

Solvent-free Hot Melt Extrusion Technique in Improving Mesalamine Release for Better Management of Inflammatory Bowel Disease

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ABSTRACT

Background: Poor oral bioavailability of mesalamine (Mes) is due to extensive metabolism in the intestinal epithelial cells in addition to the liver. **Purpose:** Improved mesalamine release by Hot-Melt Extrusion (HME) technique could be utilized for better management of Inflammatory Bowel Disease (IBD). **Methods:** Mes and hydrophilic polymers like Eudragit-EPO, KollidonVA-64 and PEG 6000 were hot-melt extruded using a co-rotating twin-screw laboratory extruder. **Results:** The minor shifting with significantly reduced intensity and disappearance of peak in the Differential Scanning Calorimetry (DSC) thermogram could be attributed to some solid–solid interaction and not necessarily any incompatibility. Fourier-Transform Infrared Spectroscopy (FTIR) and Scanning Electron Microscopy (SEM) confirmed the transformation of individual drug crystal into accumulations of small crystallites due to partial or almost complete amorphization. Continuous manufacturing of stable amorphous solid dispersion by solvent-free drug loading Hot-melt extrusion technique has been found feasible in improving drug release compared to mesalamine alone in simulated gastric fluid ($f_1 = 0.3$ to 11.1 and $f_2 = 26$ to 49). **Conclusion:** Melt dispersion samples have exhibited significantly improved mesalamine release and could be utilized for better management of Inflammatory Bowel Disease (IBD).

Key words: Hot-melt extrusion, Solvent-free drug loading, Mesalamine, Feret diameter, Improving Release.

INTRODUCTION

Inflammatory Bowel Disease (IBD) caused by bacterial or parasitic infections¹⁻³ or of unknown etiology primarily affects the small and large intestines and is subdivided into ulcerative colitis (colonic mucosa) and Crohn's disease (in any part of gastrointestinal tract).⁴ In almost all cases it affects the rectum and often extends to the colon. Such inflammation extends through the entire thickness of the bowel and can cause diarrhoea, abdominal pain, rectal bleeding and other symptoms including fever and weight loss.^{5,6} Recent preclinical studies indicated that the nanoparticle-based targeted delivery to the colon may be the promising tools in the treatment of ulcerative colitis.⁷ Mes-

alamine (Mes) is used as the drug of choice for the treatment of inflammatory bowel disease which acts locally on intestinal and colonic mucosa. Mesalamine has been recently reported as very effective treatment option for immuno-checkpoint inhibitors-induced colitis safely without counteracting the effect of immuno-checkpoint inhibitors. Mes inhibits cyclo-oxygenase and lipo-oxygenase and decreases the production of prostaglandins and leukotrienes to reduce inflammation.⁸ When mesalamine is administered orally using an unprotected delivery system, the active drug undergoes dissolution-rate-limited absorption from the upper small intestine. Rapid absorption of

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mesalamine usually is affected due to poor solubility of the drug. Improvement of bioavailability of oral preparation of allopathic and ayurvedic origin is the most challenging area faced by the recent researchers.⁹⁻¹¹ Poor oral bioavailability of mesalamine (orally: 20-30 % and rectally: 10-35%) is also due to extensive metabolism to N-Acetyl-5ASA (N-Ac-ASA) by the N-acetyltransferase 1 enzyme in the intestinal epithelial cells in addition to the liver.^{12,13} Protective enteric coated mesalamine formulations are reported by some researchers for controlling or delaying the release of the drug.^{14,15} Bruce *et al.* (2005) reported that tablets containing 25% mesalamine and Eudragit® S 100 released less than 10% after 2 h in simulated gastric medium using hot-melt extrusion technique.¹⁶ Fast absorption of mesalamine might be facilitated by increasing solubility¹⁷ in the gastric and proximal small intestinal milieu and improvement of bioavailability could be possible¹⁸ by decreasing intestinal residence time and thereby avoiding intestinal metabolism.

Co-rotating twin-screw extrusion is a promising technology in the pharmaceutical industry for the processing of various drug formulations, pharmaceutical engineering and polymers and materials science. Hot-melt Extrusion (HME) is the co-rotating twin-screw extrusion process of melting a blend of drug and polymer applying heat and pressure and forcing it through an orifice under controlled conditions in a continuous (Figure 1). Hot-melt extruded composites are combinations of Active Pharmaceutical Ingredient (API), useful excipients and dispensing aids. The technology offers a number of advantages over conventional pharmaceutical processing techniques: (i) few processing steps, (ii) absence of solvents, (iii) nonstop operation and (iv) improved physicochemical properties of the resultant solid dispersions. The applications have also been focused on a variety of drug delivery such as pellets, granules, instant and modified release tablets, implants and transdermal and transmucosal systems.

Hot melt extrusion technique has been utilized first time for preparation of solid dispersion incorporating hydrophilic polymers like Eudragit-EPO, KollidonVA-64 and PEG 6000 for improving dissolution of mesalamine. Eudragit-EPO could mask the unpleasant taste of mesalamine and help in readily solubilizing the drug in the stomach. Kollidon VA-64 was used as dry binder and highly biocompatible polyethylene glycol as plasticizer and it was reported that the stabilizing effect of polyvinyl pyrrolidone (PVP) and polyethylene glycol 4000 (PEG) on cyclodextrin–drug complexation.^{19,20} In our previous report, PVP and PEG did not show

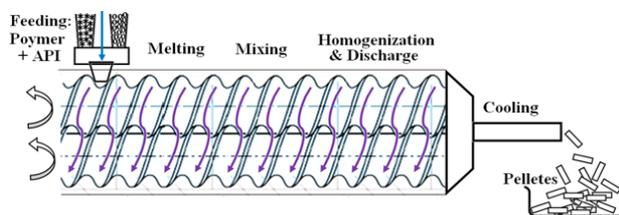


Figure 1: A schematic diagram of hot melt extrusion process.

any stabilizing effect against aqueous-mediated cefixime degradation.²¹

MATERIALS AND METHODS

Materials

Mesalamine, Kollidon VA-64, PEG 6000 were received from Steer Pharma Lab, Bangalore and Eudragit EPO was supplied by Evonik (Mumbai, India). Simulated gastric fluid without enzymes or 0.1N HCl used as dissolution medium.

Hot-melt Extrusion

Drug and polymers were sieved through the mesh screen (#20) and placed in an oven (45°C) overnight for removal of any residual moisture. The polymers were then physically mixed together with the drug as per formulation code tabulated in Table 1. Each powder mix sample was subsequently hot-melt extruded using a co-rotating twin-screw laboratory extruder (OMICRON 12 PHARMA, STEER's) with a screw diameter of 10 mm and 12 mm (Do/Di ratio of 1.45). The blends were fed and extruded as per the settings (feed rate: 240 g/h, screw speed: 130-150 rpm, torque: 1.5- 3 Nm and residence time: about 60-90 s). Different processing temperature zones maintained in the hot melt extruder as: 80, 100, 150°C and chiller < 10°C. Chill rolls were provided for instantaneous solidification of the extruded strands. A vacuum pump was connected to ensure efficient degassing of the extrudates. The extrudates were milled and passed through 60 # mesh screen.

DSC

Thermal behavior of the powder samples was characterized in differential scanning calorimeter (DSC, Universal V4.2E TA Instruments) using aluminum crucibles under dynamic nitrogen atmosphere. Heating rate of 10°C min⁻¹ under a temperature range from 30 to 280°C was maintained. The DSC cell was calibrated with indium (mp 156.6°C; $\Delta H_{fus} = 28.54 \text{ J}\cdot\text{g}^{-1}$).

FTIR

The pure drug, mesalamine and different formulations M_1E_1 , M_1E_2 , M_1E_3 , $M_1K_{0.5}P_{0.5}$, $M_1K_{1.5}P_{0.5}$ and $M_1K_2P_1$,

Table 1: Formulation of mesalamine by hot melt extrusion using polymeric carrier.

Formulation Code	Mesalamine (gm)	Polymer(s)	Polymer quantity (gm)	Drug-Polymer Ratio	Screw speed (rpm)	Feeder screw rate (rpm)	Torque (%)	Melt temp (°C)	Melt pressure (bar)	Yield (%)
M ₁ E ₁	12.5	Eudragit-EPO	12.5	1: 1	100-150	12	30-40	150-170	10 97.00 98.00 96.66 98.33 98.33	96.00
M ₁ E ₂	12.5	Eudragit-EPO	25	1: 2						
M ₁ E ₃	12.5	Eudragit-EPO	37.5	1: 3						
M ₁ K _{0.5} P _{0.5}	30	Kollidon VA-64 + PEG ₆₀₀₀	15 + 15	1: 0.5: 0.5						
M ₁ K _{1.5} P _{0.5}	20	Kollidon VA-64 + PEG ₆₀₀₀	30 + 10	1: 1.5: 0.5						
M ₁ K ₂ P ₁	15	Kollidon VA-64 + PEG ₆₀₀₀	30 + 15	1: 2: 1						

were mixed separately with IR grade KBr in the ratio of 100: 1 and corresponding pellets were prepared by applying pressure of 5 ton for 10 min in a hydraulic pellet press. The pellets were scanned 80 accumulations at a resolution of 4 cm⁻¹ over a wave number range of 400-4000 cm⁻¹ in fourier transform infrared spectrophotometer (FTIR-4100 type A, Jasco, Tokyo, Japan) using Spectra Manager software for data acquisition.

SEM

Surface morphology and crystalline nature of the particulate samples were investigated using Scanning electron microscope (Instrument JSM-6390, Jeol, Tokyo, Japan). The powder samples were dried and sputtered with gold and scanned at room temperature using an accelerated voltage of 10 kV (Wd 19 and Spot Size 48). Particle size distribution of the powder samples were determined by using Imagej software (<https://imagej.nih.gov/ij/download.html>).

In-vitro Dissolution

The *in vitro* drug release studies of all the samples were performed according to USP XXIII in dissolution apparatus (Electrolab (TDT06L) USP, rotating paddle method). Accurately weighed samples corresponding to 100 mg of mesalamine were placed in 900 ml of 0.1N HCl (Simulated gastric fluid: pH 1.2) at 37.0 ± 0.5°C and a rotation speed of 50 rpm). Samples (10 ml) were withdrawn through a 10 ml syringe at 10, 20, 30, 45, 60 and 90 min of time intervals and replaced with fresh medium. The samples were filtered through 0.45 µm membrane filter and analyzed by UV-Visible Spectrophotometer (Jasco- V360) at 232 nm. The amount of

drug release was expressed as cumulative percentage of mesalamine released in 0.1N HCl as a function of time. The dissolution experiments were repeated out in triplicate for each sample. The mean value of obtained result was calculated and used to plot *in vitro* release vs. time profile.

All the melt dispersion sample formulations were exposed at 40°C and 75 % RH for 3 weeks in a Humidity Cabinet (Thermotech, IKON Instrument, India) and DSC and FTIR spectroscopy study were performed.

RESULTS AND DISCUSSION

OMICRON 12 PHARMA is a co-rotating twin-screw laboratory Hot Melt Extruder System with the ability to generate outstanding dispersive and distributive mixing. Hot melt extrusion process parameters was adjusted for each formulated mixture depending on the physico-chemical characteristics of the individual polymer. For down-processing the temperature settings were chosen such that a semisolid, transparent strand was obtained being neither too brittle nor too soft. The feeding rate was maintained constant while the screw speed was slightly varied depending on the processability of the mesalamine-polymer mixture. After extrusion of the molten mixture through the die hole, the strand was air-cooled on an air-cooled conveyer belt and subjected to initial evaluation.

Drug excipient interaction and thermal stability of drug or drug-excipient mixtures are commonly identified by using DSC. The interactions are reflected in shifting or disappearance of characteristic melting endotherm and/or ΔH enthalpy variations.^{22,23} FTIR spectroscopy also

serves a complementary technique to identify atoms/groups²⁴ that are involved in drug-excipient interactions.¹⁸ The broadening or intensity changes of transmittance bands or appearances of new peaks represents the interactions and to sustain the results obtained by thermal analysis.²⁵

Figure 2 shows the DSC thermograms of mesalamine pure drug and hot melt dispersion samples. Thermogram of mesalamine exhibited a sharp endothermic peak at 279.29°C indicating the melting point of the drug.²⁵ In the case of the formulation $M_1K_{0.5}P_{0.5}$ and $M_1K_{1.5}P_{0.5}$, the endothermic peak intensity of mesalamine was significantly reduced, broadened and shifted to a lower temperature (from 279.29 to 263.69 and 257.29°C respectively) and almost disappearance of melting peak was observed in rest melt dispersion samples. The minor shifting with significantly reduced intensity and disappearance of peak could be attributed to some solid-solid interaction and not necessarily any incompatibility.^{19,26} Table 2 exhibits the thermal characteristics of mesalamine melt dispersion samples.

Infrared spectra of mesalamine and melt dispersion samples have shown in Figure 3: (a, b). The characteristic peaks of Mes spectra correspond to: 3435 cm^{-1} (overlapping of NH and OH stretching), 1651 cm^{-1} (C=O stretch), 1352 cm^{-1} (C-N stretch), 2000–3000 cm^{-1} (stretching vibrations of the hydrogen bonds in the mesalamine molecule).²⁷ The significantly reduced sharpness and intensity of characteristic IR bands of Mes in the spectra of Mes loaded melt extrusion samples may be explained by the existence of ionic, hydrogen and/or van der Waals' type interactions between Mes, Eudragit, Kollidon and PEG occurring during melt extrusion process.

The morphology and the surface characteristics²⁸ of Mes and melt dispersion samples were inspected using a scanning electron microscope (Figure 4a-f). Large crystalline forms of Mes were observed with ordered geometric shape and size (Figure 4a, b). Hot melt extrusion particles (M_1E_3 and $M_1K_2P_1$) are of very irregular shape and surface (Figure 4c-f). The agglomerate produced during hot melt extrusion and size of the individual crystallite comprising the agglomerate was also drastically less than the individual crystal of pure drug and the crystal geometry is significantly damaged. On overall basis it revealed that individual crystallites size comprising of M_1E_3 are less than that of $M_1K_2P_1$. This transformation of individual native drug crystal into irregular surfaced agglomerate of small crystallite could be the indication of partial or almost complete amorphization. Similar observations have been noticed during melt dispersion and comilling of ibuprofen-MCC.^{29,30}

Table 2: Thermal characteristics of mesalamine melt dispersion samples.

Formulation code	Onset (°C)	Endset (°C)	Melting peak (°C)	Enthalpy of melting (Jg^{-1})
Mes	243.50	312.50	279.29	-848.70
M_1E_1	187.50	292.00	238.81	-266.40
M_1E_2	181.00	231.00	229.95	-40.59
M_1E_3	175.00	265.50	234.37	-185.80
$M_1K_{0.5}P_{0.5}$	259.13	268.18	263.69	-301.14
$M_1K_{1.5}P_{0.5}$	252.16	262.34	257.29	-85.28
$M_1K_2P_1$	243.66	257.43	252.97	-19.28

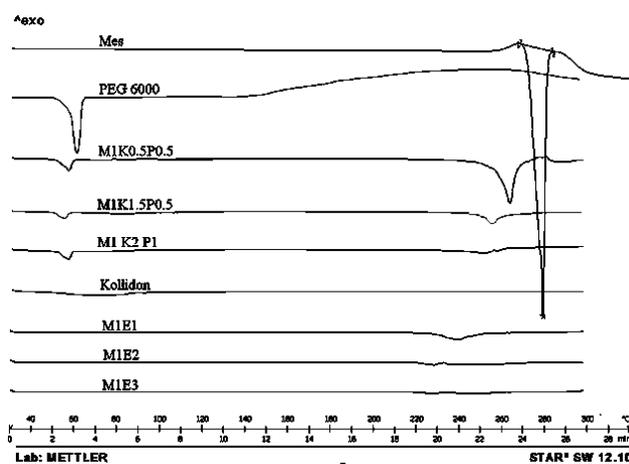


Figure 2: DSC thermogram of mesalamine, excipients and hot melt dispersion samples.

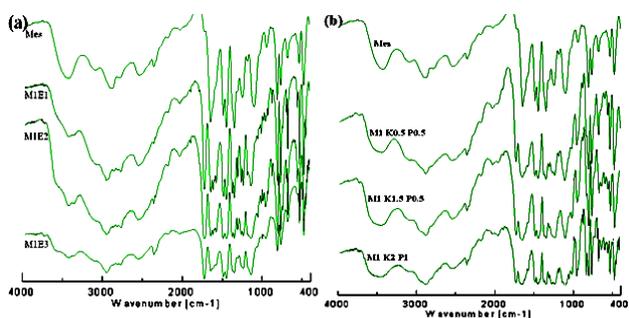


Figure 3: FTIR spectra of mesalamine and melt dispersion samples: (a) M_1E_1 , M_1E_2 and M_1E_3 ; (b) $M_1K_{0.5}P_{0.5}$, $M_1K_{1.5}P_{0.5}$ and $M_1K_2P_1$.

Particle size (Ferret diameter) distribution of the particulate powder sample was evaluated from the SEM images. An estimate of particle size along a specified direction as the distance between the two parallel planes restricting the particle perpendicular to that direction can be defined as the Ferret diameter. The crystalline micronized pure drug (mesalamine) particle size has been significantly reduced in melt extrusion technique (M_1E_3 and $M_1K_2P_1$) (Figure 5).

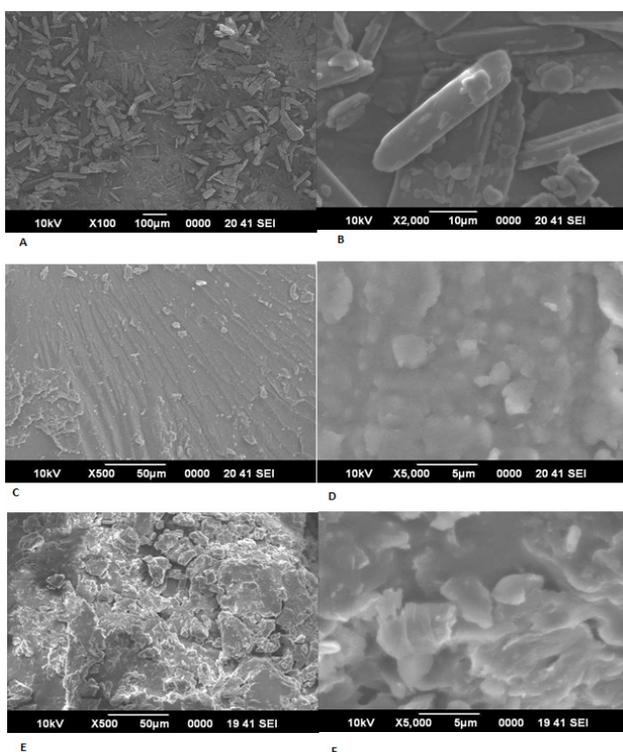


Figure 4: Photomicrographs of mesalamine and melt dispersion samples using scanning electron microscopy: (a) Mesalamine (magnification 100), (b) (magnification 2000); (c) M1E3 (magnification 500), (d) (magnification 5000); and (e) M₁K₂P₁ (magnification 500), (f) (magnification 5000).

Figure 6 depicts the dissolution profiles of six different melt dispersion samples. All the samples have shown significantly improved drug release (above 92 %) compared to mesalamine alone (78 %) in 0.1 N HCl within 90 min. M₁E₁, M₁E₂ and M₁E₃ have presented more improved dissolution (more than 97 %) than M₁K_{0.5}P_{0.5}, M₁K_{1.5}P_{0.5} and M₁K₂P₁ (more than 92 %). Eudragit EPO is highly flexible and gastric acid soluble methacrylate polymer which brought about faster drug release of M₁E₁, M₁E₂ and M₁E₃ compared to M₁K_{0.5}P_{0.5}, M₁K_{1.5}P_{0.5} and M₁K₂P₁ containing Kollidon VA-64 – polyethylene glycol. Immediate drug release in the gastric region is supposed to decrease the onset of action of mesalamine with improved bioavailability and could be formulated in tablet which can additionally mask the unpleasant taste of mesalamine.

Comparison of two dissolution profiles is based on the determination of a model independent statistical method, the difference factor f_1 and the similarity factor f_2 . Similarity or equivalence between two dissolution profiles is based on $f_1 \leq 15$ and $f_2 \geq 50$.^{31,32}

Drug release mechanism has been predicted to develop a rational formulation utilizing mathematical models. The drug release data was analyzed by applying different kinetic models as First order, Higuchi, Korsmeyer–

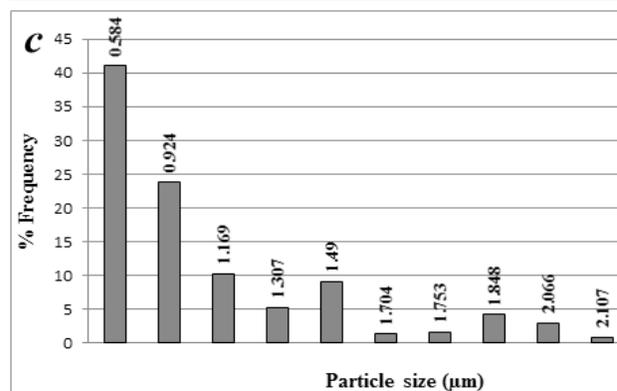
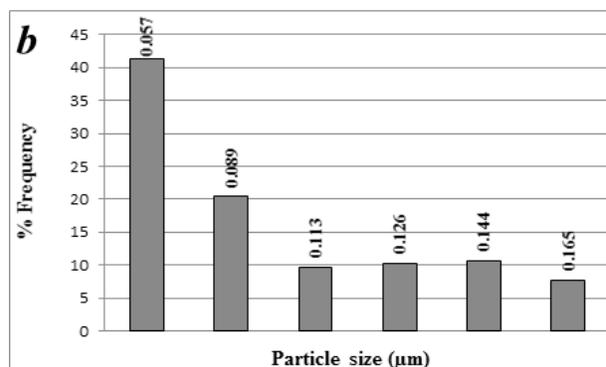
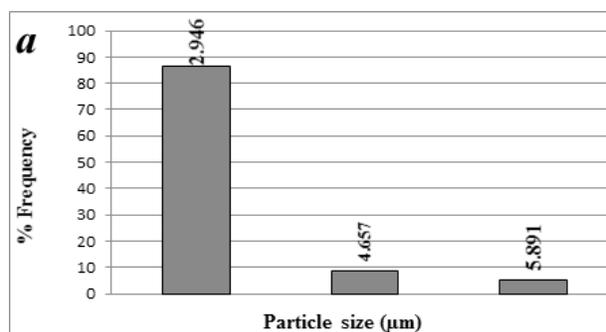


Figure 5: Feret diameter distribution of the melt dispersion powder sample estimated from SEM image: (a) Mesalamine, (b) M₁E₃, (c) M₁K₂P₁.

Peppas kinetics.³³⁻³⁵ These models are represented as follows:

$$\text{First order model: } \log(100 - Q) = \frac{K_F t}{2.303} \text{ ----- (i)}$$

$$\text{Higuchi model: } Q = K_H \times \sqrt{t} \text{ ----- (ii)}$$

$$\text{Korsmeyer-Peppas model: } Q = K_p \times t^n$$

$$\log Q = \log K_p + n \log t \text{ ----- (iii)}$$

Q = Cumulative percent drug release at time t

K_F = First order release rate constant

K_H = Higuchi release rate constant,

K_p = Parameter reflecting the structural and geometric characteristics of the delivery device, or Peppas release rate constant,

n = Power law exponent, or release exponent.

This n value indicates drug release controlled by Fick's laws and also confirmed by the Higuchi model. Matrix

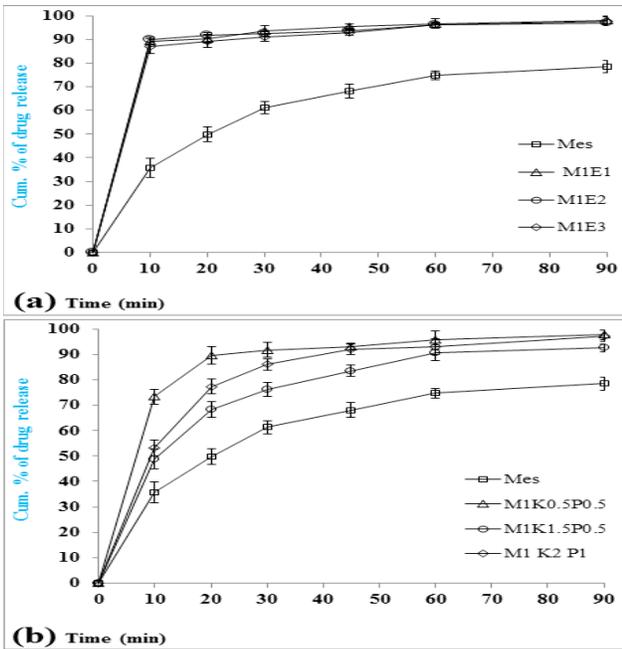


Figure 6: Dissolution profiles of melt dispersion samples of mesalamine: (a) M₁E₁, M₁E₂ and M₁E₃; (b) M₁K_{0.5}P_{0.5}, M₁K_{1.5}P_{0.5} and M₁K₂P₁.

controlled release has been followed (Figure 7). The kinetic parameters as per model are presented in the Table 3.

All the sample formulations have shown no major change in DSC and FTIR spectroscopy profiles after exposing at 40°C and 75 %RH for 3 weeks indicating good stability.

CONCLUSION

Stable solid dispersion of mesalamine formulations have been produced utilizing solvent-free continuous hot melt extrusion technique. The minor shifting with appreciably reduced intensity and disappearance of peak in the DSC thermogram indicated amorphization of the drug in the melt extrusion samples. The considerably reduced sharpness and intensity of characteristic IR bands of Mes in the spectra of Mes loaded melt dispersion samples revealed the type of interactions between Mes, Eudragit, Kollidon and PEG due to ionic, hydrogen and/or van der Waals' type forces. SEM analysis

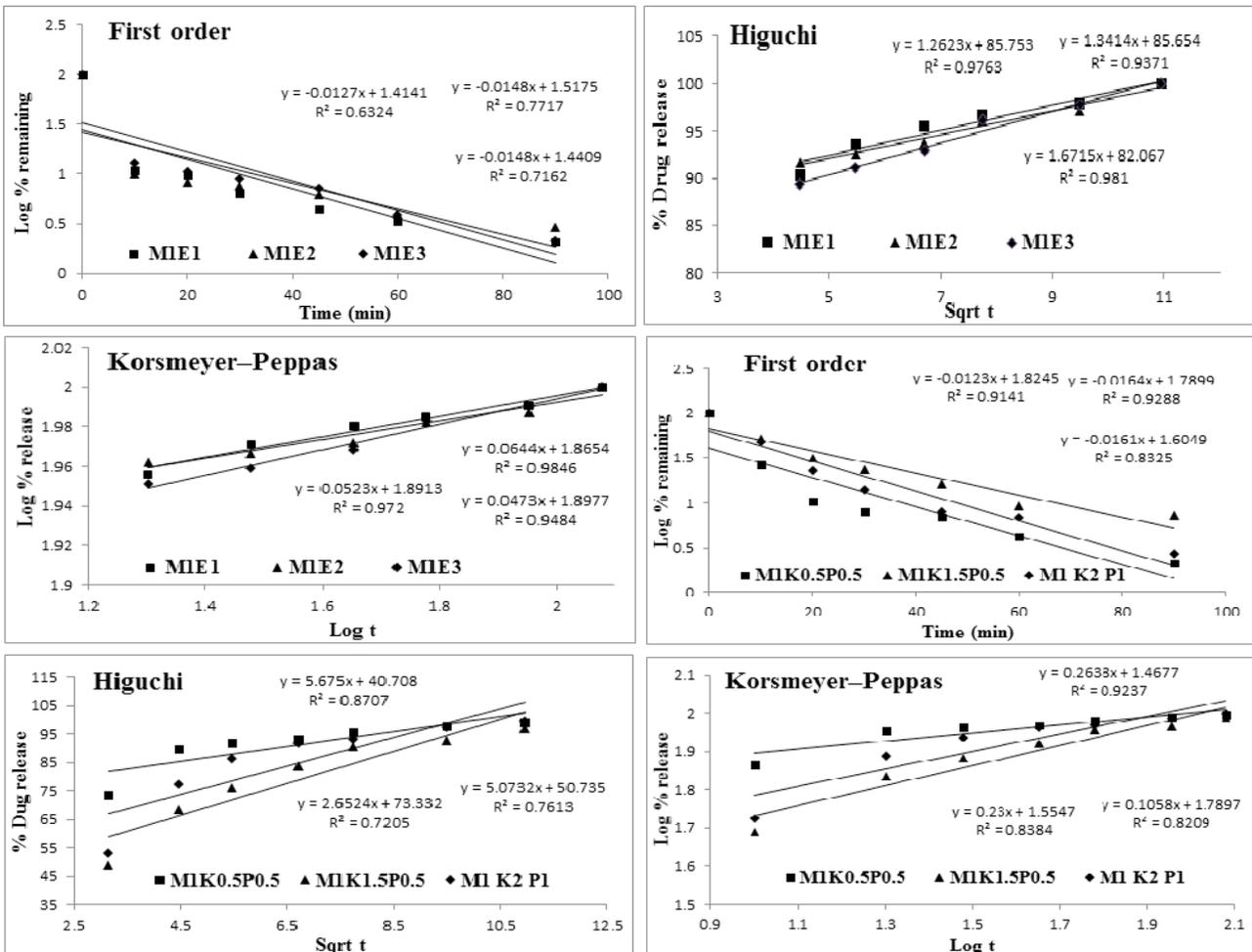


Figure 7: Model kinetics of dissolution profiles of melt dispersion samples.

Table 3: Model fitting and kinetic parameters of drug dissolution of formulations.

Formulation	f_1	f_2	First order		Higuchi		Korsmeyer–Peppas		
			K_F (min^{-1})	r^2	K_H ($\% \cdot \text{min}^{-1/2}$)	r^2	n	K_p	r^2
$M_1K_{0.5}P_{0.5}$	7.33	34.92	1.604	0.832	73.33	0.971	0.105	61.517	0.820
$M_1K_{1.5}P_{0.5}$	6.61	40.07	1.824	0.914	40.70	0.919	0.263	29.308	0.923
$M_1K_2P_1$	0.30	49.06	1.789	0.928	50.73	0.882	0.230	35.809	0.838
M_1E_1	11.13	26.68	1.440	0.716	85.65	0.937	0.052	77.803	0.972
M_1E_2	10.75	26.46	1.414	0.632	85.75	0.976	0.047	78.886	0.948
M_1E_3	9.65	27.75	1.517	0.771	82.06	0.981	0.064	73.282	0.984

confirmed the transformation of individual native drug crystal into small crystallite agglomerate due to partial or almost complete amorphization. All the samples have shown appreciably enhanced drug release compared to mesalamine alone in the simulated gastric fluid within 90 min. Presence of Eudragit EPO increased drug release of M_1E_1 , M_1E_2 and M_1E_3 relatively more compared to the presence of Kollidon VA-64 – polyethylene glycol ($M_1K_{0.5}P_{0.5}$, $M_1K_{1.5}P_{0.5}$ and $M_1K_2P_1$). Improved drug release by Eudragit EPO could be utilized in formulating tablet to decrease the onset of action, enhanced bioavailability and additionally taste masking for better management of inflammatory bowel disease.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

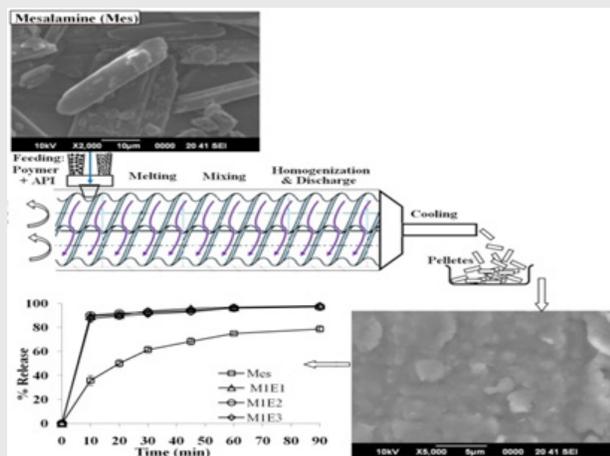
Mes: Mesalamine; **DSC:** Differential Scanning Calorimetry; **FTIR:** Fourier Transform Infrared; **SEM:** Scanning Electron Microscopy; **HME:** Hot-melt Extrusion; **IBD:** Inflammatory Bowel Disease; **API:** Active Pharmaceutical Ingredient; **PVP:** Polyvinylpyrrolidone; **PEG:** Polyethylene glycol 4000.

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PICTORIAL ABSTRACT



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SUMMARY

- Mesalamine and hydrophilic polymers were hot melt extruded using co-rotating extruder.
- Reduced intensity and disappearance of peak in DSC thermogram attributed to amorphization of mesalamine.
- FTIR and SEM confirmed accumulation of small crystallites due to amorphization of mesalamine.
- Solvent-free drug loading extrusion technique could be feasible in improving drug release.
- Melt dispersion of mesalamine with Eudragit-EPO, KollidonVA-64 and PEG 6000 may be feasible for better management of IBD.



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