Physicochemical characterization of olmesartan medoxomil: polymer solid dispersions by hot melt extrusion for dissolution rate enhancement

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Aim
The prime objective of this investigation was to improve solubility and dissolution rate of poorly water-soluble drug, olmesartan medoxomil, by preparation of stable solid dispersions (SDs) of low glass transition temperature employing hot-melt extrusion technique.
Materials and methods
Soluplus (SOL) was used as a primary solubilizing agent along with different solubility/absorption enhancers such as polyethylene glycol (PEG)-8000 and Kolliphor F127. After extrusion, the extrudates were pelletized, and physical state of the drug was assessed using powder X-ray diffraction and differential scanning calorimetry techniques.
Results
The SDs were found to be amorphous, thermodynamically and physicochemically stable. Scanning electron microscopy of the formulations revealed a surface, indicating absence of crystallinity. The drug content was found to be in the range of 98.16±1.3 to 99.98±1.1%. The dissolution performance of the extrudates was compared with that of the pure drug, and substantial improvement was observed in the order of SOL-PEG-8000>SOL-KF127>SOL only. *In-vitro* drug release rate was Higuchi matrix controlled, and the release rate mechanism was found to be non-Fickian. Stability studies over a period of 3 months indicated amorphous nature of drug in the formulation, and no significant deviations were observed in the drug content and *in-vitro* drug dissolution characteristics.
Conclusion
Hot melt extrusion technology promises an ideal platform for enhancing the solubility and dissolution of poorly water-soluble drugs. The results obtained suggest that olmesartan medoxomil in the form of SDs has potential for oral drug delivery and could be an efficacious approach for enhancing therapeutic potential.

Keywords:
hot-melt extrusion, Kolliphor F127, olmesartan medoxomil, polyethylene glycol-8000, solid dispersion, soluplus

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Introduction

Oral drug delivery is by far the most preferred route for medication, and most new chemical entities in drug discovery are intended to be used as solid oral dosage forms [1]. Owing to the emergence of high throughput screening and combinatorial chemistry in drug discovery, it is estimated that at least 40% of new chemical entities under development may exhibit very poor solubility and hence low bioavailability. The scientific framework of bio-pharmaceutical classification system (BCS) categorizes drug substances into IV groups based on their solubility and permeability characteristics [2,3]. Amongst them, dissolution will be the rate-limiting step for BCS class II and IV drug substances. Enhancing the oral bioavailability of poorly water-soluble drugs is one of the most challenging aspects of the drug product development process. Pharmaceutical scientists, over the years, have been successful in developing several strategies for improving solubility and designing of delivery systems for poorly water soluble drugs [4]. Solid dispersions (SDs) prepared by hot melt extrusion (HME) technology is one such strategy that over the past three decades has led to enhancing the aqueous solubility and innovation of several unique drug delivery systems.

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HME is a continuous process of converting a raw material into a product of uniform shape and density by forcing it through a die under high temperature and pressure, thereby making it possible to extrude solids resistant to shear forces [5]. By selecting a suitable exit die, a variety of solid dosage forms including granules, pellets, tablets, suppositories, implants, stents, ophthalmic inserts, and transdermal and transmucosal systems can be produced [6]. HME technology can be employed to formulate drug-polymer molecularly dispersed systems, which can be termed as SDs or solid solutions [7]. HME is an industrially scalable continuous manufacturing technique without the necessities of additional drying or process fragments [8]. HME technology has many advantages over traditional processing techniques such as spray drying or coevaporation, which involve use of organic solvents [9]. Homogenous monophase systems with the drug molecularly dispersed in the polymer matrix, is a challenging delivery, as such systems are intrinsically metastable [10]. The formation of melt extrusion involves the exchange of heat energy during HME process and followed by instant cooling of the melt which affects thermodynamic and kinetic properties of forming SD variance [11]. Use of highly water-soluble carrier in SD always increases the chances of crystallization owing to swelling behavior upon coming in contact with the aqueous gastrointestinal fluid [12]. Therefore, surface active agents or surfactants are used as inhibitors for recrystallization. HME has the unique property to maintain the amorphous state of the drug after the formation of SD.

Numerous methodologies have been reported in the literature for preparation of amorphous SD such as melt method, solvent evaporation, cyclodextrin inclusion complex, and cryomilling, which explains the importance of SD type of formulation strategy [13]. The underlying principles for improving the dissolution properties of drug by SD techniques is mainly attributed to reduction in particle size, alteration of the crystalline morphology, and intimate mixing of drug with hydrophilic excipients. By altering the bulk drug according to these principles, drug surface area is increased, the thermodynamic barrier to dissolution imposed by crystal lattice is eliminated, and the wetting properties of the drug particles are enhanced. In comparison with the traditional methods for preparation of SDs, HME is a promising novel technology for improving the solubility and bioavailability of water-insoluble drugs, thus offering many advantages for pharmaceutical applications [14].

Olmesartan medoxomil (OLM) is an angiotensin II receptor antagonist that has favorable safety and efficacy profile in the treatment of hypertension. OLM is an ester-type prodrug that is metabolized to the pharmacologically active compound, olmesartan, as a result of de-esterification by arylesterase in the gastrointestinal tract. OLM reduces blood pressure through arterial vasodilatation and reduced sodium retention [15]. Despite being widely used clinically, OLM has very low oral bioavailability of 26% in healthy humans owing to several factors, namely, low aqueous solubility, efflux by P-glycoprotein, and unfavorable breakage of the ester drug in the gastrointestinal fluids leading to the formation of poorly permeable parent molecule with a log *P* value of 5.55 [16,17]. The unabsorbed drug leads to gastrointestinal adverse effects such as abdominal pain, dyspepsia, gastroenteritis, and nausea [18].

OLM is a weakly basic compound (pKa: 4.3), is highly lipophilic, and has been classified as class IV, according to the BCS, where its dissolution is the rate-limiting step for absorption. The low aqueous solubility ($<5.5\,\mu g/ml$) hinders its oral absorption and bioavailability [19]. So far, only few formulation strategies for improving dissolution of OLM have been investigated, which include liquisolid compacts [20], mouth dissolving tablets [21], nanosuspensions [22], and self-emulsifying drug delivery systems [23]. However, there is no reported literature on the enhancement of solubility of OLM by HME method. Subsequently, there is a need to deliver OLM in formulation with increased solubility and improved dissolution profile.

Soluplus (SOL) – a novel polymer with amphiphilic properties – is explored for its solubilizing potential using HME technology. SOL is a polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol (PEG) graft copolymer especially designed for HME process [24]. It offers exceptional capabilities for solubilization of BCS class II and class IV drugs, with the extensive possibility of making SD by HME. PEG-8000 and Kolliphor F127 (KF127) are used as solubility/absorption enhancers for active substances usually processed in the form of a melt extrusion and as plasticizer to decrease the processing temperature in extruder. In the present investigation, the prime objective was to improve solubility and dissolution rate of OLM by preparation of stable SD of low glass transition temperature (*T*g) employing HME technique. The SDs were characterized physicochemically using various analytical techniques to understand the drug-polymer molecular interactions.

Materials and methods

OLM was obtained as a generous gift from Apotex Research Private Limited (Bangalore, India). SOL (polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer), and KF127 (poloxamer 407) were gifted by BASF Corporation (Mumbai, India). Polyethylene glycol 8000 was procured from SD Fine Chemicals (Mumbai, India). All other chemicals and reagents used were of analytical grade or equivalent quality.

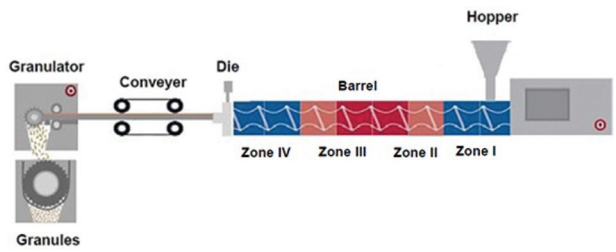
Hot melt extruder

Corotating twin screw extruder, Prism PharmaLab 16 (Thermo Fisher Scientific, Karlsruhe, Germany), with a screw diameter of 16 mm and length/diameter ratio of 40 : 1, was used for HME. A screw configuration with two kneading zones and a barrel which is divided into four zones was used. The different zones are (I) feeding zone, (II) melting zone and melt conveying zone, (III) dispersing zone and homogenizing zone, and (IV) degassing and discharging zone. In zone IV of the barrel, a venting port is present which was connected to vacuum pump for efficient degassing of the molten material. Barrel zone I is the feeding zone and cannot be heated. The temperature setting of barrel zones II, III, and IV can be set individually by the user. The same applies for the die plate. Owing to the different physicochemical characteristics of the employed carriers, the temperature and screw-speed settings were varied to obtain a semisolid, transparent strand for each formulation suitable for down-processing. The molten mixture extruded through the die system will be air cooled on a conveyer belt. The extrudate is then passed through downstreaming equipment such as chilled rolls, calendering, and pelletizing device to f inish, shape, and analyze the extruded product. A schematic diagram of a hot melt extruder is portrayed in Fig. 1.

Preparation of solid dispersion

The SDs of OLM were prepared by HME technique using SOL as hydrophilic carrier and PEG-8000/KF127 as solubility/absorption enhancers [25].

Figure 1



Schematic diagram of Hot Melt Extruder.

OLM, SOL, and PEG-8000/KF127 were weighed accurately in different ratios and passed through ASTM sieve number 40 and blended in double cone blender for 10 min. These blends were then processed in the hot melt extruder. The temperature of the heating zones was adjusted in such a manner that the drug – polymer mixture melted and did mix well to give a uniform SD. The formulation compositions of various SDs are presented in Table 1.

The temperatures for processing were selected based on the *T*g of the polymer and melting point of the drug. As a general rule, an extrusion process should be conducted at a temperature range of 20–40°C above the *T*g of the polymer and melting point of the drug. The melting point of the OLM is observed to be in the range of 175–180°C, and the *T*g of the SOL (70°C) was taken into consideration while setting the temperature of the heating zones. During the process of extrusion, temperatures of 90–130–170–190°C (±5–10°C) across the four heating zones and an rpm of 100±5 were maintained for intense mixing to obtain uniform and efficient SDs. The torque was maintained by regulating the feed rate of the blend into the screw feeder. The molten mixture was extruded through a 3-mm die hole and air-cooled on a conveyer belt (Pharma 16 mm air cooled conveyor belt; Thermo Fisher Scientific). The strand was then pelletized into pellets with a set length of 1.0 mm (Pharma 16 mm Varicut pelletizer; Thermo Fisher Scientific). The granules obtained were stored in airtight HDPE containers with desiccants at controlled room temperature of 25°C/60% RH. The SDs were then characterized by differential scanning calorimetry and powder X-ray diffraction (PXRD) to confirm the conversion of crystalline drug into amorphous form, and drug-carrier interaction studies were evaluated by Fourier transform-infra red (FTIR) spectroscopy. The granules were also subjected to solubility studies, drug content determination, *in-vitro* dissolution, and stability studies.

Table 1 Formulation composition of olmesartan medoxomil-loaded solid dispersions

Formulation code	Carrier	Surfactant	Drug : carrier : surfactant ratio	Quantity taken (g)
OS1	SOL	–	1 : 2	20+40
OS2	SOL	–	1 : 4	20+80
OSP1	SOL	PEG-8000	1 : 1.8 : 0.2	20+36+4
OSP2	SOL	PEG-8000	1 : 3.8 : 0.2	20+76+4
OSK1	SOL	KF127	1 : 1.8 : 0.2	20+36+4
OSK2	SOL	KF127	1 : 3.8 : 0.2	20+76+4

PEG, polyethylene glycol; SOL, soluplus.

Solubility studies

Saturation solubility study

An excess quantity of OLM along with SD formulations was placed in 20-ml capacity test tubes containing 10 ml of distilled water, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer separately [26]. The samples were sonicated for 20 min at room temperature, and capped glass test tubes were shaken for 48 h at 37±0.1°C, speed 75 rpm, using orbital shaking thermostable incubator (Boekel Scientific, Pennsylvania, United States). The solutions in the test tubes were centrifuged for 20 min at 10,000 rpm. The supernatant solution was then passed through a Whatman (Sigma Aldrich, Bangalore, India) filter paper (grade 1), and the amount of the drug dissolved was analyzed spectrophotometrically (Elico SL-159 UV-Visible Spectrophotometer; Elico Limited, Hyderabad, India) at 257 nm. The solubility measurements were performed in triplicate, and the data obtained are presented in Table 2.

Phase solubility study

Phase solubility study was performed according to the method described by Higuchi and Connors [27]. An excess amount of OLM along with SDs formulations was placed in 20-ml test tubes containing 10 ml of distilled water with different concentrations of SOL separately. SOL (1, 2, 3 and 4% w/v) was used as hydrophilic polymer. In the formulation containing mixture of OLM, SOL, and PEG-8000, the equivalent percentage of PEG-8000 (i.e. ratio of solubility/absorption enhancers used in different SDs formulations) was also added along with SOL (1, 2, 3, and 4% w/v). In the formulation containing mixture of OLM, SOL, and KF127, the equivalent percentage of KF127 (i.e. ratio of solubility/absorption enhancers used in different SDs formulations) was also added, respectively, along with SOL (1, 2, 3 and 4% w/v). Test tubes were covered with cellophane membrane to avoid solution loss and then shaken (75 rpm/min) in orbital shaking incubator (Boekel Scientific) for 48 h at 37± 0.1°C. The solutions in the test tubes were kept for centrifugation for 20 min at 10,000 rpm. Overall, 5 ml of supernatant was withdrawn and filtered through Whatman filter paper (grade 1). The filtrates were analyzed using a UV-visible spectrophotometer at a λ_{max} of 257 nm after suitable dilution. All solubility measurements were performed in triplicate, and the results obtained are depicted in Fig. 3.

Investigation of drug polymer compatibility

FTIR spectroscopy helps us to determine any chemical interaction between drug and excipients used in formulation [28]. FTIR analysis was performed on sample of Pure drug OLM, SOL, PEG-8000, KF127, and SD formulations using a FTIR spectrophotometer (FTIR-8400; Shimadzu, Kyoto, Japan) [29]. All the samples were crushed with dry potassium bromide using a mortar and pestle to get pellets at 600 kg/cm^2, and analyzed over a range of 4000–600 cm^{-1}.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to investigate the drug-polymer interactions and thermal behavior of drug [29]. DSC thermograms of pure drug OLM, SOL, PEG-8000, KF127, and SDs formulations were generated using differential scanning calorimeter (DSC-60; Shimadzu). DSC aluminum cells were used as sample holder, and blank DSC aluminum cell was used as reference. Overall, 2.3 mg of sample was used for analysis. The thermograms were recorded over the range of 25–325°C at a constant rate of 10°C/min under an inert atmosphere flushed with nitrogen at the rate of 20 ml/min.

Powder X-ray diffraction studies

The qualitative PXRD studies were performed using an X-ray diffractometer (X'Pert Pro; PANalytical B.V., Almelo, The Netherlands) [29]. Pure drug OLM, SOL, PEG-8000, KF127, and SD formulations were scanned from 0 to 400 diffraction angle (2θ) range under the following measurement conditions: source, nickel filtered Cu-Kα radiation; voltage 40 kV; current 30 mA; and scan speed 0.05/min. SDs formulations were triturated to get fine powder

Table 2 Saturation solubility data and %drug content for olmesartan medoxomil and solid dispersion formulations

Formulation code	Solubility (mg/ml)			%Drug content
	Distilled water	pH 4.5 acetate buffer	pH 6.8 phosphate buffer	
OS1	0.108±0.1	0.077±0.3	0.726±0.5	98.54±0.3
OS2	0.197±0.2	0.113±0.1	1.112±0.6	98.16±1.3
OSP1	0.123±0.4	0.102±0.3	0.846±0.4	99.22±1.2
OSP2	0.165±0.4	0.155±0.2	1.108±0.8	99.98±1.1
OSK1	0.119±0.3	0.092±0.5	0.780±0.5	99.54±0.8
OSK2	0.152±0.3	0.116±0.4	0.917±0.6	98.92±1.3

Values are expressed as mean±SD.

before taking the scan. X-ray diffractometry was carried out to investigate the effect of HME process on crystallinity of the drug.

Scanning electron microscopy

The shape and surface morphology of the OLM powder and OLM-loaded SD were examined using scanning electron microscope (SEM) (JSM 840A; JEOL Technics Co., Tokyo, Japan). During the analysis, double-sided adhesive tape was affixed on aluminum stubs over which powder sample of OLM and prepared SD was sprinkled. The stubs were then coated with gold using a sputter coater (JEOL Fine coat JFC 1100E, ion sputtering device; JEOL Technics Co.) under high vacuum and high voltage to achieve a film thickness of 30 nm. These prepared coated stubs were then placed in the vacuum chamber of a SEM and adjusted to maximum magnification to obtain excellent quality scanning images. Then, those samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 Torr, acceleration voltage: 10–20.00 kV). SEM images were obtained at maximum and visible magnification to understand the surface interaction between drug and polymer [30].

Estimation of drug content

SD formulations equivalent to 40 mg of drug were taken and dissolved in methanol and filtered using 0.45 µm membrane filters [31]. Then the filtrate was suitably diluted with pH 6.8 phosphate buffer and drug content was analyzed against blank by using UV visible-spectrophotometer (Elico SL-159 UV-Visible Spectrophotometer; Elico Limited, Hyderabad, India) at 257 nm. The concentration of drug present in SD is compared with that of standard solution containing 40 mg of pure drug. The percentage of drug present in the SDs was calculated in respect to standard concentration.

In-vitro dissolution studies

The *in-vitro* dissolution rate properties of pure OLM and OLM-loaded SDs were performed in Electrolab 8 stage dissolution apparatus. SD formulations equivalent to 40 mg of OLM were filled in capsules, and dissolution was carried out using rotating paddle with helical sinkers at an agitation speed of 50 rpm employing 900 ml of pH 4.5. Acetate buffer and the temperature was maintained at 37±0.5°C throughout the experiment. Samples (5 ml) were withdrawn from each vessel at predetermined time intervals, filtered over a cellulose acetate filter of 0.45 µm, diluted suitably, and the absorbance was read at the λ_{max} of 257 nm against the reagent blank. Each time, the sample withdrawn was replaced with equal volume of buffer to maintain a constant volume of dissolution medium [32]. The dissolution studies were carried out in triplicate.

Dissolution kinetics

For understanding the mechanism of drug release and release-rate kinetics of the drug from the SDs formulations, the obtained *in-vitro* drug dissolution data were fitted into software (PCP Disso-V2.08) (Poona College of Pharmacy, Pune, India) with zero order, first order, Higuchi matrix, Hixson–Crowell, Korsmeyer, and Peppas model. By analyzing the *R* (regression coefficient factor) values, the best fit model was arrived at [33].

Stability testing

To investigate the effects of temperature, humidity, and the duration of storage on the product, the stability of the extrudates was assessed. Stability studies for the formulations were carried out as per ICH guidelines [34]. Selected formulations were packed in HDPE containers, closed with airtight closures, and stored at room temperature 25±2°C/60±5% RH and at an accelerated temperature 40±2°C/75±5% RH for three months using programmable environmental test chambers (REMI Instruments Ltd, Mumbai, India). The formulations were then analyzed at the end of 30, 60, and 90 days for PXRD studies, drug content, and *in-vitro* drug release characteristics.

Results and discussion

The main advantages of HME technology is its simplicity and economy. An important requisite for the formation of SDs by the hot-melt method is the miscibility of the drug and the carrier in the molten form and thermostability of both the drug and the carrier. Various parameters such as polymer *T*g temperature, processing temperature, drug substance and polymer degradation temperature, and amount of plasticizer required dictate the ease of manufacturing of SDs using melt extruder. During the initial feasibility trials, lower drug-to-SOL ratio (1 : 0.5 and 1 : 1) was taken and extruded to prepare SDs. But the extrudates obtained were sticky, nonuniform, and unable to get powdered. Henceforth, we performed the process at higher ratios of SOL and implementing the use of various solubility/absorption enhancers for the ease of process operation as also to improve the uniformity. Higher ratios of SOL exhibited good extrudability with uniformity. Different solubility/absorption enhancers such as PEG-8000 and KF127 were used in very small concentration

SD approaches to drug dissolution enhancement typically involve the generation of a solid solution in which the drug is present in a metastable amorphous state possessing a high internal energy and specific volume. Consequently in the formulation and design of SDs, it becomes extremely important to have analytical methods that allow for screening of these factors and the role they may have on the physicochemical properties of the dispersion. In particular, methods such as DSC, PXRD, drug dissolution, SEM, and spectroscopic FTIR techniques are often used for current research studies.

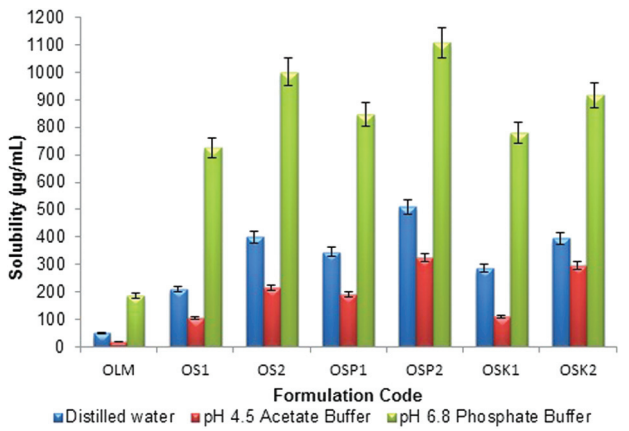
Solubility studies

The solubility of the drug in the presence of concentrated solutions of a polymeric carrier can support to determine the mechanism of dissolution from a SD. To examine the solubilizing power of SOL and used surfactants, the equilibrium solubility of crystalline OLM in distilled water, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer was determined and compared with the equilibrium solubility of the SD formulations. Aqueous solubility of all the formulations was carried out and compared with that of the pure OLM. Solubility studies revealed the significant improvement in solubility of all SD formulations in water, pH 4.5 acetate buffer, and in pH 6.8 phosphate buffer. Solubility enhancement was found be in the order of OSP>OSK>OS. All solubility measurements were performed in triplicate and are shown in Fig. 2.

Phase solubility studies

Phase inversion or transformation of phase of drug in polymeric environment with different concentration in water was studied to understand the effect of SD when it comes in contact with the gastrointestinal fluid [12].

Figure 2

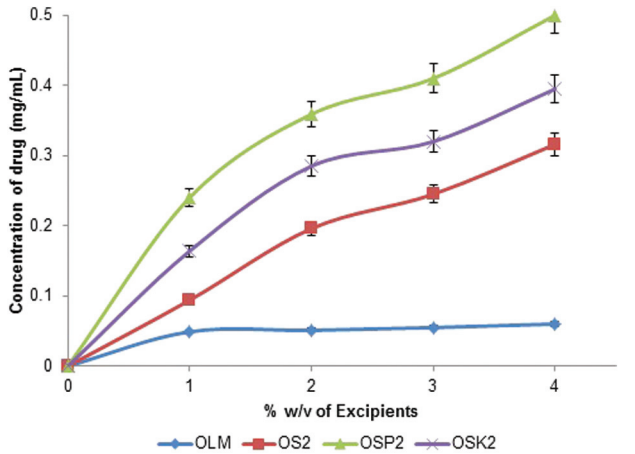


Solubility of OLM and SD formulations in water, pH 4.5 Acetate Buffer and pH 6.8 phosphate Buffer (mean ± SD ($n = 3$)).

The results of phase solubility studies are shown in Fig. 3. The phase solubility is a function to examine the solubilizing ability of polymer to solubilize drug in water in different concentrations. Phase solubility studies were carried out, as the aqueous solubility is considered to be an important criterion for bioavailability of drug in gastrointestinal fluid. In comparison with the solubility of pure OLM, a significant improvement in solubility was obtained with SDs formulations processed by HME. It can be observed that with increase in the concentration of excipient, solubility of OLM increased, and highest solubility was noted in formulation OSP2 (SOL-PEG-8000) followed by OSK2 (SOL-KF127) and then OS2 (SOL).

The possible interaction between the drug and the carrier was studied by FTIR spectroscopy. IR spectra of OLM showed characteristic peaks at 2974 cm^{-1} (aliphatic C–H stretch), 3039 cm^{-1} (aromatic C–H stretch), 3271 cm^{-1} (broad, intermolecular hydrogen bonded, O–H stretch), 1720 cm^{-1} (C=O of carboxylic group), 1504 cm^{-1} (ring C=C stretch), 1483 cm^{-1} (C–N stretch), 1371 cm^{-1} (in plane O–H bend), and 1053 cm^{-1} (ring C–O–C stretch). The characteristic peaks of OLM were not affected and prominently observed in IR spectra of OLM along with SOL and PEG-8000/KF127. Characteristic peaks of the individual excipients were also retained; moreover, no new peak was found in drug-loaded mixtures. In the FTIR study, the breakdown of the intermolecular hydrogen bond between the crystalline drug molecule and formation of hydrogen bond between the drug and the polymers might be related to the slight shift of the absorption band. However, FTIR spectra of SD formulations proved that no changes have occurred

Figure 3

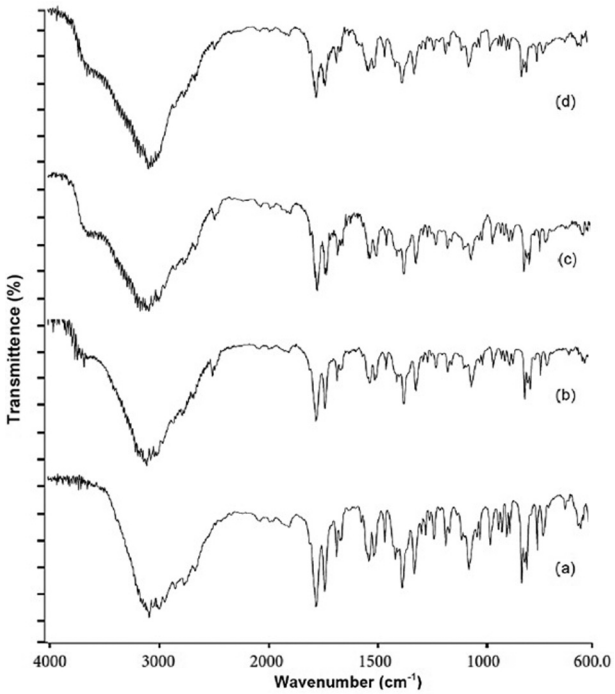


Phase solubility of OLM and SD formulations in water (mean ± SD ($n = 3$)).

in chemical structure. The strong interaction between drug and carrier often leads to identifiable changes in the IR profile of the drug but the results of IR spectra indicated an absence of any well-defined interaction or incompatibility between OLM and SOL, PEG-8000, and/or KF127. The FTIR spectra of pure drug OLM and SDs formulations (OS2, OSP2, and OSK2) are presented in Fig. 4.

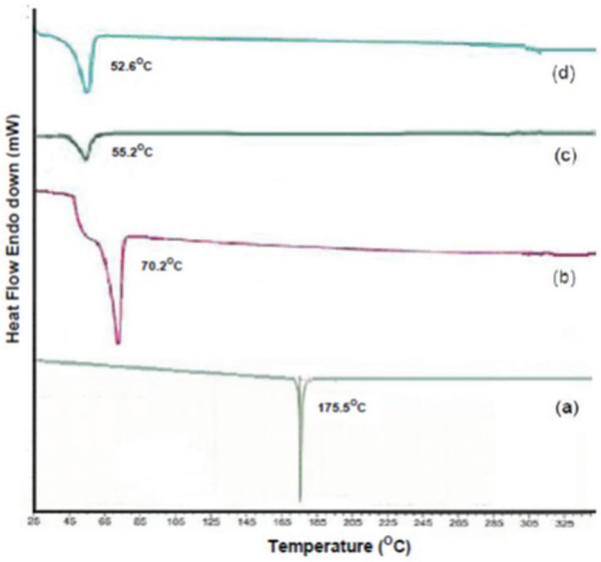
The DSC thermograms of pure OLM, SOL, PEG-8000, and KF127 are represented in Fig. 5, and DSC thermograms of the SD formulations are presented in Fig. 6. The DSC thermogram of crystalline OLM showed a single peak endotherm at 175.5°C, which was ascribed to drug melting. SOL exhibited a sharp endothermic peak at 70.2°C whereas KF127 and PEG-8000 revealed shallow endotherms at 55.2 and 52.6°C, respectively. The DSC thermogram of SDs formulation OS1 and OS2 showed a sharp endotherm at 70.5°C, indicating *T*g of SOL, and no characteristic peak was observed at 175.5°C, suggesting that OLM is molecularly dispersed in the matrix. SD formulations OSP1 and OSP2 composed of OLM, SOL, and PEG-8000 exhibited a smaller broad endotherm in the region of 51.9–53.5°C, corresponding with the melting of PEG-8000, and a sharp endotherm at 70.1°C, corresponding with the melting of SOL, whereas in the endotherm of OLM was completely absent. Similarly, SD formulations of OLM with SOL and KF127 (OSK1 and OSK2) exhibited a first endothermic peak in the region of 55.4–55.7°C, ascribed to the melting of KF127 and a second sharp endotherm at 70.4°C, corresponding with the melting of SOL, whereas in the endotherm of OLM was completely absent. It appears that the *T*g and melting peak of carriers and surfactants were merged. The melting peak of OLM in all the SDs formulations

Figure 4



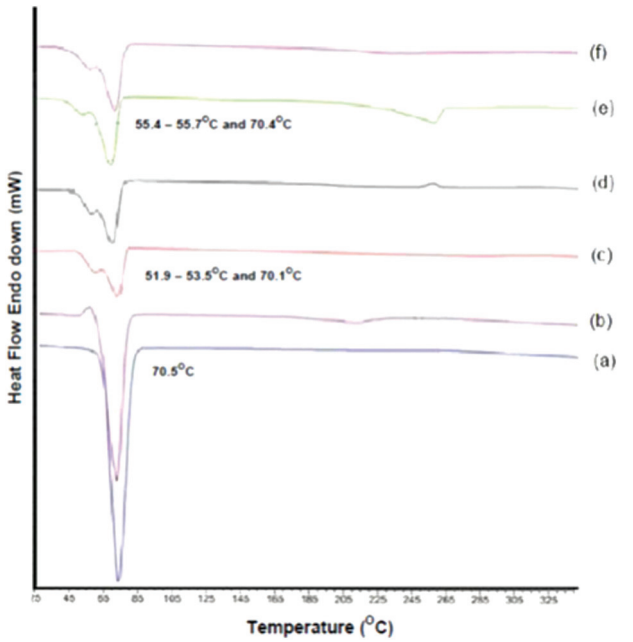
FTIR spectroscopic diagrams of OLM (a), SD formulation OS2 (b), OSP2 (c) and OSK2 (d).

Figure 5



DSC Thermogram of pure drug OLM (a), SOL (b), PEG-8000 (c) and KF 127 (d).

Figure 6



DSC Thermogram of SD formulations – OS1 (a), OS2 (b), OSP1 (c), OSP2 (d), OSK1 (e) and OSK2 (f).

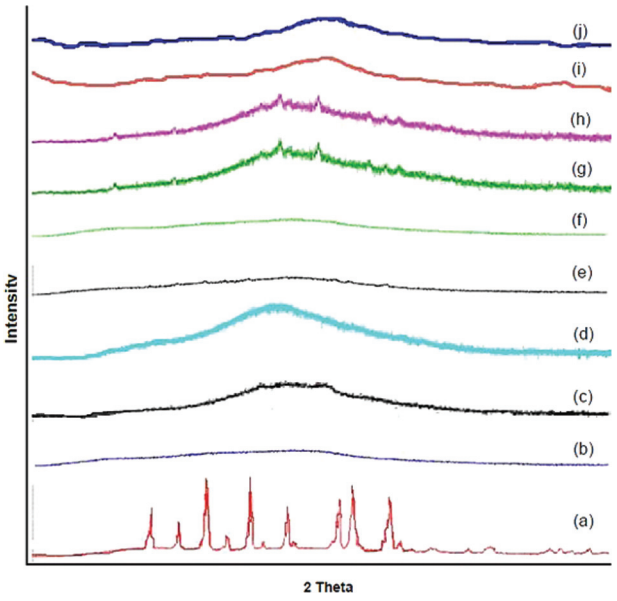
was absent which confirms the transformation of crystalline OLM into an amorphous OLM. The aforementioned hypothesis has been additionally clarified by PXRD analysis.

The PXRDs recorded for pure OLM, SOL, KF127, PEG-8000, and SD formulations are portrayed in Fig. 7. OLM exhibited numerous distinctive peaks in the region of 7°–35° (2θ), of which characteristic intense peaks are at 2θ of 16°, 21°, and 22° that indicated the crystalline nature of OLM. The diffractograms of SOL, PEG-8000, and KF127 showed a halo pattern with only few peaks with very weak intensities indicating the amorphous nature of the carrier and surfactants. On the contrary, the diffraction patterns of SD formulations showed decrease in the peak intensity and finally absence of peaks which indicated the amorphous nature of OLM in SDs is considered to be the reason for the dissolution and solubility enhancement.

The results of surface morphology studies are shown in Fig. 8. The pure drug OLM appeared in the form of irregular-shaped crystals, whereas SD formulations revealed homogenous uniform surface of extrudates which indicates the miscibility of OLM and polymer. Moreover, no drug crystals were observed on the surface of the extrudates.

The drug content in prepared SDs was estimated spectrophotometrically by measuring the absorbance at 257 nm, and the recordings are presented in Table 2. All the SDs were found to have excellent entrapment of drug in the carrier. The OLM drug content in all the dispersions was found to be in the range of 98.16±1.3 to 99.98±1.1%.

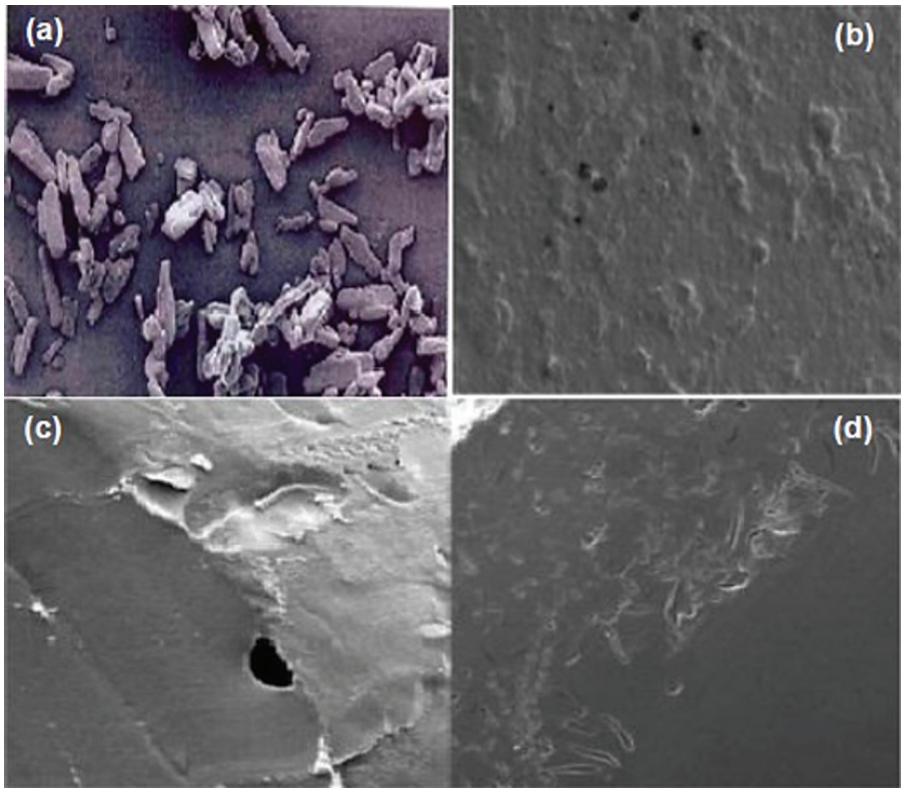
Figure 7



PXRD diffractograms of pure drug OLM (a), SOL (b), PEG-8000 (c), KF127 (d), OS1 (e), OS2 (f), OSP1 (g), OSP2 (h), OSK1 (i) and OSK2 (j).

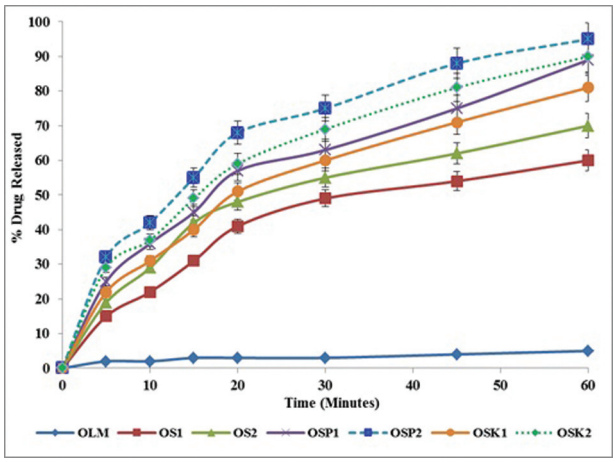
OLM is highly soluble in acidic media and in media with a pH value more than 6.8. The solubility of OLM is too high to allow the monitoring of differences among the HME formulations. OLM is poorly soluble in the pH range of 2–6.0, for this reason, acetate buffer pH 4.5 was chosen to ensure a discriminatory dissolution method. Higher apparent drug solubility and improved dissolution profiles are attributed to the amorphous nature of OLM in SD system where OLM is molecularly dispersed in the polymer matrix. Lattice energy of SD system is because of the short-range intermolecular interaction in amorphous system. When drug in SD dissolves, then change in lattice energy is not destructed by the drug itself, so the dissolution rate improved, whereas in crystalline form, lattice energy has to be destructed for the drug to get dissolved. Hence we do not observe improved dissolution by simple physical mixing of drug and polymer [35]. Dissolution profiles of various SD are as shown in Fig. 9. The dissolution of the SD with SOL alone (OS1 and OS2) revealed only 60.12 and 70.15% release at the end of 60 min, whereas formulations OSP1, OSP2, OSK1 and OSK2 released 89.16, 95.22, 81.35, and 90.16%, respectively, at the end of 60 min. The increase in dissolution was ~16–19-fold higher than pure OLM. Dissolution of the drug in SOL alone is governed by the carrier, whereas in the case of SOL–surfactant systems (OSP1, OSP2, OSK1 and OSK2), the dissolution rate is governed by solubilization of the polymer to create a hydrotropic environment for the insoluble drug. It was observed that SOL-PEG-8000 SD dissolved rapidly than that of SOL-KF 127 SD. The high dissolution rate of OLM from the SOL–surfactant systems dispersion is believed to be because of the drug-polymer molecular intermixing at microlevel. The dissolution rate of prepared SD was also significantly enhanced. The dissolution of extrudates was markedly enhanced with total release occurring within 60 min. This clearly shows that the remarkable improvement in dissolution performance was achieved by HME. From the dissolution profiles it is evident that HME processing can be employed for the manufacture of OLM immediate release SD by processing polymer-surfactant combination. The preferred dissolution patterns can be achieved through the drug loading percentage and the extrusion process. The extrusion appeared to be an

Figure 8



SEM photograph of pure drug OLM (a), OS2 (b), OSP2 (c) and OSK2 (d).

Figure 9



In vitro dissolution profile of pure drug OLM and SD formulations.

effective approach for the development of diffusion controlled SDs of OLM.

The observed *in-vitro* drug release pattern strongly indicated the influence of surfactants along with SOL on the dissolution rate enhancement from the SD. The release data were fitted into various kinetic models like zero order, first order, Higuchi matrix, Korsmeyer–Peppas, and Hixson–Crowell to establish the mechanism of drug release from prepared SD. The *in-vitro* release kinetic parameters of the SD formulations are presented in Table 3. In all the cases, the R values of Higuchi matrix model were close to 1. The diffusion coefficient (n) values ranged between 0.4912 and 0.6362. As the R values of Higuchi matrix were close to 1, the prepared SDs were found to follow Higuchi release mechanism and demonstrated the immediate drug release ($n<0.05$) mechanism, which is significant with the exposure of more surface area of drug inside SD to the dissolution medium [36]. Further, the observed diffusion coefficient values are indicative of the fact that the drug release from the formulation follows non-Fickian transport mechanism.

SDs are thermodynamically metastable system that favors the conversion of amorphous form to crystalline form under storage [37]. To evaluate the physical state of the drug, the select formulation (OSP2 and OSK2) were characterized by PXRD after storage for 3 months. The systems were stable during a 3-month period. In the case of SD, no substantial recrystallization was observed by PXRD over the 3 months storage suggesting OLM is more stable in this formulation. This may be because SOL can engage in more extensive hydrogen bonding with OLM and used surfactants, resulting in less molecular mobility.

Table 3 *In-vitro* release kinetics parameters of olmesartan medoxomil-based solid dispersion formulations

Formulation code	Correlation coefficient (R^2)				*r*	*n*	*K*
	Zero order	First order	Higuchi matrix	Hixson–Crowell	Korsmeyer–Peppas		
OS1	0.8765	0.8519	0.9940	0.8271	0.9641	0.4912	0.3611
OS2	0.9123	0.9624	0.9882	0.9348	0.9372	0.5106	0.3921
OSP1	0.9065	0.9351	0.9917	0.9562	0.9516	0.4992	0.2961
OSP2	0.9142	0.9460	0.9864	0.9543	0.9717	0.5362	0.2289
OSK1	0.8972	0.9312	0.9913	0.9139	0.9712	0.6362	0.3166
OSK2	0.9164	0.9602	0.9899	0.9436	0.9549	0.6011	0.3295

In addition, there were no significant variations in content of drug and in dissolution profiles after storage. The enhanced physical stability of the SD upon storage is attributed to drug-polymer interactions and solubilization effects of the polymer. SOL–surfactant systems had strong intermolecular interactions, particularly hydrogen bonding between amorphous OLM and the polymer. These might further reduce the molecular mobility and retard recrystallization during storage.

Conclusion

The current investigation successfully demonstrates the application of HME technology for the solubility and dissolution rate enhancement of the poorly water-soluble drug OLM. Novel polymer (SOL) along with solubility/absorption enhancers (PEG-8000/KF127) combinations was optimized and stable SDs systems were developed successfully. Utilization of SOL along with suitable surfactants offers excellent possibilities to develop stable amorphous SDs. Selective use of solubility/absorption enhancers at low concentrations improves process workability, increase melt viscosity with torque reduction, reduce *Tg* of blend, augments quality of extrudes, and reduce residence time of extrusion. The study revealed importance of suitable carrier and processing technique selection which are critical parameters during HME. The improvement in the dissolution rate was found to be in order of SOL-PEG-8000>SOL-KF127>SOL only. The study revealed the importance of a suitable carrier and processing technique selection, which can eventually enhance bioavailability of poorly soluble drug.

As a summary, it was successfully demonstrated that the appropriate choice of polymeric carriers may result in a disproportionately high improvement of the dissolution profile of a poorly water-soluble drug if applied as a polymeric blend. The application of mixtures of polymers as a carrier for HME solid dosage forms offers remarkable opportunities for dissolution enhancement that are yet to be explored.

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Conflicts of interest

There are no conflicts of interest.

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