Fast Disintegrating Tablets of Olmesartan Medoxomil Using Solid Dispersion Technique

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Abstract

Aim: Olmesartan medoxomil (OLM) is a poorly soluble drug and its low aqueous solubility leads to poor dissolution and bioavailability. The aim of this work was to improve the solubility of poorly aqueous soluble drug OLM by solid dispersion (SD) technique. **Materials and Methods:** A phase solubility study was performed to determine the effect of various polymers on aqueous solubility of drug. The binary SD of OLM was prepared by using poloxamer 407. The SDs were prepared by kneading, melting and solvent evaporation (SE) method by varying drug to carrier ratio. The optimized SD formulations were characterized by Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and powder X-ray diffraction (XRD). Fast disintegrating tablets (FDTs) of OLM were formulated using optimized SD. The *in vitro* evaluation of FDTs was done including stability studies. **Results:** Phase solubility study indicated 5.3 fold increase in solubility of OLM by Poloxamer 407. The results of FTIR, DSC, SEM, and XRD study showed the conversion of crystalline form of OLM to amorphous form. The results revealed that SD prepared by SE method showed rapid dissolution as compared to other methods. The FDTs of optimized SD containing croscarmellose sodium showed faster and complete *in vitro* drug release within 20 min. Formulation M6 was found to be optimized formulation owing to its 84.09 dissolution efficiency, 4.82 min mean dissolution time and 100% drug release. Optimized formulation was found to be stable for 3-month period. **Conclusion:** The results conclusively confirmed successful improvement in dissolution of poorly water-soluble drug OLM.

Key words: Dissolution enhancement, olmesartan medoxomil, solid dispersion

INTRODUCTION

Aqueous solubility of any therapeutically active substance is a key property which governs dissolution, absorption and thus the efficacy *in vivo*.[1] Poorly water-soluble drugs are associated with slow drug absorption leading to inadequate and variable bioavailability. About 40% of the new chemical entities currently being discovered are poorly water-soluble drugs.[2] Therefore, improvement in the dissolution and bioavailability of these poorly water-soluble drugs various techniques have been employed such as salt formation, solubilization, micronization, complexation with polymers, use of prodrug, addition of surfactants, and solid dispersion (SD) techniques.[3]

SDs are one of the most successful strategies to improve dissolution rate, solubility and consequently, the bioavailability of poorly water-soluble drugs. These can be defined as molecular mixtures of poorly water-soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties.[4,5] Many water-soluble carriers such as polyvinyl pyrrolidone, polyethylene glycol, and poloxamer have been employed for the preparation of SD of poorly soluble drugs. Poloxamer 407 has been widely used as wetting, surface adsorption, and solubilizing excipient and acts as polymeric carrier and surface active agent in SD formulation.[6]

Fast disintegrating tablets (FDTs) are the recent developments to present viable dosage alternatives for patients who

have difficulty in swallowing.[7] They are the products that disintegrate rapidly in saliva without need of water. The disintegrated mass can slide down smoothly along the esophagus with the help of saliva, so people who have swallowing difficulties can take with ease.[8]

Olmesartan medoxomil (OLM) is a selective AT1 subtype angiotensin II receptor antagonist that is approved for treatment for hypertension. A sartan is preferred over other antihypertensive drugs in diabetic patients where they slow the progression of nephropathy. OLM belongs to BCS class II. It is practically insoluble in water and has oral bioavailability of 26%.[9,10] The unabsorbed drug may cause gastrointestinal side effects such as abdominal pain, dyspepsia, gastroenteritis, and nausea.[11] In the literature nanoparticles,[12] nanosuspension[10] and complexation with cyclodextrin[11] have been reported to improve solubility of OLM. Therefore, formulation approaches are being explored to enhance dissolution of OLM using poloxamer 407. The SDs of OLM with poloxamer 407 were prepared by different techniques (physical mixture [PM], kneading, melting, and solvent evaporation [SE] method).

The aim of this study was to investigate the possibility of improving the release of OLM through SDs with poloxamer 407. The prepared SDs were characterized by differential scanning calorimetry (DSC), scanning electron microscopy (SEM), X-ray diffractometry (XRD), Fourier transform infrared spectroscopy (FTIR), and solubility studies. The optimized SD of drug was formulated as fast dissolving tablet.

MATERIALS AND METHODS

The OLM was obtained as a gift sample from Merck Ltd., Mumbai, India. Poloxamer 407 was obtained as a gift sample from BASF, Mumbai, India. All other chemicals and solvents were of analytical grade.

Saturation solubility studies

An excess quantity of OLM was placed in 25 ml capacity glass flasks containing 20 ml of different solutions (distilled water, 0.1 N HCl and phosphate buffer at pH 6.8). The samples were sonicated for 10 min at room temperature and capped conical flasks were shaken for 24 h at 37°C ± 2°C using water bath shaker (Rivotek, India). The supernatant solution was then passed through a membrane filter (0.45 μm), and the amount of the drug dissolved was analyzed spectrophotometrically (Shimadzu, Pharmspec UV 1700, Japan) at 257 nm after suitable dilution.[13]

Phase solubility studies

Solubility measurements were performed using the method reported by Higuchi and Connors.[14] Different hydrophilic

carriers such as polyethylene glycol 6000, polyvinyl pyrrolidone K30, and poloxamer 407 were used to perform phase solubility study. An excess amount of OLM was added to the aqueous solutions of each carrier containing increasing concentrations of the individual carrier (i.e., 0.5-2.5% w/v). Then, the flasks were shaken at 37°C for 48 h in water bath shaker. The supernatant was filtered through a 0.45 μm membrane filter. The filtrate was suitably diluted and analyzed spectrophotometrically (Shimadzu, Pharmspec UV 1700, Japan) at 257 nm.

The change in Gibbs free energy transfer (ΔG°tr) value provides information about whether the treatment is favorable or unfavorable for drug solubilization in an aqueous medium. Negative Gibbs-free energy values indicate improved dissolution. The Gibbs free energy of transfer ($\Delta G°_{tr}$) of OLM from pure water to aqueous solutions of different hydrophilic carriers was calculated using the following equation:[15]

$$\Delta G°_{tr} = -2.303RT \log S_c/S_o \qquad (1)$$

Where S_c/S_o is the ratio of molar solubility of OLM in aqueous solution of different hydrophilic carriers to that of pure water. The value of gas constant (R) is 8.31 J/K/mol and T is temperature in degree Kelvin.[16]

Preparation of PM

PM of OLM and Poloxamaer 407 were prepared by simple mixing method using glass morter and pestle in different ratios such as (1:0.5 PM1, 1:1 PM2, 1:1.5 PM3, 1:2 PM4 w/w).

Preparation of SD

Three methods were used to prepare SD of OLM with poloxamer 407, which are as follows:

The SDs containing OLM and carrier in different proportions were prepared by kneading method. A mixture of OLM and poloxamer 407 (1:0.5 KM1, 1:1 KM2, 1:1.5 KM3, 1:2 KM4 w/w) was wetted with water and kneaded thoroughly for 30 min in a glass mortar. The paste formed was dried under vacuum for 24 h. Dried powder was passed through #60.

The SD of OLM was prepared by SE method for which accurately weighed amounts (1:0.5 SE1, 1:1 SE2, 1:1.5 SE3, and 1:2 SE4 w/w) of OLM and poloxamer 407 were dissolved in methanol. After complete dissolution, solvent was evaporated under reduced pressure at room temperature. Subsequently, the solid mass was ground.

The SDs containing OLM and carrier in different proportions were prepared by melting method (MM). Poloxamer 407 (1:0.5 MM1, 1:1 MM2, 1:1.5 MM3, and 1:2 MM4 w/w) was melted by heating and drug was dispersed in molten solution. After complete dispersion, it was cooled by keeping

in ice bath and solid mass was obtained. Dried powder was passed through #60.

Solid state characterization

Solid state study was performed for OLM, poloxamer 407 and selected batch of SDs and their PMs.

FTIR spectroscopy

Infrared spectra of OLM, Poloxamer 407, PM and SD were recorded using FTIR spectrophotometer (Alpha E Bruker, Germany). The baseline correction was done by blank background measurement. The scanning range was 500-4000/cm.

DSC

DSC of pure OLM, poloxamer 407, PM and SD complex were recorded using Mettler-Toledo DSC 821e instrument equipped with an intracooler (Mettler-Toledo, Switzerland). Samples were sealed in aluminum pans and heated at the rate of 10°C/min from 30°C-300°C under nitrogen atmosphere of flow rate 10 ml/min.

X-ray diffraction (XRD) analysis

XRD patterns of pure OLM, poloxamer 407, PM and SD complex were recorded using XRD (PW 1729, Philips, The Netherlands) with a copper target, voltage 30 kV and current 30 mA.

SEM

The morphology of pure OLM, poloxamer 407, PM and SD complex was studied using SEM, (JSM 5600 LV, Joel, Japan). Samples were sprinkled onto double sided tape, sputter coated with platinum and examined under the microscope at 10 kV.

In vitro dissolution study of SDs

Dissolution studies of the SD complex and OLM were performed in 900 ml phosphate buffer pH 6.8 using Indian Pharmacopoeia type I dissolution apparatus at a stirring speed of 50 rpm. The temperature of dissolution medium was maintained to 37°C. Powder sample equivalent to 40 mg of drug was used for dissolution study. 5 ml aliquot was withdrawn at different time intervals and replaced with the same volume of fresh dissolution medium maintained at the same temperature. Filtered samples were assayed spectrophotometrically at 257 nm. Experiments were made in triplicate.

Preparation of FDT tablets

Different batches of OLM containing FDT were prepared according to the proportions given in Table 1. Powdered SD

Table 1: Formulations of fast disintegrating tablets

Ingredients	M1	M2	M3	M4	M5	M6	M7
SD (drug equivalent to 40 mg)	80	80	80	80	80	80	80
SSG	6	10	-	-	-	-	-
CP	-	-	6	10	-	-	-
CCS					6	10	-
Avicel PH 101	103	99	103	99	103	99	110
Mannitol	8	8	8	8	8	8	8
Sodium saccharin	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1

SSG: Sodium starch glycolate, CP: Crosspovidone, CCS: Crosscarmelose sodium, SD: Solid dispersion; *All quantities in mg

containing amount equivalent to 40 mg of OLM, was mixed with other excipients and compressed on a rotary punch tablet machine (Karnavati, Mumbai, India) equipped with flat-faced 8 mm punch. Final weight of each tablet was kept constant (200 mg) by varying the weight of microcrystalline cellulose.

Evaluation of FDTs

The crushing strength (hardness) was determined using a Monsanto hardness tester. The friability of a sample of 33 tablets was measured using a Roche friabilator (Electrolab, Mumbai, India) as per the pharmacopoeial procedure.[17] Thickness of tablet was determined using a vernier caliper. 20 tablets were randomly selected from each batch and weighed individually. The average weight and standard deviation were calculated. 20 tablets from each batch were crushed and tablet powder equivalent to 40 mg of OLM was weighed and estimated for drug content using earlier reported UV spectrophotometric method.[12] Wetting time and *in vitro* disintegration test (Electrolab, Mumbai, India) were performed for all the prepared batches as per the procedure laid down in the previously published literature.[18]

In vitro drug release

The *in vitro* drug release of different formulation batches was studied using six rotating paddle apparatus (Electrolab, Mumbai, India). Each tablet was placed in the paddle dissolution assembly containing 900 ml of phosphate buffer (pH 6.8). The paddle was rotated at 50 rpm and temperature of dissolution medium was thermostatically controlled at 37°C ± 0.5°C. At predetermined time intervals, 5 ml of the sample was withdrawn, filtered through a Whatman filter

paper and equal volumes of fresh dissolution medium was replaced. Samples were analyzed for OLM content by using UV spectrophotometer (Shimadzu, Pharmspec UV 1700, Japan) at 257 nm. Dissolution profiles of formulations were compared on the basis of dissolution efficiency (DE) and mean dissolution time (MDT) with marketed formulation (MF).[19]

Stability studies

The tablets were wrapped in aluminum foil and subjected to stability test at temperature 40°C with relative humidity of 75% RH (Bio-Technics, India). The strips were withdrawn after 90 days and evaluated for drug content, wetting time, disintegration time, and *in vitro* dissolution. The *in vitro* dissolution data of the optimized formulation before and after stability studies was compared using similarity factor (f_2). The formulation before stability studies was considered as reference formulation, whereas formulation after stability studies was considered as test formulation.[20] Dissolution profiles were considered as similar if f_2 value lied between 50 and 100.[21]

Statistical analysis

The results were expressed as mean ± standard deviation. Statistical analysis was performed by one-way analysis of variance using GraphPad Prism. $P < 0.05$ was considered as the minimal level of statistical significance.

RESULTS AND DISCUSSION

Saturation solubility study

The solubility of OLM in distilled water was found to be 0.0237 ± 0.009 mg/ml, 0.1 N HCl 0.272 ± 0.04 mg/ml and phosphate buffer (pH 6.8) 2.989 ± 0.13 mg/ml. The pH of solution showed a significant impact on the solubility of OLM. OLM exhibited low solubility in water and in acidic media, whereas the high solubility in phosphate buffer pH 6.8.

Phase solubility study

Phase solubility studies showed that highest solubility of OLM in poloxamer 407. Therefore, poloxamer 407 was selected as carrier for SD. Phase-solubility studies showed a linear increase in drug solubility with increased carrier levels up to 1.5% and then shows decrease in solubility due to "A_N type" profile of drug molecule.[22] Solubility of pure drug (PD) was found to be increased 5.3 folds with 1.5% poloxamer 407 [Table 2] and above 1.5% solubility was found to be decreased due to its gel forming property.[23] The values of Gibbs-free energy (ΔG°tr) associated with the aqueous

solubility of OLM in polymeric solution of poloxamer 407 are given in Table 2. The ΔG°tr values were negative at the different concentrations of the polymers, which showed the spontaneous nature of the OLM solubilization. Lower the value of Gibbs free energy, greater will be the solubilization of drug. From the results of phase solubility study, it was revealed that poloxamer 407 increases solubility of OLM.

Solid state characterization

FTIR spectroscopy

FTIR spectroscopy was performed to study compatibility of drug with poloxamer 407. The FTIR spectrum of pure OLM, PMs and optimized SDs is shown in Figure 1. The OLM spectrum shows characteristic peak of NH and OH stretching vibration between 3200 to 3600/cm, C-H deformation at 1472.68/cm, ester peak at 1293.40/cm, and C=O at 1701.33/cm. The FTIR spectrum of poloxamer 407 showed characteristic peaks at 3424.06/cm of OH, 2880.81/cm of alkane and 1143.72/cm of ether. All characteristic peaks of drug were observed in the spectra of PM and SD. From FTIR spectra of PM, it was observed that there was no any unusual interaction between drug and carrier.

In case of SD, there is slight shift of absorption band of drug towards lower frequency with reduction in intensity which

Table 2: Effect of poloxamer 407 concentration on solubility of OLM

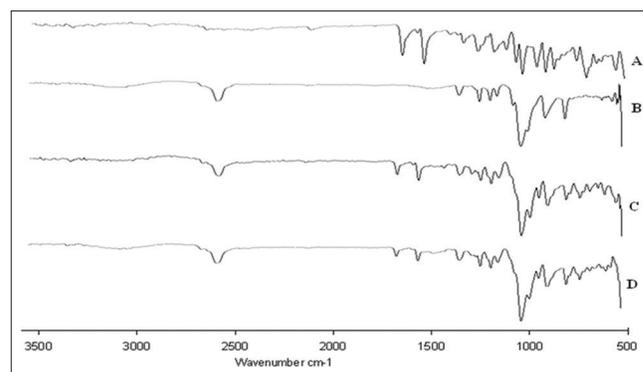| Poloxamer 407 (%)	Solubility (mM/ml)	Gibbs free energy change (ΔG°tr) (J/K/Mol)
0	0.0425	-
0.5	0.0963	−2107.73
1	0.1187	−2645.22
1.5	0.2251	−4294.88
2	0.1619	−3445.32
2.5	0.1444	−3152.34

OLM: Olmesartan medoxomil

Figure 1: Fourier transform infrared spectra of olmesartan medoxomil (A), poloxamer 407 (B), physical mixture (C), solid dispersion (D)

might be attributed to the hydrogen bonding interaction between the N-H and C=O groups of drug and the hydroxyl group of carrier. The slight shift of absorption bands to a lower frequency may be attributed to the formation of hydrogen bonds.[24] Hydrogen bonding between drug and poloxamer could be one of the reasons for dissolution enhancement of OLM.

DSC

DSC analysis was conducted to study the interaction in between CBZ and poloxamer 407. The DSC curves obtained for pure OLM, poloxamer 407 SDs, and their corresponding PMs are shown in Figure 2. DSC analysis of OLM showed single sharp endothermic peak at 180.78°C corresponding to its melting point. In the case of PM, there is decrease in sharpness and intensity of endothermic peak. The endothermic peak obtained in PM and SD at ~54°C was due to melting of poloxamer 407. The endothermic peak of drug was found to be disappeared in the SD which could be attributed to conversion of crystalline form of drug to amorphous form.[15]

XRD analysis

XRD analysis was performed to study the change in the crystallinity of OLM. The XRD pattern of OLM, poloxamer 407, PM and SDS by SE method is shown in Figure 3. XRD study of pure OLM showed high-intensity peak at 2θ of 12.70 and proved its crystalline nature. Poloxamer 407 showed prominent peak with the highest intensity at 2θ of 19.10. For the calculation of disorderness of SD, the term relative degree of crystallinity (RDC) was used. The XRD scan of pure OLM shows intense peak of crystallinity, whereas the XRD scans of PMs and SDs shows reduction in both number and intensity of peaks as compared to PD. The RDC value was found to be 0.52 for SD. It indicates that amorphization or reduction in crystallinity of drug takes place due to the poloxamer.[15] Peak intensity of SD was found to be low as compared to PM indicating amorphization of drug which might be one of the reasons for drug dissolution enhancement.

SEM

SEM study was performed to check morphological changes in the drug. SEM photomicrographs of OLM, poloxamer 407, PM and SD at different magnifications are shown in Figure 4. The PD appeared as a fine crystal with smooth surface partially agglomerated in bundles. Poloxamer 407 exists in spherical particles. The PM of the drug and the carrier at weight ratio of 1:1 showed the presence of drug in the crystalline form along with irregular microparticles of poloxamer 407, which may be due to size reduction process at the time of preparation of the PM. In contrast, the photomicrographs of the prepared SD showed the morphological changes occurred in the drug particles, were more porous in nature and particles of poloxamer 407 were attached onto the surface.[15] From SEM photomicrographs, it can be concluded that OLM which
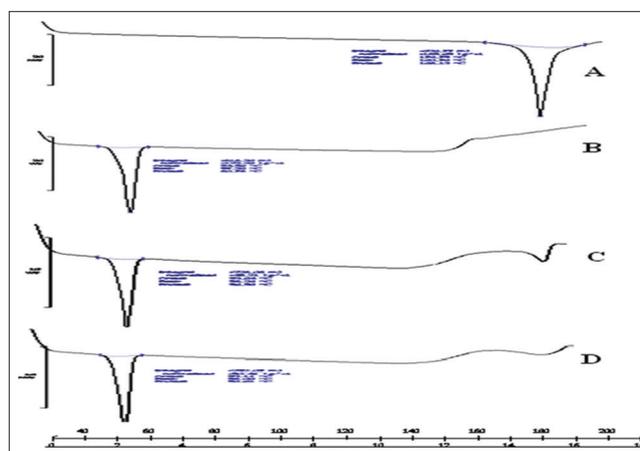

Figure 2: Differential scanning calorimetry analysis of olmesartan medoxomil (A), poloxamer 407 (B), physical mixture (C), solid dispersion (D)
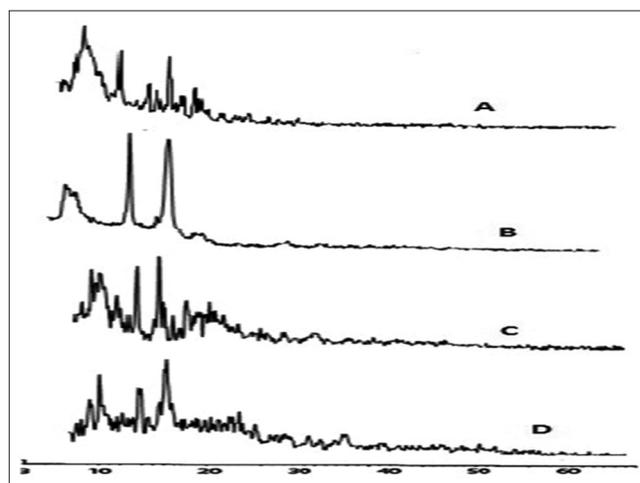

Figure 3: X-ray diffraction pattern of olmesartan medoxomil (A), poloxamer 407 (B), physical mixture (C), solid dispersion (D)
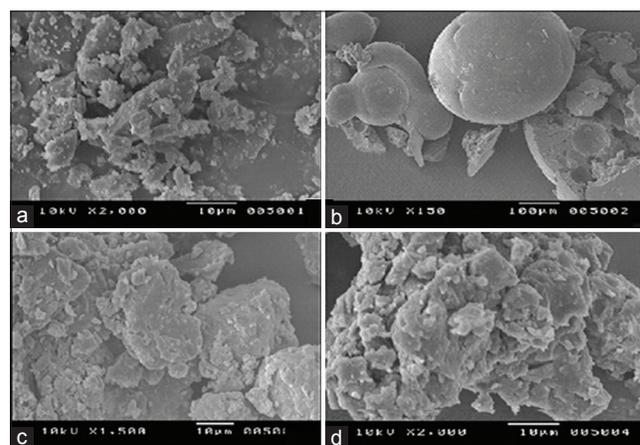

Figure 4: Scanning electron microscopy photographs of (a) olmesartan medoxomil, (b) poloxamer 407, (c) physical mixture, (d) solid dispersion

existed in crystalline form has been converted in amorphous form in case SD.

In vitro drug release studies of SDs

The dissolution profiles of SD prepared by different methods are presented in Figure 5. Dissolution profile of pure OLM, PM and SDs prepared by kneading, SE and MM indicate difference in dissolution rates. SDs showed enhancement in dissolution as compared to pure OLM which may be due to intermolecular interactions with carrier poloxamer 407 playing important role in solubilization, stability and maintaining supersaturation.[25]

Onset of dissolution of pure OLM is very low, about 17.59% drug released at the end of 30 min. The PM containing drug to polymer ratio 1:0.5 showed only 59.77% of drug release while the PM containing drug to polymer ratio 1:1 showed 97.77% of drug release at the end of 30 min. Further increase in concentration of poloxamer retarded the drug release due to gel forming property.[23]

The SD formulations prepared by kneading method and MM showed higher dissolution compared to PD and PM prepared. This may be due to partial to complete dispersion of drug in hydrophilic carrier poloxamer 407. The drug release from different SD formulations prepared by SE method followed the order SE2 > SE3 > SE4 > SE1. The SD containing drug to polymer ratio 1:0.5, 1:1, 1:1.5 and 1:2 showed 79.23%, 99.94%, 94.21% and 82.59% drug release, respectively, at 10 min.

SD formulation prepared by SE method showed higher dissolution compared to formulations prepared by other methods. This may be due to complete dispersion of drug in hydrophilic carrier as both the drug and carrier are dissolved in a common solvent. Which results in a lack of crystallinity, solubilization effect of carrier and improved wettability.[26]

Preparation of FDTs

The optimized SD was taken for preparation FDTs by direct compression method. Superdisintegrants at different concentration levels (3% w/w and 5% w/w) were included to assist faster disintegration. The absorption of water is an important step for subsequent disintegration process of tablets. When higher concentrations of super disintegrant were added to tablet formulations, they absorbed considerable amount of water and resulted in increase in viscosity of fluid within the tablet mass. This delayed further water penetration into the tablets. Therefore, it was decided to use super disintegrant concentrations only up to 5% w/w.

Evaluation of powder blends

The prepared blends were evaluated for bulk density, tap density, angle of repose and Car's index. The prepared powder blends showed good flow properties as the angle of repose values varied from 26.74°to 27.90° while Carr's Index values found to be in the range of 17-20%. This indicated good flow of the prepared powder blends.

Evaluation of FDTs

All the batches of prepared tablets were evaluated for the different parameters. Weight variation for prepared tablets was found within specifications of Indian Pharmacopoeia 1996. Average weight for tablet was in the range of 197-201 mg. Hardness values for tablets of all formulations were found to be in the range of 2.5-3.5 kg/cm^2 indicating good mechanical strength of prepared tablets. Thickness values obtained for all the tablets were in the range of 2.94-2.96 mm. Friability of all the formulations was in the range
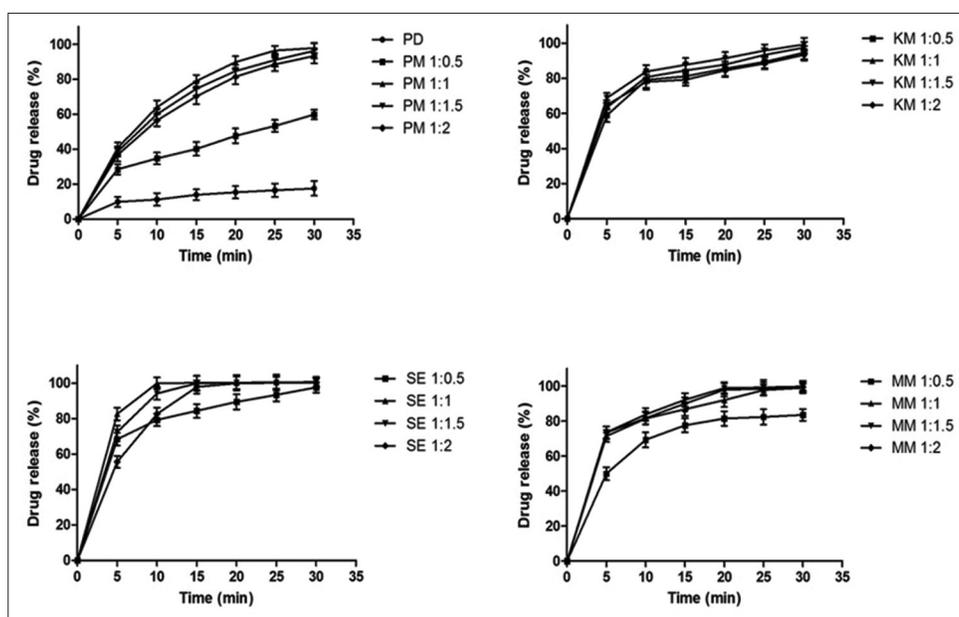

Figure 5: Olmesartan medoxomil release from PM - physical mixture and SD - solid dispersion by KM - Kneading method, SE - solvent evaporation and MM - melting method; PD - pure drug

of 0.14-0.56%. Drug contents for all the formulations were found in the range of 99.23-103.23% [Table 3]. All tested parameters were well within the prescribed limit.

All tablet formulations indicated disintegration time in between 29.66 to 55.66 s [Table 3]. The control formulation (M7) showed disintegration time of 200.6 s. The results revealed that the addition of the superdisintegrants has improved the disintegration rate of tablets. It was observed that the disintegration time of the tablets decreased with increase in the level of superdisintegrants. The disintegration time of tablets was in order of croscarmellose sodium > crospovidone > sodium starch glycolate (SSG). Among the above superdisintegrants, formulation M6 containing croscarmellose sodium showed fastest disintegration to its three dimensional swelling.

In vitro dissolution studies

All the formulations showed rapid drug release due to improved solubility of drug and fast disintegration of tablets [Figure 6] and showed ~100% of drug release at the end of 30 min. However, the rapid drug dissolution was noticed in M6 formulation compared to other formulations, which released 87.94% at the end of 10 min. The fast dissolution might be due to quick disintegration of the tablets to form particles. Croscarmellose sodium-containing formulations showed the maximum drug release as compared to crospovidone and SSG. The variation of drug release from the other formulations may be due to slow breakdown of particles from the tablet. Due to gelling property of SSG the tablet containing this superdisintegrant (M2) showed slow disintegration and slow dissolution. While formulation containing crospovidone showed faster disintegration as compared to SSG but due to its little swelling capacity, it has slower disintegration as compared to croscarmellose sodium.[27] Croscarmellose sodium is a cross-linked polymer of carboxymethylcellulose sodium. Cross-linking makes it an insoluble, hydrophilic, highly absorbent material, resulting in excellent swelling properties and its unique fibrous nature gives it excellent water wicking capabilities.[28] Croscarmellose sodium provides superior drug dissolution and disintegration characteristics,

thus improving bioavailability of formulations. The relative efficiency of different superdisintegrants to improve the dissolution rate of tablets was found in order: Croscarmellose sodium > crospovidone > SSG > control (formulation without superdisintegrant).[25] All FDTs of optimized SD showed improved dissolution than the marketed tablet and PD.

DE is commonly applied for comparison of dissolution profiles to decide better formulation. The MF showed 35.48% DE whereas the formulation M6 showed more than 80% DE at the end of 30 min. Higher DE indicated that FDT has significantly enhanced dissolution rate [Table 4]. MDT of MF was found to be 8.77 min while that of formulation M6 was found to be 4.82 min. Lower MDT values indicated faster release of drug from FDT. Finally, on the basis of total drug release and drug release at 15 min, DE (%) and MDT, formulation M6 was considered as an optimized formulation.

Stability studies

The stability data for optimized formulation M6 are given in Table 5. No significant change was noticed in the drug content, wetting time and disintegration time after 3 months stability study of M6 formulation. The *in vitro* release profile of M6 before and after the stability study is given in Figure 7. The value
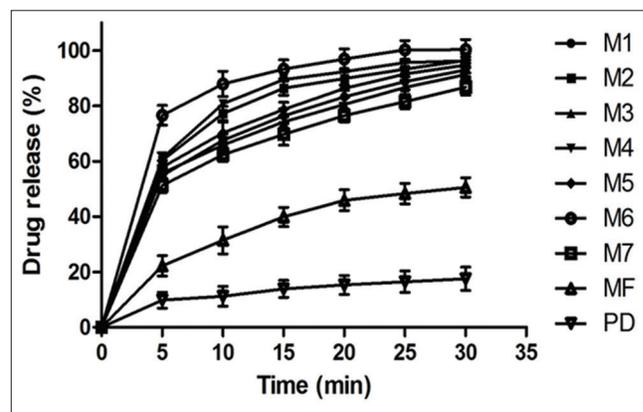

Figure 6: *In vitro* dissolution studies (M1-M7: Fast disintegrating tablets, MF: Marketed formulation, PD: Pure drug)

Formulations	Average weight (mg) (*n*=20)	Drug content (%) (*n*=20)	Wetting time(s) (*n*=3)	Disintegration time(s) (*n*=6)
M1	198.88±1.31	100.44±0.19	112.36±2.64	55.66±0.57
M2	197.6±0.90	101.54±0.14	90.33±1.52	52.33±1.15
M3	199.01±1.40	99.99±0.26	69.66±1.52	47.66±0.57
M4	198.92±1.60	103.23±0.32	56.08±2.08	41.00±1.00
M5	197.92±1.51	100.01±0.27	52.33±2.08	41.33±0.57
M6	198.14±0.39	100.74±0.18	40.33±1.15	29.66±0.57
M7	200.09±2.45	99.23±0.13	208.66±1.52	200.66±1.15

Table 3: Evaluation of FDTs

Data expressed as mean±standard deviation. FDTs: Fast disintegrating tablets
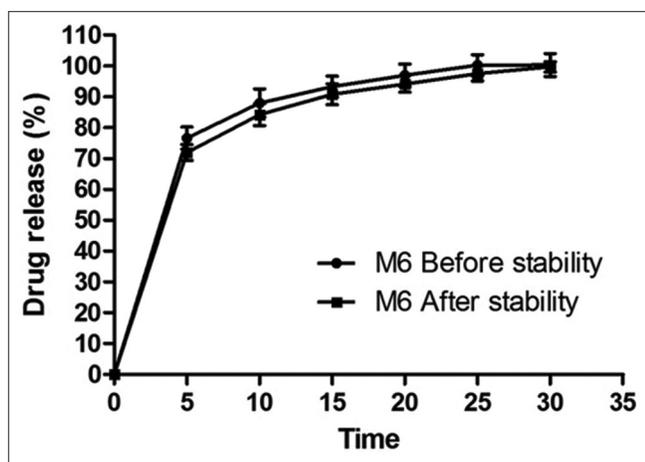
Figure 7: *In vitro* dissolution of M6 before and after stability

Table 4: DE and MDT of FDTs

Batch	Q5 (%)	Q15 (%)	DE (%)	MDT (min)
M1	54.89	76.43	69.57	7.55
M2	60.34	86.42	75.88	6.39
M3	55.67	74.23	68.11	7.63
M4	61.23	89.47	77.93	5.73
M5	57.85	78.67	71.99	7.21
M6	76.56	93.31	84.09	4.82
M7	51.32	62.41	64.14	7.82
Pure drug	9.82	13.89	12.58	8.53
Marketed formulation	22.24	39.89	35.48	8.77

Q5: Drug release at 5 min, Q15: Drug release at
15 min, DE: Dissolution efficiency, MDT: Mean dissolution time

Table 5: *In vitro* parameters of batch M6 before and after stability study

Parameter	Before stability study (*n*=3)	After stability study (*n*=3)
Drug content (%)	100.74±0.18	99.42±1.32
Disintegration time (s)	29.66±0.57	30.34±2.14
Wetting time (s)	40.33±0.1	42.29±0.42
Drug release at the end of 30 min (%)	100.3±3.7	99.67±1.71

Values are expressed as mean±standard deviation

of f_2 after 90 days was found to be 74.38 whereas the difference factor (f_1) value was found to be 3.07. This indicates that the *in vitro* drug release from formulation M6 was not markedly affected by the changes in the temperature and humidity.

CONCLUSION

The results of phase solubility exhibited an increase in the solubility of OLM with the help of poloxamer 407. Among the various methods of preparation of SD the SE method showed significant enhancement in dissolution rate. The solid state characterization for SD indicated the conversion of crystalline form of OLM to amorphous form. It is well known that the solubility of drug hastens the *in vitro* dissolution of OLM that leads to increase in bioavailability. It can be concluded from the results that the carrier poloxamer 407 has the ability to improve solubility and dissolution of OLM which may avoid unwanted gastrointestinal tract side effects as well as improve bioavailability. The FDT of optimized SD was successfully formulated. The FDTs of optimized SD showed improved dissolution than MF. Formulation M6 was found to be optimized formulation due to its high DE with fast and complete drug release. The optimized formulation was found to be stable for 3 months period. Hence, FDT with SD of OLM could be best alternative to MF of OLM.

REFERENCES

1. Tayade P, Modi A. A comparative solubility enhancement profile of valdecoxib with different solubilization approaches. Indian J Pharm Sci 2007;69:274-8.
2. Urbanetz NA, Lippold BC. Solid dispersions of nimodipine and polyethylene glycol 2000: Dissolution properties and physico-chemical characterisation. Eur J Pharm Biopharm 2005;59:107-18.
3. Rao M, Mandage Y, Khole I, Munjapara G. Characterization of solid dispersions of simvastatin with PVP K30 and poloxamer 188. Indian J Pharm Educ Res 2011;45:145-52.
4. Jain SK, Shukla M, Shrivastava V. Development and *in vitro* evaluation of ibuprofen mouth dissolving tablets using solid dispersion technique. Chem Pharm Bull (Tokyo) 2010;58:1037-42.
5. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today 2007;12:1068-75.
6. Mehanna MM, Motawaa AM, Samaha MW. In sight into tadalafil - Block copolymer binary solid dispersion: Mechanistic investigation of dissolution enhancement. Int J Pharm 2010;402:78-88.
7. Mali KK, Dias RJ, Ghorpade VS, Havaldar VD, Rupnoor BK, Dhane NS. Taste masked oral fast dissolving sublingual strips of rizatriptan benzoate for migraine therapy. Marmara Pharm J 2017;21:235.
8. Sammour OA, Hammad MA, Megrab NA, Zidan AS.

Formulation and optimization of mouth dissolve tablets containing rofecoxib solid dispersion. AAPS PharmSciTech 2006;7:E55.

9. Ritter JM, Lewis LD, Mant TG, Ferro A. A Textbook of Clinical Pharmacology and Therapeutics. 5th ed. UK: Hodder Arnold; 2008.

10. Thakkar HP, Patel BV, Thakkar SP. Development and characterization of nanosuspensions of olmesartan medoxomil for bioavailability enhancement. J Pharm Bioallied Sci 2011;3:426-34.

11. Thakkar HP, Parmar MP, Patel AA, Patel BV, Chauhan NP. Studies on inclusion complex as potential systems for enhancement of oral bioavailability of olmesartan medoxomil. Chron Young Sci 2012;3:129.

12. Chavan AA, Shete AS, Janugade BU, Doijad RC. Formulation, solid state characterization and enhancement of dissolution rate of olmesartan medoxomil by polyvinyl alcohol-polyethylene glycol graft copolymer based nanoparticles. Indian J Pharm Educ Res 2016;50:676-88.

13. Mali KK, Dias RJ, Ghorpade VS, Havaldar VD. Sodium alginate microspheres containing multicomponent inclusion complex of domperidone. Lat Am J Pharm 2010;29:1199-207.

14. Higuchi T, Connors K. Phase-solubility techniques. In: Reilly C, editor. Advances in Analytical Chemistry and Instrumentation. New York: Wiley-Interscience; 1965. p. 117-212.

15. Ghorpade VS, Remeth D, Vijay H. Preparation and evaluation of domperidone/β -cyclodextrin/citric acid/ mannitol quaternary inclusion complex: An *in vitro* study. Asian J Pharm 2016;2016:1-11.

16. Aggarwal AK, Jain S. Physicochemical characterization and dissolution study of solid dispersions of ketoconazole with nicotinamide. Chem Pharm Bull (Tokyo) 2011;59:629-38.

17. Ministry of Health and Family Welfare. Indian Pharmacopoeia. Vol I & II. New Delhi: The Controller of Publications; 1996.

18. Khan S, Kataria P, Nakhat P, Yeole P. Taste masking of ondansetron hydrochloride by polymer carrier system and formulation of rapid-disintegrating tablets. AAPS PharmSciTech 2007;8:Article 46.

19. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001;13:123-33.

20. Dinge A, Nagarsenker M. Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity. AAPS PharmSciTech 2008;9:349-56.

21. Ma M, Lin R, Liu J. Statistical evaluations of dissolution similarity. Stat Sin 1999;9:1011-27.

22. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. Adv Drug Deliv Rev 2007;59:645-66.

23. Vyas V, Sancheti P, Karekar P, Shah M, Pore Y. Physicochemical characterization of solid dispersion systems of tadalafil with poloxamer 407. Acta Pharm 2009;59:453-61.

24. Chavan BA, Mali KK, Dias RJ, Kate LD. Solid state characterization of multicomponent inclusion complex of domperidone with β-cyclodextrin, polyvinyl pyrrolidone and citric acid. Pharm Lett 2011;3:281-90.

25. Suryadevara V, Lankapalli S, Sunkara S, Sakhamuri V, Danda H. Dissolution rate enhancement of irbesartan and development of fast-dissolving tablets. Egypt Pharm J 2016;15:150.

26. Modi A, Tayade P. Enhancement of dissolution profile by solid dispersion (kneading) technique. AAPS PharmSciTech 2006;7:68.

27. Setty CM, Prasad DV, Gupta VR, Sa B. Development of fast dispersible aceclofenac tablets: Effect of functionality of superdisintegrants. Indian J Pharm Sci 2008;70:180-5.

28. Satyanarayana DA, Keshavarao KP. Fast disintegrating films containing anastrozole as a dosage form for dysphagia patients. Arch Pharm Res 2012;35:2171-82.