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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF OLMESARTAN MEDOXOMIL BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

The present study involved preparation of solid dispersions of Olmesartan medoxomil to improve the aqueous solubility and dissolution rate in order to enhance bioavailability. Olmesartan is a BCS Class II anti-hypertensive drug, having low aqueous solubility and low bioavailability of 26%. In the present study, solid dispersions of Olmesartan with different carriers like poly ethylene glycol 4000 (PEG 4000), HPMC K4, HPMC K100, Poloxamer-407 and crospovidone in different ratios (1 : 1, 1 : 2, 1 : 4, 1 : 6) were prepared by melting, solvent evaporation and kneading methods. The formulations were further characterized for percentage yield, drug content, *in vitro* release study, solubility study and stability study. *In vitro* release studies revealed that the solid dispersions prepared by solvent evaporation method showed faster drug release than melting and kneading method. Solid dispersion containing crospovidone (1 : 4) was considered as the best formulation because of its faster drug release among all formulations. Differential scanning calorimetry (DSC) and infrared spectroscopy (IR) studies revealed that no interactions exist between drug and polymer. Powder X-ray diffraction studies showed a significant decrease in crystalline nature of drug in solid dispersions. In conclusion, solid dispersions of Olmesartan in crospovidone (1:4) have shown to be a promising approach to enhance the bioavailability of Olmesartan.

Key words: Solid dispersion, Dissolution enhancement, Olmesartan, Crospovidone, Solvent Evaporation, Poloxamer 407.

INTRODUCTION

The oral route of administration is the most common and preferred method of delivery due to convenience and ease of ingestion. Even though the oral drug route is preferred it can be problematic for number of reasons the most significant contributors being poor aqueous solubility and or poor membrane permeability of the drug molecule. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability and presents one of the major challenges to formulation scientists in the industries. There are many approaches for enhancing solubility like solubilization, complexation, particle size reduction, salt formation etc., but each of them has practical limitations. 1n 1961, Sekiguchi and Obi[1] developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water soluble drugs can be overcome. The method was termed as "solid dispersion". Solid dispersion is a promising drug delivery forms, which offer the possibility to disperse a hydrophobic drug in a hydrophilic matrix and thereby improve the dissolution rate and bioavailability of the drug. Olmesartan is a specific angiotensin II type I antagonist used alone or with other anti-hypertensive agents to treat hypertension. Olmesartan has poor aqueous solubility and low bioavailability of 26%[2]. In the present study, an attempt was made to increase the solubility and dissolution rate of Olmesartan by solid dispersion technique using water soluble carriers like PEG4000, HPMC K4,

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HPMC K 100, poloxamer 407 and crospovidone. The prepared solid dispersions were evaluated for drug content, *in vitro* dissolution rate studies, solubility studies, crystallinity studies and interactions between drug and carriers using IR and Powder X-ray diffraction study.

EXPERIMENTAL

Materials and methods

Olmesartan medoxomil was obtained as a gift sample from Micro Labs, Bangalore, India. Crospovidone and HPMC K4 were obtained as gift samples from Pharmafabrikon, Madurai, (TN), India. Poloxamer 407 was purchased from Nice Chemicals, Kochi. Methanol was purchased from Astron Chemicals, Ahmedabad. PEG 4000 and HPMC K100 were purchased from S.D. Fine Chemicals Ltd, Mumbai. All other chemicals used were of analytical grade.

Preformulation studies

Infra red spectroscopy (IR)[3]

Infrared red spectroscopy was performed to confirm any interaction of drug with other excipients. IR spectra (Spectrum RX^{-1} Perkin-Elmer, German) for the drug and various physical mixtures were obtained in the transmission mode with the wave number region 4000-400 cm^{-1} at a resolution of 4 cm^{-1}. Samples were prepared using KBr discs by means of hydraulic pellet press at a pressure of five tons for 30 seconds.

Differential scanning calorimetry (DSC)[4]

The possibility of drug-polymer interaction was investigated by Differential scanning calorimetry (DSC Q200 V 24.4 Instruments, USA). The DSC thermograms of pure drug and the polymers were recorded to study the interactions between drug and polymers. The samples were separately sealed in aluminium pans and heated under nitrogen flow (20 mL/min) at a scanning rate of 10°C per minute from 25-250°C. An empty aluminium pan was used as reference standard.

Preparation of Olmesartan solid dispersion

Solvent evaporation method[5]

Olmesartan solid dispersion was prepared by solvent evaporation method using carrier HPMC K4, HPMC K00 and crospovidone in proportions viz., (1 : 1, 1 : 2, 1 : 4 and 1 : 6). The drug and carrier were dissolved in methanol in a china dish and the mixture was heated until the solvent gets evaporated and clear film of drug and carrier was obtained. The resultant solid dispersion was scraped out with a spatula. Solid dispersions were pulverized in a mortar and pestle and passed through sieve No. 60 before packing in an airtight container.

Melting method[6,7]

The carrier was taken in a china dish and heated at 60°C in a water bath, until it melted completely. The drug (Olmesartan) was added to the molten polymer and mixed thoroughly. Poloxamer 407 and PEG 4000 were used in this method and solid dispersion was prepared. The dispersion was cooled to ambient condition. Solidified mass was crushed, pulverized and passed through sieve No. 60 and stored in a desiccator.

Kneading method[8]

A mixture of drug (Olmesartan) and carriers (HPMC K4 and crospovidone) in different ratios (1 : 1, 1 : 2, 1 : 4, 1 : 6) were wetted with solvent (methanol) and water (1 : 1 ratio) and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried under vacuum for 24 hours. Dried powder was scrapped, crushed, pulverized and passed through sieve No. 60 and stored in a desiccator.

Preparation of physical mixture[9]

The physical mixture was prepared by mixing of drug and carrier in a glass mortar. Solid mass was pulverized and passed through sieve No. 60 to get uniform sized particles. The physical mixture was then stored in desiccator until further use.

Characterization

Estimation of drug content[10]

The physical mixtures and solid dispersions equivalent to 10 mg of Olmesartan were weighed accurately and dissolved in few mL of methanol. The solution was filtered, diluted suitably with 10 mL of phosphate buffer pH 6.8 and drug content is analyzed at 257 nm by UV-spectrophotometer.

In vitro dissolution studies[11]

In vitro dissolution study of Olmesartan medoxomil in pure drug form, physical mixture and solid dispersion was carried out by using USP rotating paddle apparatus (Type II) for 1 hour with the paddle rotation speed of 50 rpm. Phosphate buffer pH 6.8 was used as dissolution medium (900 mL) and temperature was maintained at 37°C ± 0.5°C. Samples equivalent to 40 mg of Olmesartan was filled in hard gelatin capsules and used for dissolution studies. Samples were collected at regular interval of time (10, 20, 30, 40, 50, 60 min). The absorbance of the samples was measured at λ_{max} 257 nm after suitable dilution using appropriate blank. The dissolution study was conducted in triplicate.

Solubility studies[10,12]

Solubility study was assessed using shake flask method. The solubility of Olmesartan as pure drug, physical mixture and solid dispersion (SEM 11) were determined in distilled water and phosphate buffer pH 6.8. Excess quantities of pure drug, physical mixture and solid dispersions were added in 25 mL of distilled water in 250 mL conical flask and shaken for 72 hours at room temperature on rotary flask shaker (Secor, India). The entire samples were protected from light by wrapping the flask by aluminum foil. Absorbance of resulting solution was measured by UV spectrophotometer at 257 nm.

Powder X ray diffraction (PXRD) studies[3]

Powder X-ray diffraction patterns (PXRD) of the pure drug, physical mixture (PM19) and solid dispersion (SEM 11) were monitored with an X-Ray diffractometer (XD, Shimadzu, Japan) using copper as X-ray target, a voltage of 45 mv, a current of 20 amp. The diffraction patterns were run at 2. 4°/min over the 2θ range of 2-50°.

Stability studies[13]

The stability studies of best formulation (SEM 11) was carried out at an ambient temperature and relative humidity (40°C±2°C, RH 75% ± 5%) for a period of 45 days to find out the physicochemical changes in the dispersions as per the modified ICH guidelines. Periodically samples were withdrawn to estimate the drug content.

RESULTS AND DISCUSSION

Preformulation studies

Infra red spectroscopic study[3,14]

The IR spectra of Olmesartan and its binary systems with crospovidone, PEG 4000, HPMC K4, HPMC K 100 and poloxamer 407 are present in Fig. 1. Pure Olmesartan spectra showed sharp characteristic

peaks at 3291.28, 2928.38, 1832.14, 1707.78, 762.43 cm^{-1}. All the above characteristic peaks appear in the spectra of all binary systems and are within the same wave number indicating no modification or interaction between drug and carrier.

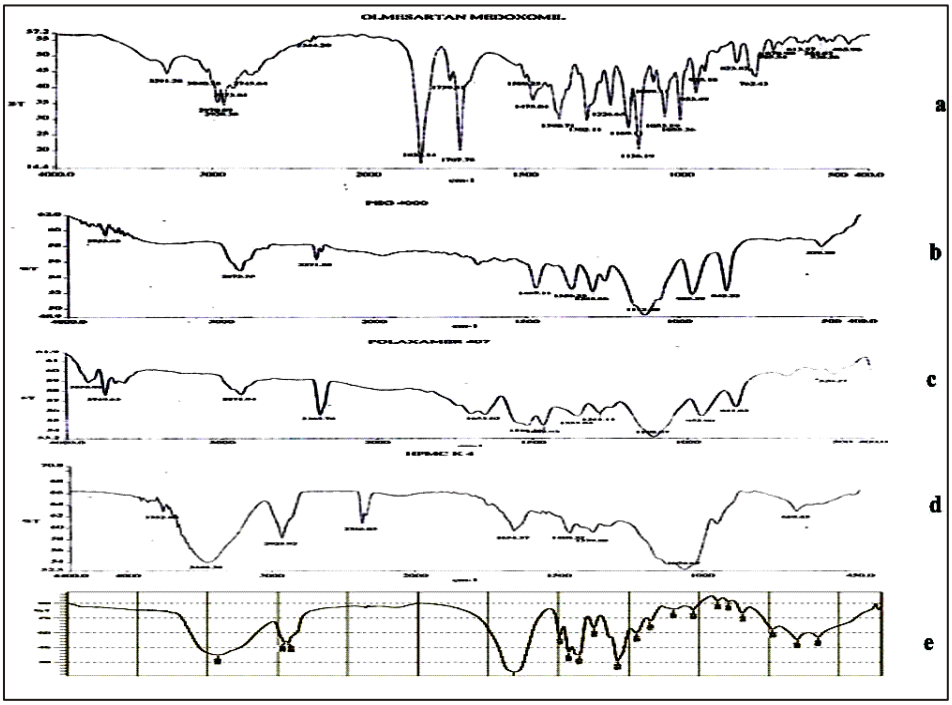


Fig. 1(a): IR spectra of (a) Pure drug olmesartan (b) PEG 4000 (c) Poloxamer 407 (d) HPMC K4 (e) Crospovidone

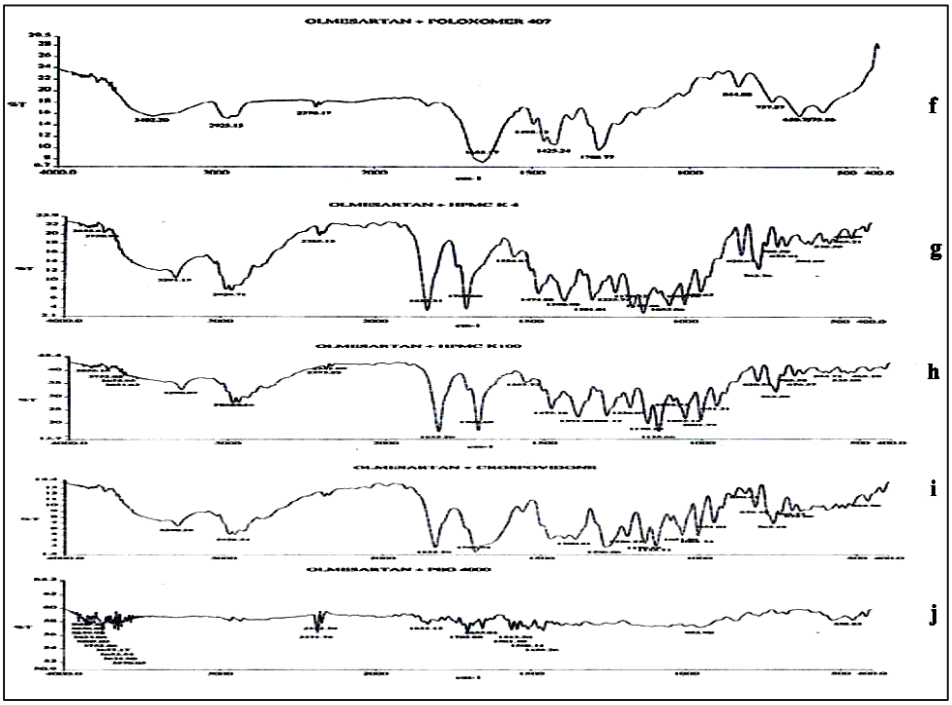


Fig. 1(b): IR spectra (f) Olmesartan + Poloxamer 407 (g) Olmesartan + HPMC K4 (h) Olmesartan + HPMC K100 (i) OLMESARTAN + CROSPOVIDONE (j) Olmesartan + PEG 4000

Differential scanning calorimetric (DSC) study[4]

The DSC thermograms of Olmesartan medoxomil and its physical mixtures are shown in Fig. 2. The sharp melting point peak of pure Olmesartan medoxomil appeared at 177.5°C, whereas no such peak was observed in physical mixtures prepared with PEG 4000, HPMC K4, HPMC K100, Poloxamer 407 and crospovidone suggesting that Olmesartan is molecularly dispersed and in amorphous form.

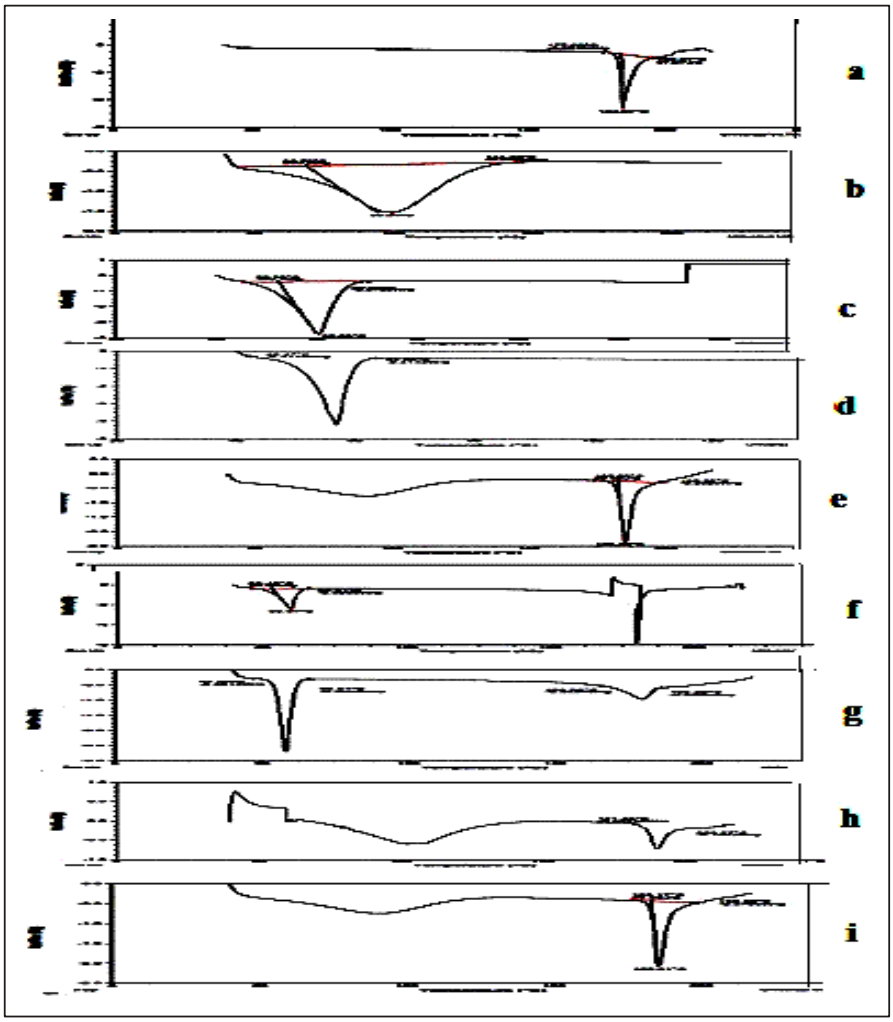


Fig. 2: DSC study (a) Pure drug-olmesartan medoxomil (b) HPMC K4 (c) PEG 4000 (d) Poloxamer 407 (e) Olmesartan medoxomil + HPMC K4 (f) olmesartan medoxomil + PEG 4000 (g) Olmesartan medoxomil + Poloxamer 407 (h) Olmesartan Medoxomil + Crospovidone (i) Olmesartan medoxomil + HPMC K100

Preparation of olmesartan solid dispersions[5-8]

In the present study, 28 formulations of Olmesartan solid dispersions were prepared by using water soluble carriers like PEG4000, poloxamer 407, HPMC K4, HPMC K 100 and crospovidone in the ratio of 1: 1, 1 : 2. 1 : 4 and 1 : 6 in three methods (melting method, kneading method and solvent evaporation method) (Table 1). The prepared solid dispersions were found to be uniform and homogeneous in appearance. PEG 4000 and poloxamer 407 were used in the preparation of melting method (8 formulations), HPMC K4, HPMC K100 and crospovidone were used in the preparation of solvent evaporation method (12 formulations). HPMC K4 and crospovidone were used in the kneading method (8 formulations).

Table 1: Preparation of Olmesartan solid dispersions and drug content

S. No.	Formulation code	Composition	Ratio	Method	Drug content (mean ± SD*)
1	KM1	Drug : HPMC K4	1 : 1	Kneading	93.45 ± 0.45
2	KM2	Drug : HPMC K4	1 : 2	Kneading	94.60 ± 0.53
3	KM3	Drug : HPMC K4	1 : 4	Kneading	93.90 ± 0.76
4	KM4	Drug : HPMC K4	1 : 6	Kneading	94.60 ± 0.39
5	KM5	Drug :C rospovidone	1 : 1	Kneading	95.30 ±0.43
6	KM6	Drug : Crospovidone	1 : 2	Kneading	96.3 ± 0.22
7	KM7	Drug : Crospovidone	1 : 4	Kneading	95.9 ± 0.45
8	KM8	Drug : Crospovidone	1 : 6	Kneading	97.8 ± 0.32
9	MM1	Drug : PEG 4000	1 : 1	Melting	93.3 ± 0.50
10	MM2	Drug : PEG 4000	1 : 2	Melting	92.4 ± 0.78
11	MM3	Drug : PEG 4000	1 : 4	Melting	92.5 ± 0.62
12	MM4	Drug : PEG 4000	1 : 6	Melting	93.4 ± 0.45
13	MM5	Drug : Poloxamer 407	1 : 1	Melting	94.3 ± 0.39
14	MM6	Drug : Poloxamer 407	1 : 2	Melting	93.9 ± 0.62
15	MM7	Drug : Poloxamer 407	1 : 4	Melting	94.4 ± 0.80
16	MM8	Drug : Poloxamer 407	1 : 6	Melting	95.5 ± 0.74
17	SEM1	Drug : HPMC K4	1 : 1	Solvent evaporation	96.7 ± 0.39
18	SEM2	Drug :HPMC K4	1 : 2	Solvent evaporation	95.3 ± 0.51
19	SEM3	Drug : HPMC K4	1 : 4	Solvent evaporation	94.8 ± 0.46
20	SEM4	Drug : HPMC K4	1 : 6	Solvent evaporation	95.1 ± 0.66
21	SEM5	Drug : HPMC K100	1 : 1	Solvent evaporation	94.9 ± 0.82
22	SEM6	Drug : HPMC K100	1 : 2	Solvent evaporation	96.8 ± 0.61
23	SEM7	Drug : HPMC K100	1 : 4	Solvent evaporation	96.3 ± 0.54
24	SEM8	Drug : HPMC K100	1 : 6	Solvent evaporation	97.2 ± 0.62
25	SEM9	Drug : Crospovidone	1 : 1	Solvent evaporation	98.3 ± 0.49
26	SEM10	Drug : Crospovidone	1 : 2	Solvent evaporation	99.6 ± 0.52
27	SEM11	Drug : Crospovidone	1 : 4	Solvent evaporation	99.8 ± 0.36
28	SEM12	Drug : Crospovidone	1 : 6	Solvent evaporation	98.9 ± 0.42

*n = 3

Characterization

Estimation of drug content[10]

The drug content in all the formulations was estimated spectrophotometrically at 257 nm (Shimadzu UV 1700, Pharmaspec, Japan). The drug content of the prepared solid dispersions was found to be in the range of 93.3 % to 99.8% indicating the uniform distribution of drug in the formulation (Table 1).

In vitro release studies[5,11,15]

The *in vitro* release studies were carried out for the Olmesartan solid dispersions prepared by three methods, namely kneading melting and solvent evaporation methods. In all the three methods the drug and polymer ratio used was 1 : 1, 1 : 2, 1 : 4 and 1 : 6.

In kneading method, two different carriers were used. The release profiles of HPMC K4,in the ratios of 1 : 1, 1 : 2, 1 : 4, 1 : 6 were found to be 77.23% (KM1), 75.03% (KM2), 75.10% (KM3) and 72.60% (KM4) after 1 hour. From the results, it was observed that KM1 (1 : 1 ratio) exhibited maximum release of 77.23% and it was rated as the best formulation in kneading method using HPMC K4. In case of crospovidone, in the ratios of 1 : 1, 1 : 2, 1 : 4, 1 : 6 were found to be 91.17% (KM5), 92.91% (KM6), 93.8% (KM7) and 95.56% (KM8) after 1 hour. From the results, it was observed that KM8 (1 : 6 ratio) exhibited maximum release of 95.56% and it was rated as the best formulation in kneading method using crospovidone (Fig. 3).

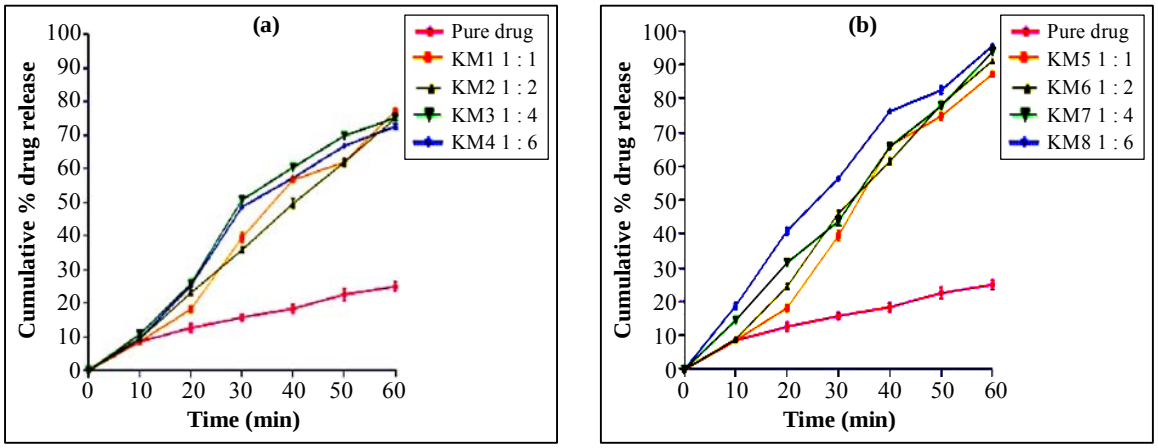


Fig. 3: Comparison of *in vitro* release profile of solid dispersion by kneading method (a) HPMC K4 (b) Crospovidone

In melting method, two different carriers (PEG 4000 and poloxamer 407) were used. The release profile of PEG 4000 in the ratios of 1 : 1, 1 : 2, 1 : 4, 1 : 6 were found to be 71.29% (MM1), 69.26% (MM2), 68.29% (MM3), 66.95% (MM4) after 1 hour). The results indicated that MM 1 (1 : 1 ratio) exhibited maximum release of 71.29% and it was rated as the best formulation in melting method using PEG 4000.

In case of poloxamer 407, in the ratios of 1 : 1, 1 : 2, 1 : 4, 1 : 6 were found to be 89.0% (MM5), 86.90% (MM6), 85.72% (MM7), 85.0% (MM8) after 1 hour. From the results, it was observed that MM1 (1 : 1 ratio) exhibited maximum release of 89.0% and it was rated as the best formulation in melting method using poloxamer 407 (Fig. 4).

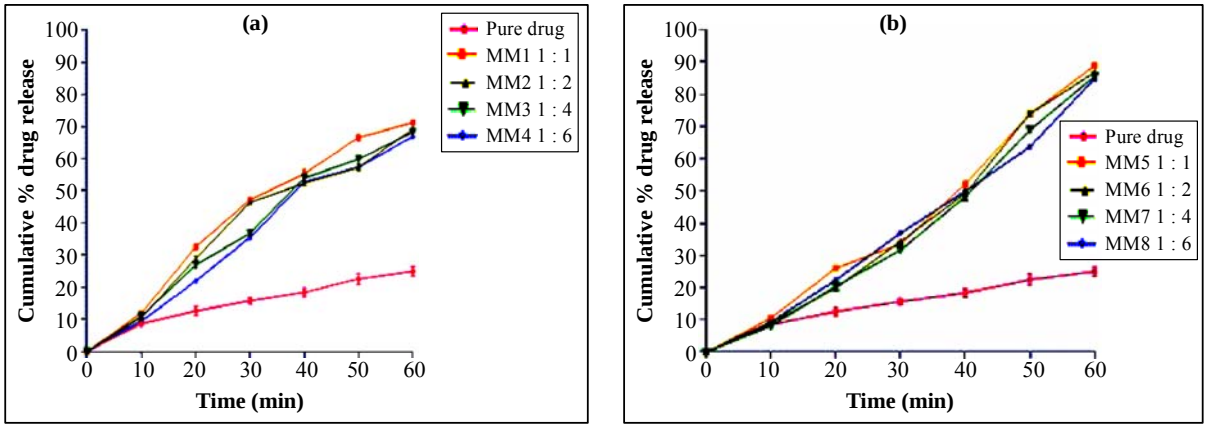


Fig. 4: Comparison of *in vitro* release profile of solid dispersion by melting method (a) PEG 4000 (b) Poloxamer 407

In solvent evaporation method, HPMC K4, HPMC K100 and crospovidone were used as carriers. The release profiles of HPMC K4, in the ratios of 1 : 1, 1 : 2, 1 : 4, 1 : 6 were found to be 72.88% (SEM1), 75.38% (SEM2), 71.63% (SEM3), 70.90% (SEM4) after 1 hour . The release profiles of HPMC K100 ,in the ratios of 1 : 1, 1 : 2, 1 : 4, 1 : 6 were found to be 70.20% (SEM5), 68.91% (SEM6), 68.85% (SEM7), 67.90% (SEM8) after 1 hour. The release profiles of crospovidone, in the ratios of 1 : 1, 1 : 2, 1 : 4, 1 : 6 were found to be 92.37% (SEM9), 95.85% (SEM10), 97.80% (SEM11), 94.47% (SEM12) after 1 hour (Fig. 5).

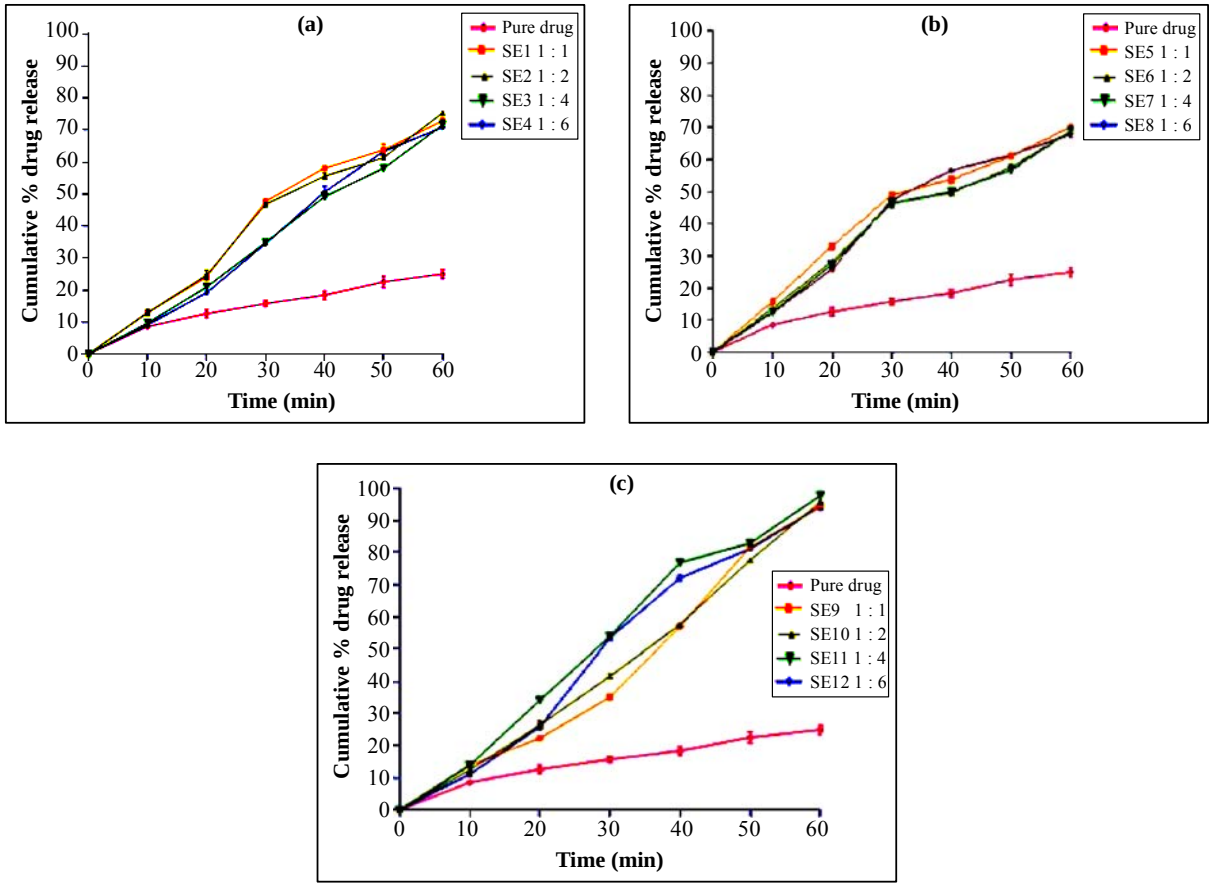


Fig. 5: Comparison of *in vitro* release profile of solid dispersion by solvent evaporation method (a) HPMC K4 (b) HPMC K100 (c) Crospovidone

In vitro release studies revealed that there is marked increase in the dissolution rate of Olmesartan solid dispersion when compared to physical mixture and pure drug. From the *in vitro* release studies, it can be observed that (SEM 11) containing crospovidone (1 : 4 drug : carrier) exhibited maximum release of 99.8% after one hour and so it was considered as the overall best formulation (Fig. 6).

The Olmesartan solid dispersion showed maximum release when compared to the pure drug and physical mixture. The increase in dissolution of the drug in both, the physical mixtures and solid dispersions was reported because of the enhanced wettability, hydrophilic nature of the carriers and possibility of reduced crystallinity of the drug in the formulations.

As the amount of PEG4000, poloxamer 407, HPMC K4 and K100 were increased in all formulation, the dissolution rate was decreased. This decrease in dissolution rate may be due to increased viscosity of coating materials.

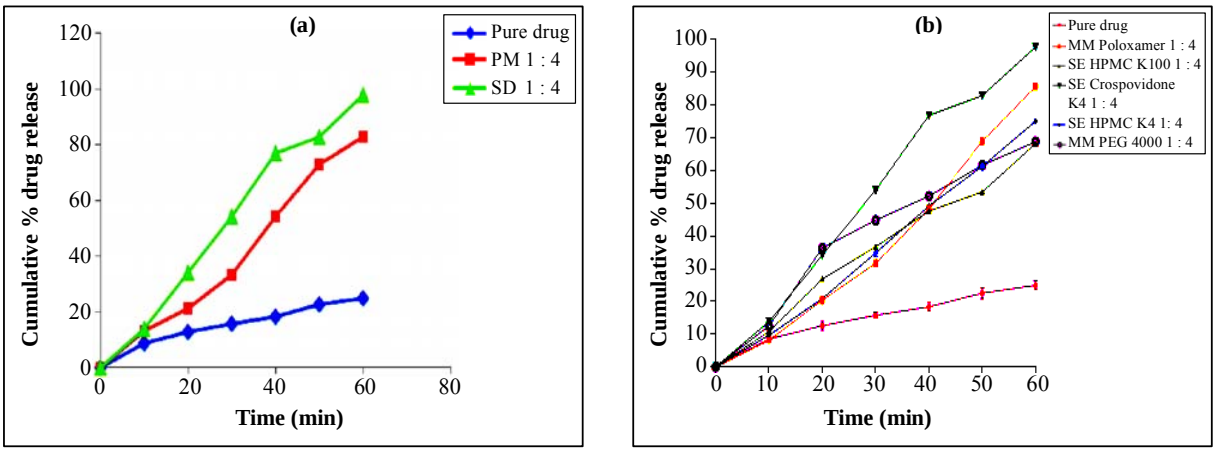


Fig. 6: Comparison of in *vitro* release profile of solid dispersion in 1 : 4 ratio (a) physical mixture and pure drug (b) different carriers

Solubility studies[10,12]

The solubility study was conducted with pure drug, physical mixture and solid dispersion using distilled water and phosphate buffer pH 6.8 as shown in Table 2. It was observed that the solid dispersion (SEM 11) had highest solubility compared to pure drug and physical mixture (PM 19) in both distilled water and phosphate buffer.

Table 2: Comparision of solubility study of olmesartan medoxomil

S. No.	Formulation	Distilled water) (µg/mL)	Buffer pH (6.8) (µg/mL)
1	Pure drug	0.185	0.194
2	Physical mixture (Drug : Crospovidone)	1.198	1.402
3	Solid dispersion (SEM11) (Drug : Crospovidone 1 : 4)	1.335	1.723

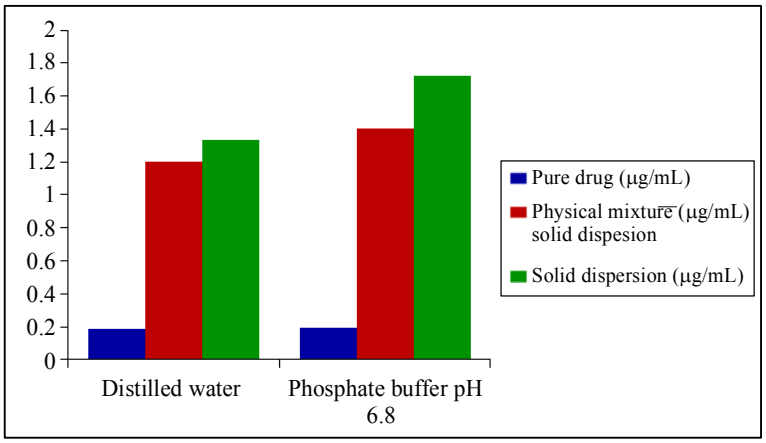
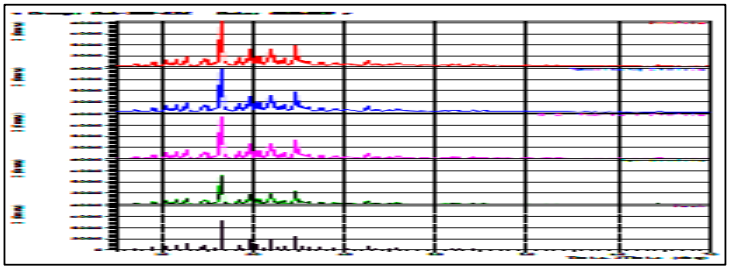


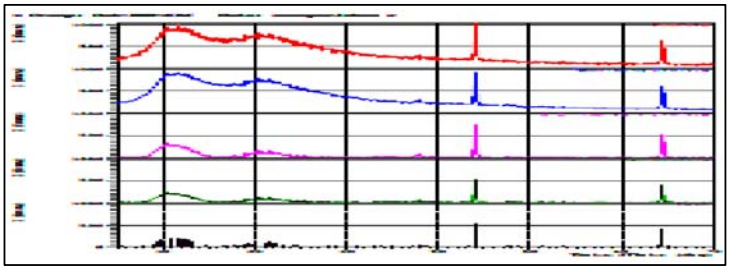
Fig. 7: Comparison of solubility study of olmesartan

Powder X-ray diffraction studies[3]

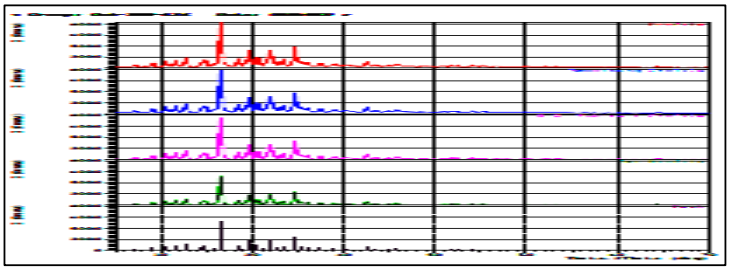
The Powder X-Ray Diffraction patterns of solid dispersion of Olmesartan medoxomil (SEM11) with the physical mixture (PM19) and pure drug are shown in Fig. 8. The crystalline nature of drug was studied by the characteristic PXRD pattern which showed sharp peaks at 16 and 24 at 2θ. PXRD for pure drug, crospovidone, physical mixture and solid dispersion were shown in Fig 8. In both physical mixture and solid dispersion no strong characteristic peaks were obtained which indicated that the drug is converted from crystalline to amorphous upon physical mixing and dispersion by the solvent evaporation method.



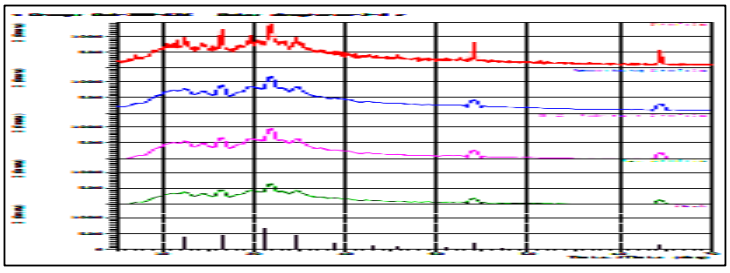
(a) Crospovidone



(b) Olmesartan medoxomil



(c) Physical mixture- Olmesartan medoxomil + Crospovidone



(d) Solid dispersion-Olmesartan medoxomil + Crospovidone 1 : 4

Fig. 8: X-ray diffraction

Stability studies[13]

The stability studies was conducted for a period of 45 days at an ambient temperature and relative humidity ($40^oC \pm 2^oC$, RH 75% ± 5%) for a period of 45 days to find out the physicochemical changes in the dispersions as per the modified ICH guidelines. Periodically samples were withdrawn to estimate the drug content which showed no significant changes in the drug content and the results are given in Table 3.

Table 3: Stability studies-drug content estimation

Formulaton code	0 Day	7th Day	15th Day	30th Day	45th Day
M-11 (1 : 4) (Drug : Crospovidone)	98.44%	98.26%	97.92%	97.74%	96.88%

CONCLUSION

It was concluded that the kneading, melting and solvent evaporation methods are useful methods for the successful enhancement of solubility of poorly water soluble drug Olmesartan with faster dissolution rate. Further, it may be assumed that the solubility and dissolution rate can be increased due to the conversion of crystalline matter into amorphous powder. Hence we can conclude that solid dispersion of Olmesartan by using the water soluble carrier crospovidone in the ratio 1 : 4 prepared by solvent evaporation method provide best release of drug (99.8% released in 60 min.) among all the formulations, and this ratio can be used to enhance the solubility and dissolution rate of poorly water soluble drug Olmesartan**.**

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