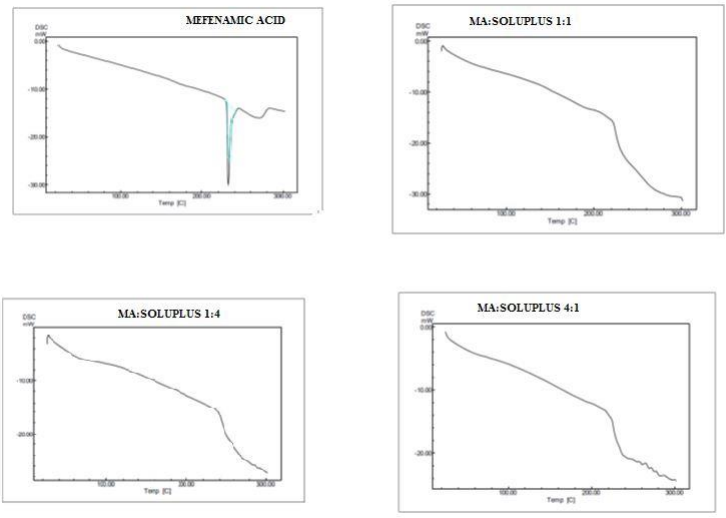

Figure 2. DSC thermograms of MA, MA: Soluplus (1:1,1:4 and 4:1)

FTIR

The FTIR spectra of pure MA shows N-H stretching, N-H bending and stretching vibrations of the COOH moiety. Characteristic peaks at 3309 and 1575 cm^{-1} indicate N-H stretching and N-H bending of secondary amine. The C=O stretch of carboxylic acid appears at 1649, C=C stretch at 1508. C-H symmetric bending vibrations of side chain, O-H stretching of C=O and C-OH appear at 2571 cm^{-1}. For the solid dispersions (extrudates) all assigned peaks showed no significant difference in comparison with pure drug except for some changes with

respect to H bond formation. The probability of H bonding is high in the amine and carbonyl groups of MA. Carboxyl group of MA strongly contributes to intermolecular interaction with Soluplus®.

4:1 indicated involvement of both C=O, C-H and N-H is not much affected. 1:1 only C=O not N-H but C-H bending is affected. 1:4 C=O, N-H, C-H all are affected. In conclusion both C=O, C-OH (of COOH) and N-H seem to have involved in H bonding within the MA. The H bond is cleaved and new H bond formed with the polymer-OH function at either end of the polymer chain.

XRD

The overlayed XRD spectra of MA and the extrudates is presented in figure 3. The characteristic XRD peaks of pure MA were observed at 2 θ equal to 6.5, 21.5 and 26.3 that coincided with those reported previously and thus confirming crystalline structure of pure MA[25,29]. XRD of solid dispersions showed disappearance of characteristic peaks of MA. The peaks of crystalline MA completely disappeared. This observation indicates amorphisation of MA due to molecular interaction with the carrier.

X-ray diffraction analysis can be useful to determine the amorphous or crystalline structure of the samples, as the beams go in different directions and layers. The straight peaks in the results indicate that the sample is in a crystalline form and when I t shows a halo it is much disorganised form, amorphous.

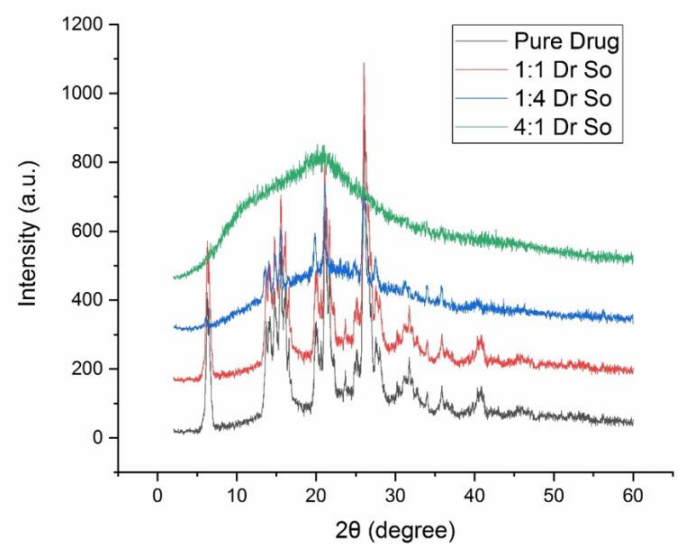

Figure 3. Xray diffractograms of MA, MA: Soluplus (1:1,1:4 and 4:1)

SEM analysis

SEM images of MA solid dipersions and pure MA captured at various magnifications is shown in figure 4. When compared to the extrudates the surface of pure MA was coarse in appearance.

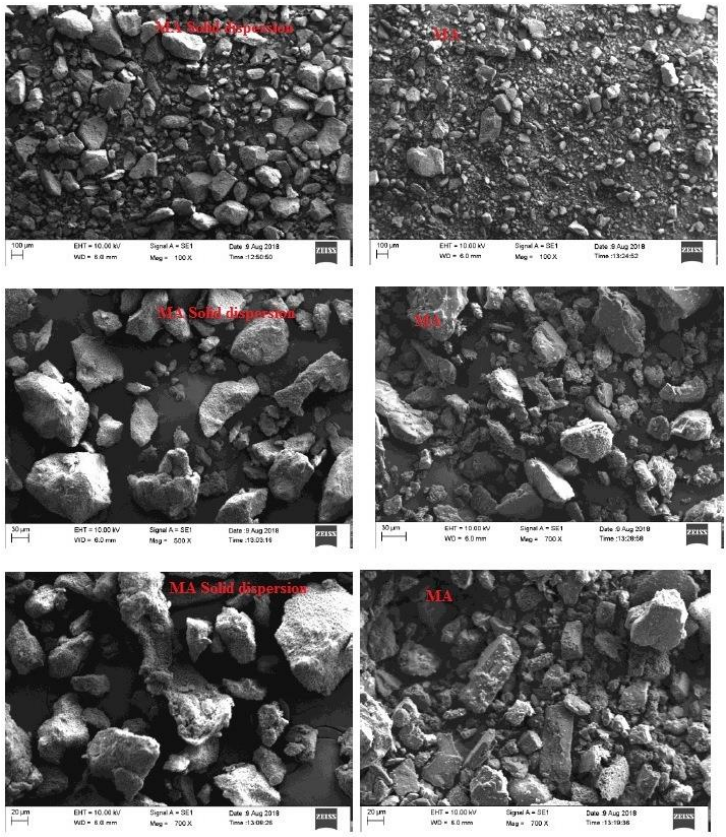

Figure 4. SEM images of MA solid dipersions and pure MA captured at various magnifications

In vitro dissolution

The dissolution data (Table 2) clearly indicates that the dissolution rate is controlled by the drug/carrier ratio of the formulation.

Table 2. In vitro Dissolution of MA and MA Solid Dispersions

Time (Min)	Cummulative Percent Released			
	MA	1:1	1:4	4:1
15	1.5	7.6	0.5	25.7
30	3.2	14.5	1.3	35.7
60	4.5	21.6	7.2	52.8
90	5.4	25.6	9.0	60.2
120	8.9	32.2	12.9	70.8
180	11.7	40.2	24.1	86.0
240	17.2	49.9	28.4	91.3

The dissolution rate increases with increasing the drug amount in the blend up to a drug load of 80% and decreases markedly from amounts with higher polymer load.

This observation leads to the assumption that the improvement of drug release is based on a chemical interaction between drug and carrier. The release of MA was less than 20% owing to hydrophobic nature of the drug. The release of MA from the ASDs was higher. Though solid dispersion transformed the drug into amorphous form, drug release was influenced by drug: polymer ratios. Slow release with higher polymer was hypothetised due to aggregation of the dispersion in the media. Initially, a polymer-rich diffusion layer is formed between the solid dispersion and the dissolution médium. When the amorphous molecules diffuse through the polymer-rich diffusion layer, crystallization may occur, which creates a high-energy interfacial boundary that slows down the dissolution rate. The viscosity of the polymer will also influence the dissolution rate of the drug from the amorphous solid dispersion.

In silico simulation of oral absorption

The built base absorption model was validated using the plasma data comparing the predicted with the observed values. The accuracy of prediction of the pharmacokinetic (PK) parameters was based on prediction fold error. The simulated model was considered to be of high prediction accuracy if prediction values were within two-fold of observed values[30]. Table 3 represents a summary of the input parameters used in the study. Figure 5 shows the predicted and observed plasma concentration-time profile of oral administration of 250 mg capsule of MA.

Table 3. Basic modeling parameters of MA fed into the Gastro-Plus™ software

Parameters	Value
Molecular weight ($gmol^{-1}$)	241.29[a]
PKa	3.95[a]
Solubility ($mgml^{-1}$)@pH4.5	0.0097[a]
Human permeability [$P_{eff}(cms^{-1}x10^{4})$]	6.5[b]
Particle density (gml^{-1})	1.2[b]
Diffusion coefficient (cm^2s^{-1})$x10^5$	0.6[b]
Log P	4.9[a]
Mean precipitation time (s)	900[b]
CL/F L/h	18.7[c]
Oral dose for Cp-time profile (mg)	250[d]

a. Predicted by ADMET predictor (Version 7.2.0.0, Simulations Plus, Inc., Lancaster, CA, USA)

b. Default GastroPlus™

c. Calculated by GastroPlus™

d. Literature value

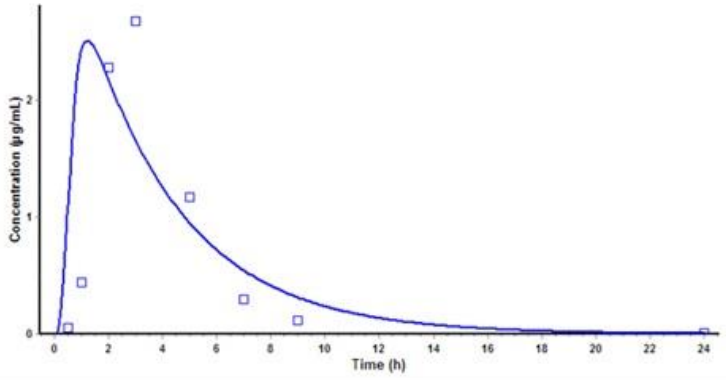

Figure 5. Observed (in square) and predicted (continuous line) plasma concentration–time profile following oral administration of 250 mg MA Capsule

The simulated profile fitted well with the observed (reported) curve. The observed and predicted PK parameters are displayed in Table 4. The fold error for the prediction accuracy of PK parameters was found to be < 2 indicating good prediction.

Table 4. Pharmacokinetic parameters of MA obtained from literature (observed) and Calculated by GastroPlusTM (predicted) for building absorption model

Pharmacokinetic Parameter	Observed	Calculated	Fold Error
Cmax(µg/ml)	2.68	2.5	0.932
Tmax (h)	3	1.2	0.4
$AUC_{(0-t)}$µg-h/ml	10.67	11.38	1.06

Among the solid dispersions the best disolution profile was seen with 4:1, so the dissolution data of 4:1 solid dispersión was used to simulate oral absorption profile in humans. The predicted PK parameters of the solid dispersión in comparison with pure MA is presented in Table 5. Solid dispersión of MA showed improvement in the PK parameters.

Table 5. Pharmacokinetic parameters generated by loading dissolution data into the developed absorption model of GastroPlusTM

Pharmacokinetic Parameter	MA	MA Solid dispersion (4:1)
Cmax(µg/ml)	0.39	1.24
Tmax (h)	10	3.04
AUC(0-t)µg-h/ml	6.44	8.73

Stability studies

The physical and chemical stability of the solid dispersions prepared by HME is of paramount importance as it can limit the commercial outcomes of solid dispersions. Recrystallization of the drug in the amorphous systems generally takes place with aging due to the high free energy of amorphous molecules compared to the crystalline form. The addition of a suitable polymer can delay this crystallization phenomenon according to many studies[31-34]. The viscosity of the polymer, as well as the intermolecular interactions (hydrogen bonds) that can occur between the API and the polymer, are most key factors in the stabilization of solid dispersion systems.

In the present study, we stored our samples of interest for a period of 12 months at normal conditions (30 °C/75% RH).

XRD analysis demonstrated the appearance of crystalline peaks in solid dispersions of 1:1 and 4:1 dispersions. However, they were not seen in 1:4 indicating stable dispersions (Figure 6).

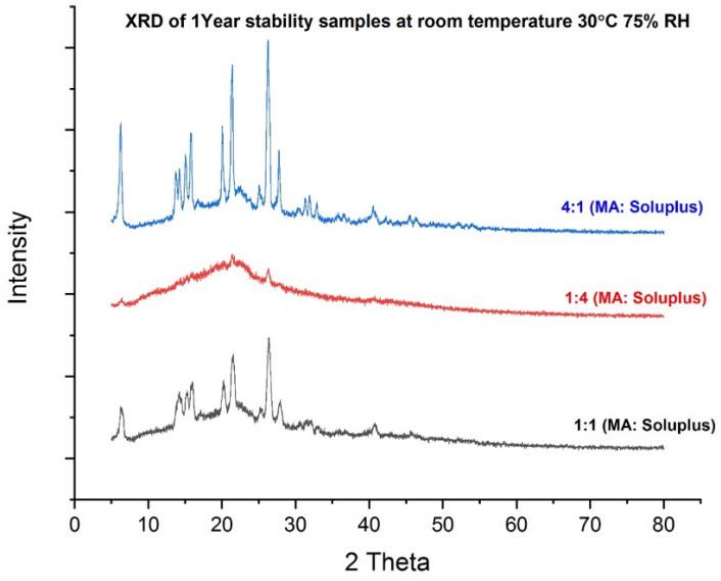

Figure 6. Diffractograms of the stability samples of MA solid dispersions

Steric hindrance by a polymer of different concentrations may slow crystallization mechanisms. Steric hindrance acts by preventing drug molecule aggregation and/or interaction that are the precursors for crystallization[35].

The appropriate use of polymer is very important to the physical stability of an ASD. The drug–polymer interactions are indicated by peak shifts or peak intensity changes corresponding to specific vibrational modes of the functional groups involved in intermolecular interactions in FTIR. From the FTIR results of the solid dispersions, 1:4 showed involvement of all N-H, C=O and C-H of COOH in the formation of hydrogen bonds which may also be the reason for better stability. Also in the 1:4 dispersion, the drug is well dispersed in the polymer and so the chances of self-contact interactions (drug-drug) which can be precursor for crystal growth is minimum. Moreover, hydrogen bonds between drug molecules and polymers not only increase the nucleation activation energy but also reduce crystal growth.

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CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

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AUTHOR CONTRIBUTIONS

Estrella Chavero and Aleksandra Kurowska carried out the experiments and generated the data. Shaila Lewis supervised the project and wrote the manuscript with input from the co-authors.

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