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Comparison of Polymers In Enhancing the Dissolution Rate of Olmesartan Medoxomil By Solid Dispersion Technique Using Solvent Evaporation Method

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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 Poloxamer 407, PEG 4000 and crospovidone in different ratios (1 : 1, 1 : 2, 1 : 3, 1 : 4) were prepared by solvent evaporation method. The formulations were further characterized for percentage yield, drug content, *in vitro* release study, and stability study. *In vitro* release studies revealed that the solid dispersions prepared by solvent evaporation method crospovidone (1 : 4) was considered as the best formulation because of its faster drug release among all formulations. 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.

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

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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. The solid dispersion was introduced in early 1970s refers to a group of solid products containing at least two different components generally a hydrophilic matrix and hydro phobic drug[1]. Solid dispersion is a promising drug delivery forms, which offer the possibility to disperse 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 [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 Poloxamer 407, PEG 4000 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.

MATERIALS AND METHOD

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

Calibration of Olmesartan medoxomil[3]

A standard curve was prepared with different concentration (1to 10 µg/ml) using pH6.8 phosphate buffer solution. The absorbance of these solutions was measured at λmax by uv-spectrophotometer. The calibration graph was drawn taking concentration on X-axis and respective absorbance in the Y axis to get a straight line as per Beer's law. This standard curve was used to estimate the concentration of the drug release from the formulation during the in vitro dissolution studies.

Preformulation studies

Infra red spectroscopy (IR)[4]

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.

Preparation of Olmesartan solid dispersion

Solvent evaporation method[5]

Olmesartan solid dispersion was prepared by solvent evaporation method using carrier Poloxamer 407, PEG 4000 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. The composition of various polymers and drug are shown in **table** 2.

Preparation of physical mixture[6]

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[7]

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.

Determination of Percentage practical Yield[8]

The % practical yield of all the formulations were calculated using the formula

% Practical Yield =Practical Mass/Theoretical Mass X100

***In vitro* dissolution studies**[9 -13]

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 37ºC ± 0.5ºC. 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 λmax 257 nm after suitable dilution using appropriate blank. The dissolution study was conducted in triplicate.

Powder X ray diffraction (PXRD) studies[4]

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. 4o/min over the 2θ range of 2-50.

Stability studies[11]

The stability studies of best formulation (**SEM 8)** was carried out at an ambient temperature and relative humidity (40oC±2oC, 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

The λmax of Olmesartan medoxomil was determined by scanning the 10µg/ml of the drug solution in phosphate buffer solution pH 6.8 by UV-spectrophotometer. It showed the λmax of 257nm and obeys the Beer's law with the concentration range of 1-10 µg/ml was shown in **Figure 1-**

Table 1 :Calibration of Olmesartan Medoxomil (pH 6.8)

S.No	Concentration (µg/ml)	Absorbance at 257 nm (Avg ± SD)
1	1	0.065±0.001
2	2	0.118±0.005
3	3	0.173±0.006
4	4	0.23±0.003
5	5	0.284±0.002
6	6	0.343±.004
7	7	0.404±.006
8	8	0.460±.005
9	9	0.515±.007
10	10	0.577±.007

*Mean±SD (n=6)

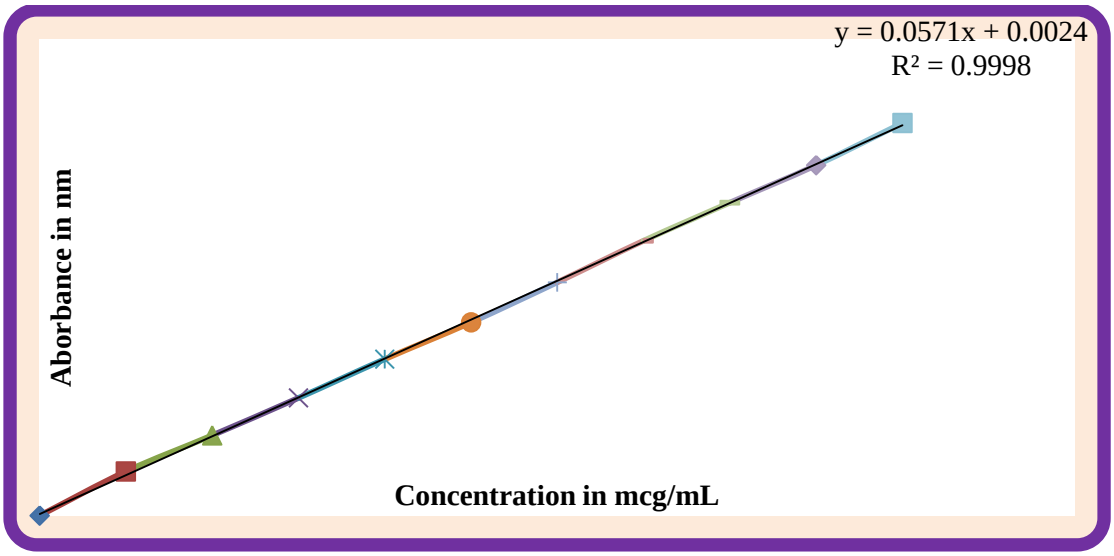


Figure 1: Calibration curve of Olmesartan Medoxomil

Infra red spectroscopic study[4, 12]

The IR spectra of Olmesartan and its binary systems with crospovidone, PEG 4000, poloxamer 407 and are present in **Fig. 2a-f.** 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.

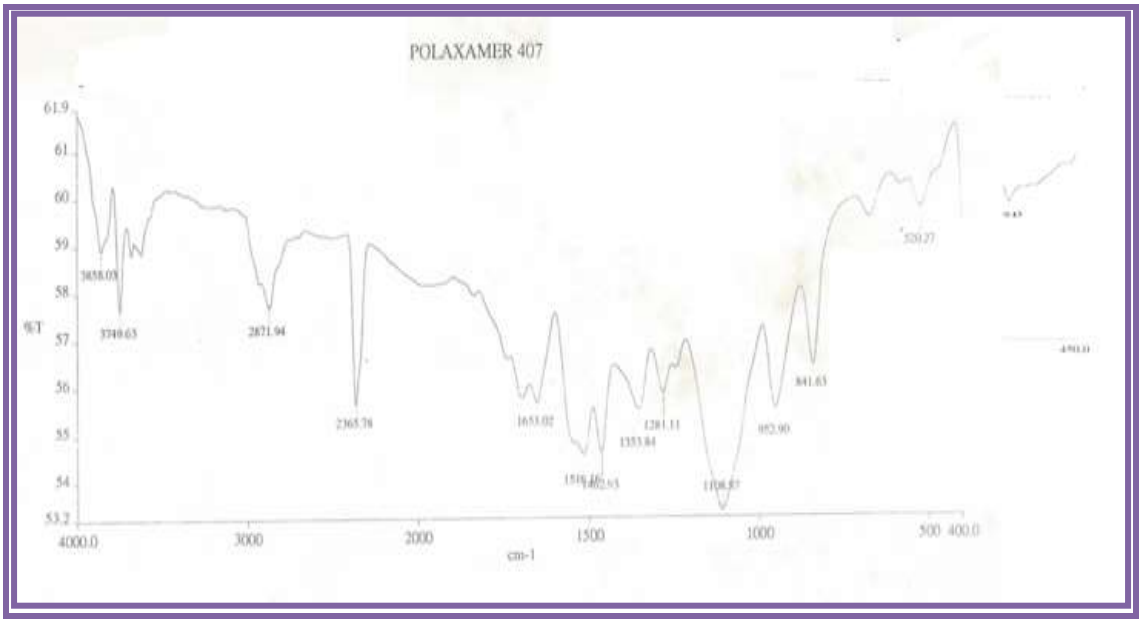


Figure 2a: IR Spectra of Poloxamer 407

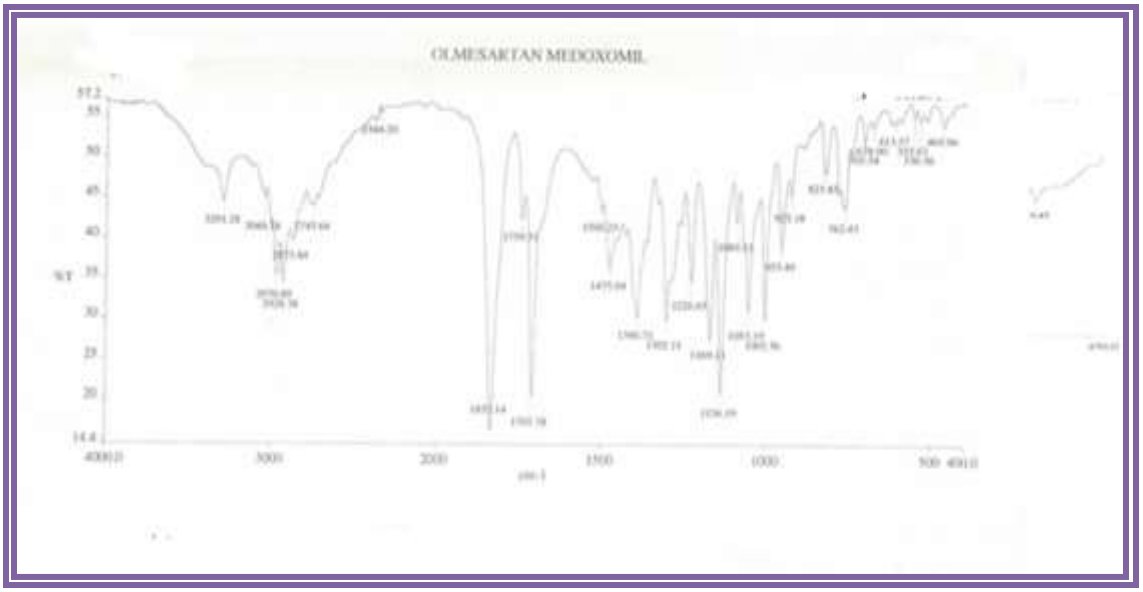


Figure 2b: IR Spectra of Olmesartan Medoxomil

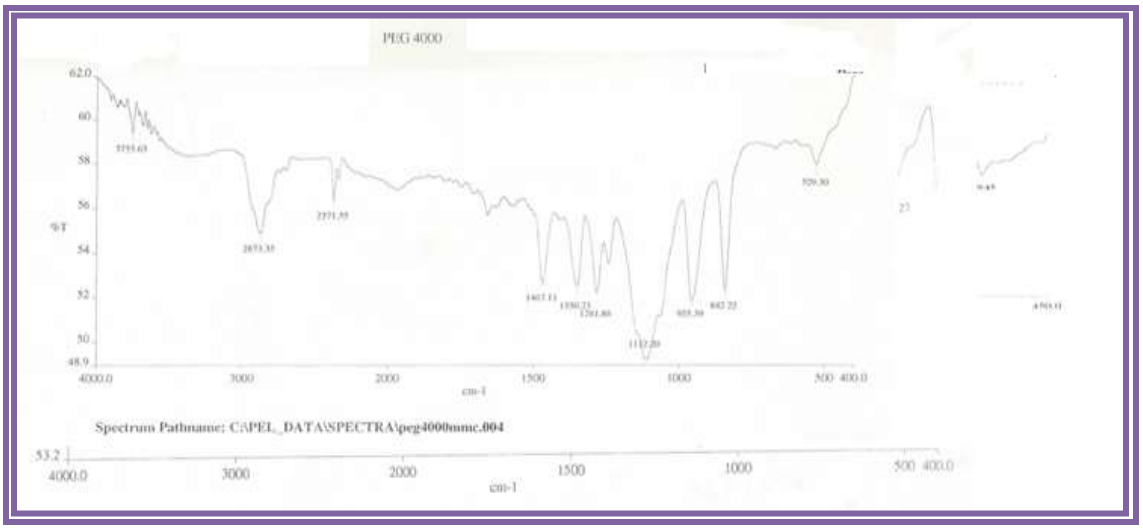


Figure 2c: IR Spectra of PEG 4000

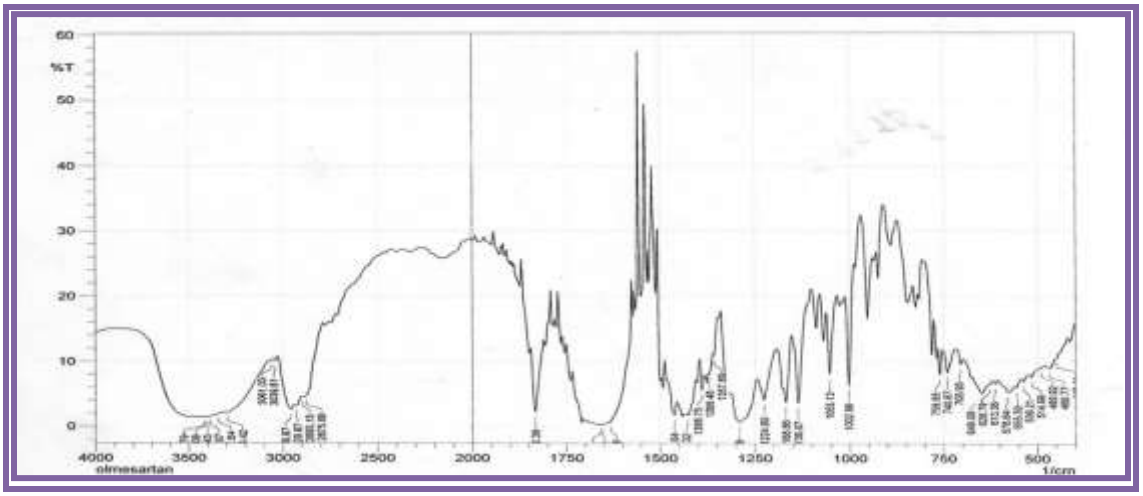


Fig 2d: IR Spectra of solid dispersion using Crospovidone

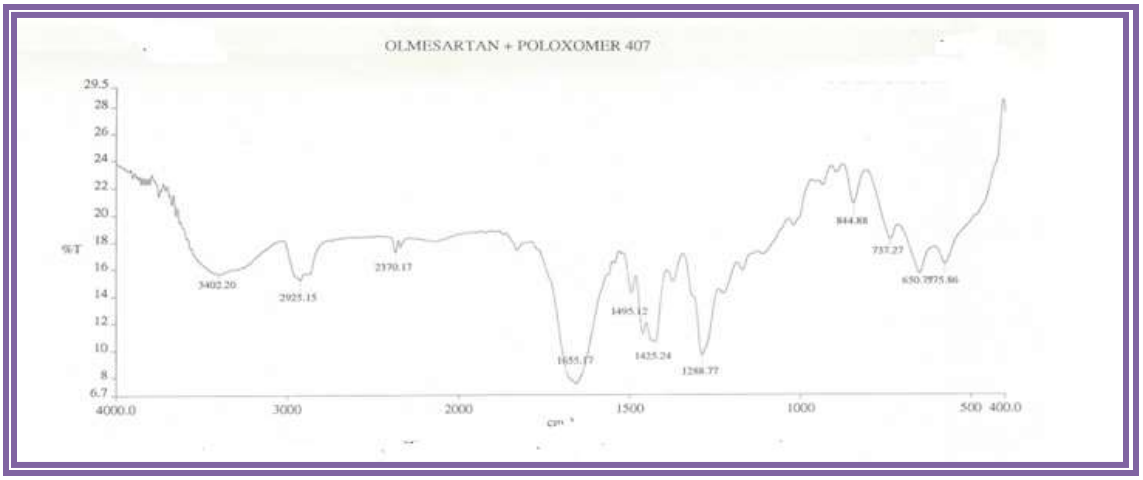


Figure 2e: IR Spectra of solid dispersion using Poloxamer 407

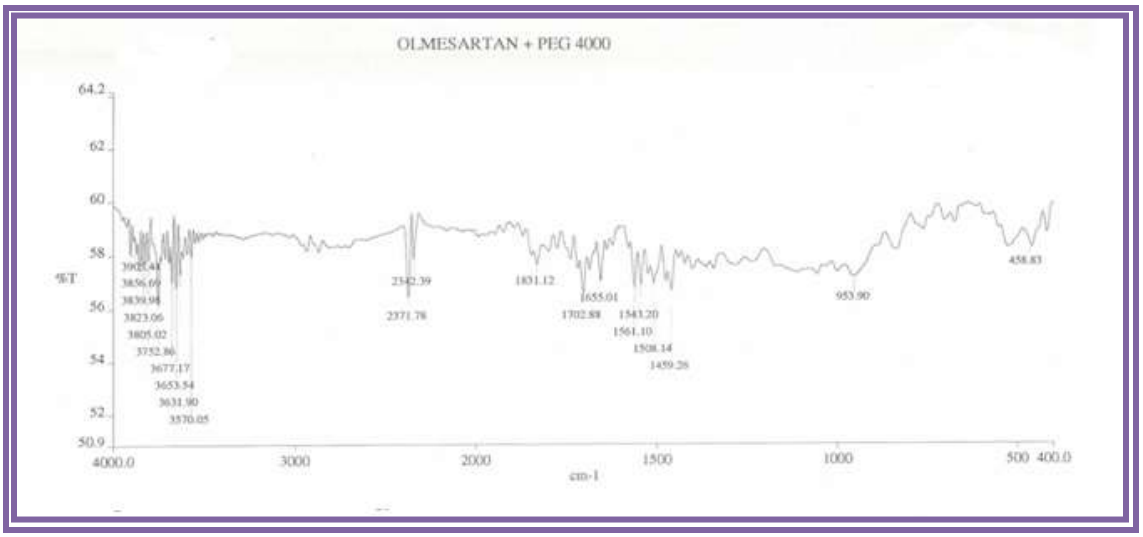


Figure 2f: IR Spectra of solid dispersion using PEG 4000

Characterization

Estimation of drug content

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 98.8% indicating the uniform distribution of drug in the formulation (Table 2).

Twelve formulations were prepared using polymers Crospovidone, Poloxamer 407 and PEG 4000 in four different ratios using solvent evaporation method. The % yield and drug content were shown in table 3.

Table 2 Formulation with Drug Content and % Practical Yield

S.No	Formulation Code	%Percentage Yield	% Drug Content Average ±SD
1.	SEM1	95.3	96.7± 0.39
2.	SEM2	95.4	95.3± 0.51
3.	SEM3	94.7	94.8± 0.46
4.	SEM4	96.2	94.1± 0.66
5.	SEM5	97.1	94.9± 0.82
6.	SEM6	96.8	95.8± 0.61
7.	SEM7	93.3	96.3±0.54
8.	SEM8	97.8	97.2±0.62
9.	SEM9	96.3	97.3± 0.49
10.	SEM10	98.6	97.6±0.52
11.	SEM11	97.9	98.8±0.36
12.	SEM12	98.1	98.9± 0.42
13.	PM 1	97.0	95.3± 1.04
14.	PM 2	98.1	96.5± 1.39
15.	PM 3	99.3	93.5±0.86
16.	PM 4	98.4	94.9± 0.72
17.	PM 5	97.2	93.2± 0.65
18.	PM 6	98.3	93.8± 0.56
19.	PM 7	98.6	95.8± 0.58
20.	PM 8	98.8	96.3±0.79
21.	PM 9	98.4	95.1± 032
22.	PM 10	97.9	94.3± 0.46
23.	PM 11	98.3	95.1± 0.38
24.	PM 12	99.1	96.4±0.62

*Mean±SD (n=6)

Table 3 Formulation- Drug and Polymer Composition Ratio

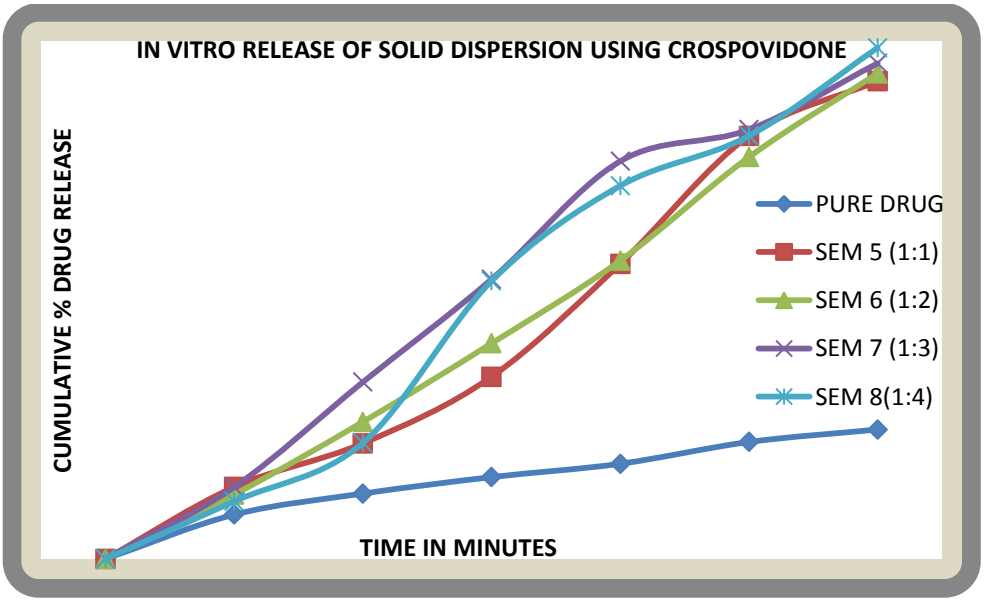
S.no	Formulation code	Composition	Ratio	Method
1.	SEM1	DRUG: POLOXAMER 407	1:1	Solvent Evaporation
2.	SEM2	DRUG: POLOXAMER 407	1:2	Solvent Evaporation
3.	SEM3	DRUG: POLOXAMER 407	1:3	Solvent Evaporation
4.	SEM4	DRUG: POLOXAMER 407	1:4	Solvent Evaporation
5.	SEM5	DRUG:CROSPOVIDONE	1:1	Solvent Evaporation
6.	SEM6	DRUG: CROSPOVIDONE	1:2	Solvent Evaporation
7.	SEM7	DRUG: CROSPOVIDONE	1:3	Solvent Evaporation
8.	SEM8	DRUG: CROSPOVIDONE	1:4	Solvent Evaporation
9.	SEM9	DRUG: PEG4000	1:1	Solvent Evaporation
10.	SEM10	DRUG: PEG4000	1:2	Solvent Evaporation
11.	SEM11	DRUG: PEG4000	1:3	Solvent Evaporation
12.	SEM12	DRUG: PEG 4000	1:4	Solvent Evaporation
13.	PM 1	DRUG: POLOXAMER 407	1:1	Grinding
14.	PM 2	DRUG: POLOXAMER 407	1:2	Grinding
15.	PM 3	DRUG: POLOXAMER 407	1:3	Grinding
16.	PM 4	DRUG: POLOXAMER 407	1:4	Grinding
17.	PM 5	DRUG: CROSPOVIDONE	1:1	Grinding

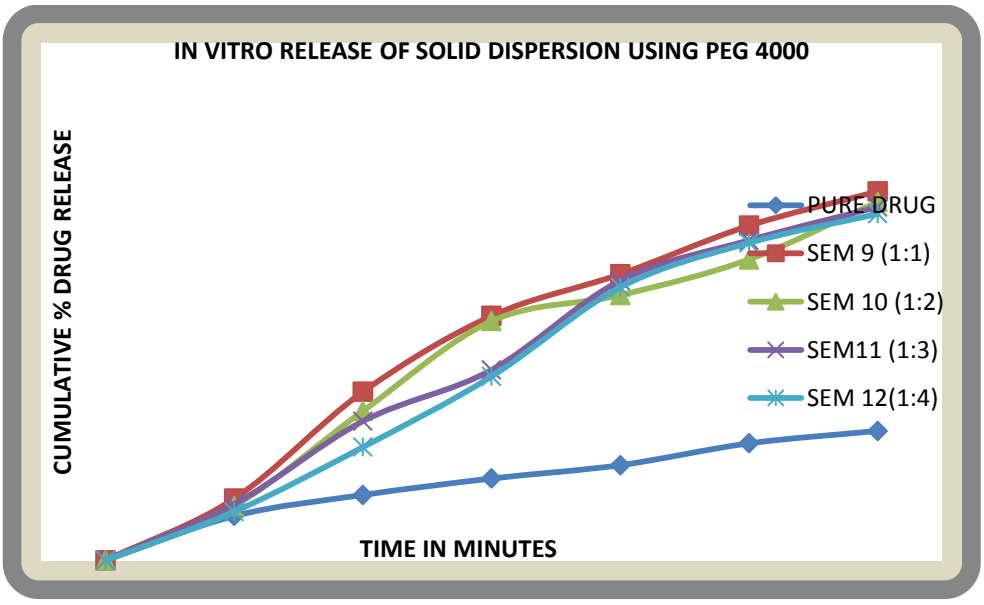
18.	PM 6	DRUG: CROSPOVIDONE	1:2	Grinding
19.	PM 7	DRUG: CROSPOVIDONE	1:3	Grinding
20.	PM 8	DRUG: CROSPOVIDONE	1:4	Grinding
21.	PM 9	DRUG: PEG4000	1:1	Grinding
22.	PM 10	DRUG: PEG4000	1:2	Grinding
23.	PM 11	DRUG: PEG4000	1:3	Grinding
24.	PM 12	DRUG: PEG 4000	1:4	Grinding

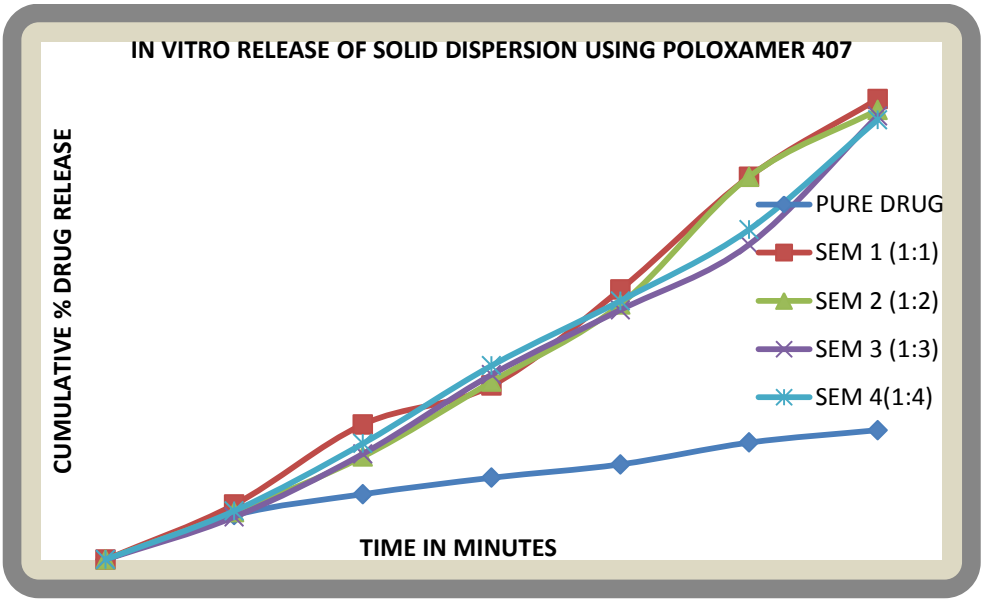
*Mean±SD (n=6)

***In vitro* release studies**

The *in vitro* release studies were carried out for the Olmesartan solid dispersions prepared by solvent evaporation methods. The drug and polymer ratio used was 1 : 1, 1 : 2, 1 : 3 and 1 : 4. From the results it was observed that SEM8 (DRUG:CROSPOVIDONE 1:4) exhibited the best release of 98.8%in 60 minutes.







Powder X-ray diffraction studies [4]

The Powder X-Ray Diffraction patterns of solid dispersion of Olmesartan medoxomil (SEM8) with the physical mixture (PM) 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 (Figure 4a-c)

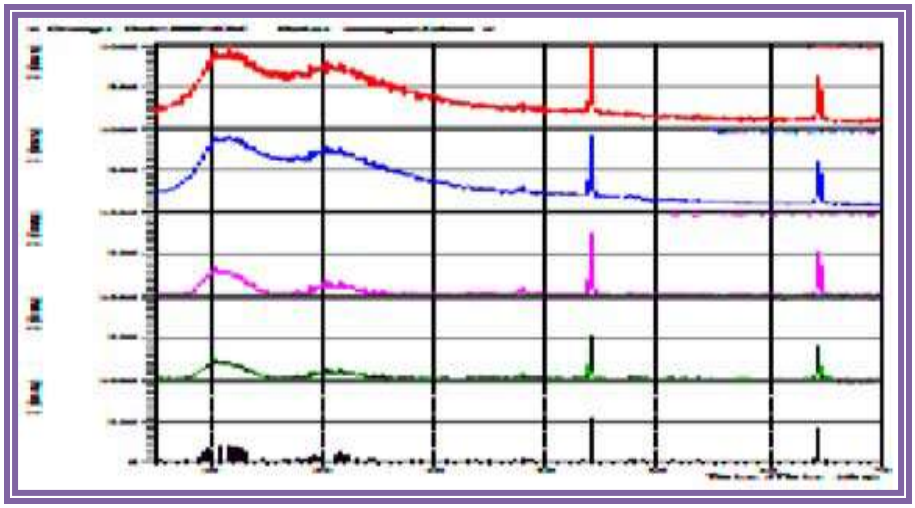


Figure 4 a Crospovidone

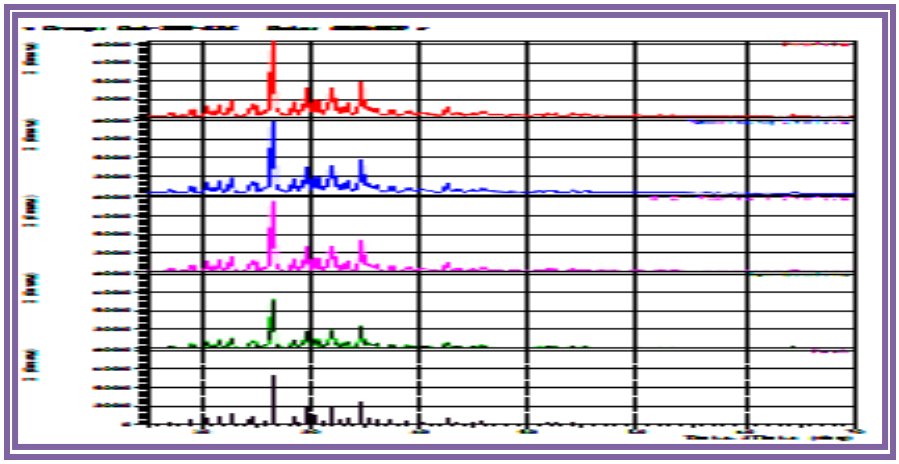


Figure: 4b Physical mixture- Olmesartan medoxomil + Crospovidone

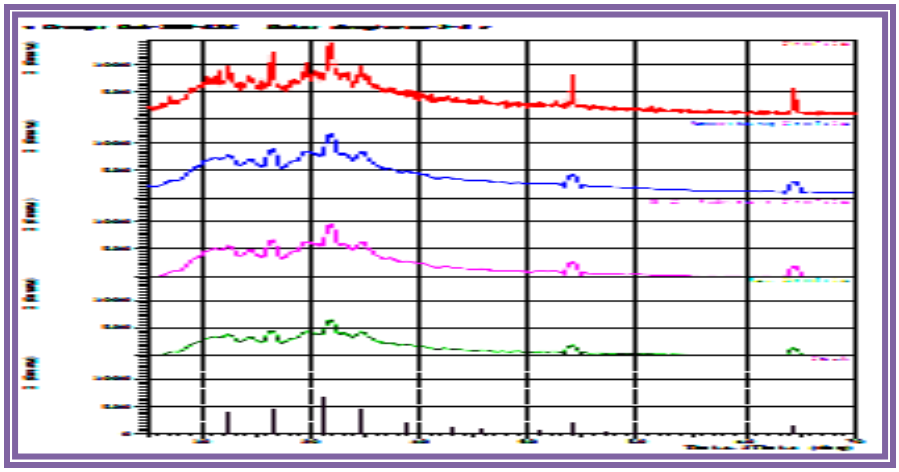


Figure 4C : (d) Solid dispersion-Olmesartan medoxomil + Crospovidone 1 : 4

Stability studies

The stability studies was conducted for a period of 45 days at an ambient temperature and relative humidity (40oC ± 2oC, 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 4.

Table 3: Stability Studies-Drug Content Estimation

Formulation Code	0 Day	7th Day	15th Day	30th Day	45th Day
SEM 8	98.44	98.26	97.92	97.74	96.88

*Mean±SD (n=6)

CONCLUSION

It was concluded that the solvent evaporation methods is an useful method 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 (98.8% 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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