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A COMPARATIVE STUDY OF FIVE DIFFERENT SOLID DISPERSION TECHNIQUES TO INCREASE DISSOLUTION RATE OF OLMESARTAN MEDOXOMIL

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ABSTRACT

The present study involved preparation of solid dispersions of Olmesartan medoxomil by different solid dispersion techniques to improve the aqueous solubility and dissolution rate in order to enhance bioavailability. Olmesartan medoxomil is a BCS class II antihypertensive drug with low water solubility and bioavailability of 26%. In the present study solid dispersions of Olmesartan medoxomil with Poloxamer 407 in the ratio of 1:4 was prepared by five different techniques like melting method, Kneading method, solvent evaporation, Co-grinding method, and Lyophilization method. The Formulations were assessed for percentage yield, dissolution study, drug content, solubility study and stability study. *In vitro* release studies revealed that the solid dispersions prepared by solvent evaporation method showed faster drug release than other methods. Solid dispersion containing Poloxamer (1:4) prepared by solvent evaporation technique 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. In a nutshell, solid dispersions of Olmesartan medoxomil in Poloxamer 407 (1:4) by solvent evaporation have shown to be a promising approach to enhance the bioavailability of Olmesartan medoxomil.

KEYWORDS

Solid dispersion, Dissolution enhancement, Olmesartan medoxomil, Poloxamer 407, Solvent Evaporation and Melting method.

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INTRODUCTON

The oral route of administration is the widely used and preferred method of delivery due to convenience and ease of ingestion but it can be problematic for many reasons most significant being its 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. Conventional dosage form is very popular because of ease of self administration, compact in nature, easy to manufacture and it can be delivered in accurate dose.

Poor solubility is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products, since nearly half of the active substances are either insoluble or poorly soluble in water. At present 40% of the drugs in the development pipelines and approximately 60% of the drugs coming directly from synthesis are poorly soluble[1] (Vekariya Dhaval Kumar *et al*, 2012). Solid dispersion offers the possibility to disperse a hydrophobic drug in a hydrophilic matrix and thereby improve the dissolution rate and bioavailability. Olmesartan is a specific angiotensin II type I antagonist used alone or in combination with other anti-hypertensive agents to treat hypertension. Olmesartan has poor water solubility and low bioavailability of 26 %[2]. (www.drug bank.ca). The study was initiated to increase the solubility of Olmesartan medoxomil using Poloxamer 407 using five different solid dispersion techniques.

MATERIAL AND METHODS

Olmesartan medoxomil was obtained as a gift sample from Torrent Pharmaceuticals, India. Poloxamer 407 was obtained as gift sample from Pharmafabrikon, Madurai, (TN), India. 07 Methanol was purchased from Astron Chemicals, Ahmedabad. All other chemicals used were of analytical grade.

Calibration of Olmesartan medoxomil[3]

A standard curve was prepared with different concentration (1 to 10µg/ml) using pH 6.8 phosphate buffer solution. The absorbance of these solutions was measured at λmax by UV-spectrophotometer. The calibration graph was drawn by taking the concentration on the X axis and respective absorbance in the Y axis, to get a straight line as per like 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.

Fourier Transform Infrared spectroscopic studies (FTIR)[4]

FTIR Spectroscopic study was carried out to check the compatibility between drug and polymer. The spectrum of Olmesartan medoxomil (pure drug), Poloxamer 407 and its physical mixture were recorded using Fourier transform infrared spectrometer (Spectrum RX-1 Perkin-Elmer, German). Samples were prepared using KBr (Spectroscopic grade) discs by means of hydraulic pellet press at a pressure of five tons for 30 seconds at a resolution of 4cm-1.

Differential Scanning Colorimetric Analysis (DSC)[5]

DSC study of pure drug, Poloxamer 407, PM and solid dispersions 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.

Preparation of solid dispersions

Solid dispersions were prepared by using Poloxamer 407 in the ratio of 1:4 by five different techniques namely

1. Melting method
2. Kneading method
3. Solvent evaporation method
4. Co-grinding method
5. Lyophilization

Melting method[6]

In melting method the drug and carrier (Poloxamer 407) was mixed in 1:4 ratio in a china dish and heated on a water bath until it is completely melted. Then the molten mass is poured on a tile and cooled. The solidified mass is dried pulverized and passed through sieve No, 40 and stored in a desiccator.

Kneading method[7]

The drug and the carrier was weighed in the ratio of 1:4 and transferred to mortar for kneading using hot water up to 45 minutes. Methanol was slowly added to maintain paste like consistency. The resulting paste was then dried in hot air oven at 45^{o} for 24

hours. The dried dispersions were milled and passed through sieve No.18. The prepared dispersions were stored in glass vials and used for further studies.

SOLVENT EVAPORATION METHOD[8]

Solid dispersions were prepared by solvent evaporation method. The carrier was dissolved in methanol with continuous stirring until clear solution is obtained. The drug was then added to above said mixture with continuous stirring for 45 minutes. The solvent was removed under reduced pressure and the resulting solid dispersions were kept at room temperature in a dessicator, which is then subjected to pulverization and sieving.

Co-grinding method[9]

The drug and carrier were mixed in the ratio of 1:4 and was further ground in Planetary Ball Mill (Fritsch, Pulverisette 7, Germany) at 500 rpm for 30, 60, and 90 minutes. The co-grinded powder was kept in desiccator. The different formulations including its ratios were given in Table No.1.

LYOPHILIZATION[10]

The drug and carrier were mixed in the ratio of 1:4. The drug was dissolved in 5mL of 96% methanol, whereas Poloxamer 407 was dissolved in 20 ml of distilled water. The solution was mixed on a magnetic stirrer and then homogenized. After attaining the homogeneous state the mixture undergone drying in a freeze dryer (Christ Alpha 1-2 LD Plus, France) and they were stored in a sealed container and put in desiccator.

Physical mixing method[11]

Using this method, it can be prepared by mixing the drug and carrier in the ratio of 1:4 in a glass mortar. The solid mass is pulverized and passed through sieve No. 40 to get uniformly sized particles and stored in desiccators until further use.

Determination of percentage practical yield[12]

Percentage practical yield is calculated to determine percent yield or efficiency of any method, thus it is helpful in the selection of appropriate methods of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following formula

$$\text{Practical Yield Mass of Solid dispersions} = \frac{\text{Practical mass}}{\text{Theoretical mass}} \times 100$$

Determination of drug content[13]

Solid dispersions equivalent to 10 mg of Olmesartan medoxomil were weighed accurately and dissolved in 10 ml of methanol, diluted with phosphate buffer pH 6.8 at λmax by UV-spectrophotometer.

% Drug content = Sample absorbance/Standard absorbance X 100

***In-Vitro* Dissolution Study**[14]

In vitro dissolution study was performed in 900 ml Phosphate buffer pH 6.8 using USP Type II (paddle) apparatus at 30 rpm for 60 minutes (37 ± 0.50C). Samples (10 ml) were withdrawn at specific time intervals analyzed for drug content by measuring the absorbance at 257 nm. The percentage drug release in one hour was plotted against time to determine the release of the drug.

Stability studies[15]

The stability studies of best formulation (SE4) was carried out at an ambient temperature and relative humidity (40oC ± 2oC, RH 75% ± 5%) for a period of 45 days to determine the physicochemical changes in the formulations as per the modified ICH guidelines. The samples were withdrawn at specific intervals to estimate the drug content.

RESULTS AND DISCUSSION

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 257 nm and obeys the Beer's law within the concentration range of 1- 10µg/ml was shown in Figure No.1. Linear correlation coefficient obtained was r2 = 0.9998 for its calibration. The dissolution graph is given below. (Figure No.1)

Infra red spectroscopic study

The IR spectra of Olmesartan and its binary systems with Poloxamer 407 is present in Figure No.2a-c. Pure Olmesartan spectra showed sharp characteristic peaks at 3291.28, 2928.38, 1832.14, 1707.78, 762.43 cm-.

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 No.2a-c).

Differential Scanning Colorimetric Analysis (DSC)

The DSC of pure drug and its physical mixtures are shown in Figure No.3a-c. The sharp melting point peak of pure Olmesartan medoxomil appeared at 177.5^{o}C, whereas no such peak was observed in physical mixtures prepared with Poloxamer 407 suggesting that Olmesartan is molecularly dispersed and in amorphous form.

Preparation of Olmesartan solid dispersions

Six formulations were prepared by using the drug Olmesartan and Poloxamer 407 in the ratio of 1:4 by different solid dispersion techniques namely melting method, kneading method, solvent evaporation method, co-grinding method. They are shown below in Table No.1.

Determination of drug content[14]

Solid dispersions equivalent to 10 mg of Olmesartan medoxomil were weighed accurately and dissolved in 10 ml of methanol, diluted with phosphate buffer pH 6.8 at λmax by UV-spectrophotometer. The drug content of all the formulations were within the range of 94.2%-98.8% that was shown in Table No.1.

% drug content = Sample absorbance/Standard absorbance X 100

***In vitro* release studies**

The *in vitro* release studies were carried out for the Olmesartan solid dispersions prepared by five methods, namely melting method, kneading melting solvent evaporation method, Co-grinding method and Lyophilization. The pure drug exhibited very less drug release of 32.7% at the end of 60 minutes. In all the five methods the drug and polymer ratio used was 1:4. In kneading method the drug release was 83.5%. In melting method it exhibited drug release of 86.5%. Solid dispersion prepared by solvent evaporation method exhibited maximum drug release of 94.7%. Co-grinded solid dispersion showed drug release of 85.8%. Lyophilized solid dispersions exhibited drug release of 82.2%. From the results it can be observed that the solid dispersion prepared by solvent evaporation method exhibited maximum drug release of 94.7% at the end of 60 minutes.

The less release in melting method can be attributed to the factor that there may be incompatibility between drug and polymer to a lesser extent. Co-grinded and melted showed more or less similar drug release (MM1-86.5% and CG3.85.8%). The in vitro release exhibited by the solid dispersions, pure drug and physical mixture is given below in Figure No.4.

It can be concluded that the solid dispersions prepared by solvent evaporation exhibited maximum drug release of (94.7%) in 60 minutes when compared with pure drug, physical mixture and other four solid dispersion techniques. Hence it can be considered to enhance the dissolution rate of Olmesartan Medoxomil.

Solubility studies[15]

The solubility study was carried out with pure drug, physical mixture and solid dispersion using distilled water and phosphate buffer pH 6.8 as shown in Table No.2. It was observed that the solid dispersion (SE4) had highest solubility compared to pure drug and physical mixture. 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 No.2. It was observed that the solid dispersion (SE4) had highest solubility compared to pure drug and physical mixture (PM) in both distilled water and phosphate buffer.

Stability studies[16]

The stability study was also done on the best formulation (SD 6) where it was sealed in aluminum packaging coated inside with polyethylene and various replicates were kept in humidity chamber (Bio-Technics, Ltd, India) maintained at 40 ± 2^{o}C/ 75 ± 5% RH for 3 months to assess its stability. At a interval of 45 and 90 days respectively, the formulations were taken and evaluated for physical appearance, drug content (%) and cumulative drug release (%). They showed no significant changes in the drug content and the results are given in Table No.3.

Table No.1: Formulation

S. No	Formulation Code	Drug: Carrier	Techniques Used	Drug content	Percentage Yield
1	MM1	1:4	Melting Method	95.9 ± 0.45	94.5%
2	KM2	1:4	Kneading Method	97.8 ± 0.32	96.1%
3	CG3	1:4	Co-grinding	96.8 ± 0.76	98.2
4	SE4	1:4	Solvent evaporation Method	98.8 ± 0.26	98.9%
5	LY5	1:4	Lyophilization Method	94.2 ± 0.65	95.3%
6	PM6	1:4	Physical mixing Method	97.8 ± 0.39	97.7%

Table No.2: Comparison of solubility study of Oabllmesartan medoxomil

S.No	Formulation	Distilled water	Buffer ph 6.8
1	Pure drug	0.732	0.916
2	Physical mixture	1.185	1.391
3	Solid dispersion Drug: Poloxamer SE4 (1:4) SE 4	1.342	1.723

Table No.3: Stability studies-drug content estimation

S.No	Formulation code	0 Day	7th Day	15th Day	30th Day	45th Day
1	SE4(Drug : Poloxamer 407)	98.14%	98.0%	97.83%	97.62%	96.74%

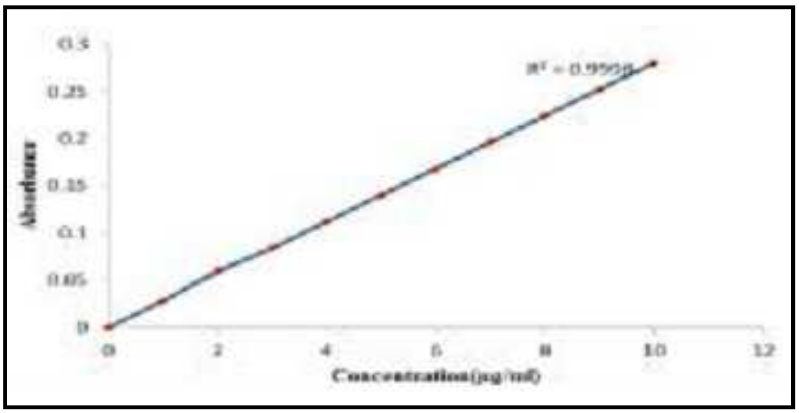

Figure No.1: Standard curve of Olmesartan medoxomil

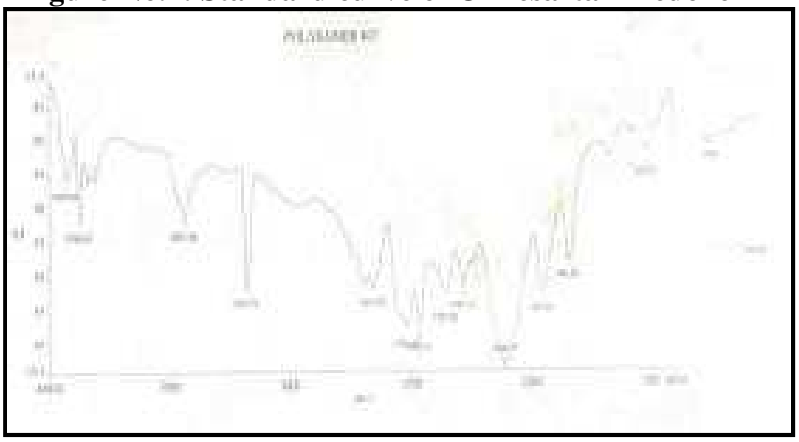

Figure No.2a: IR Poloxamer 407

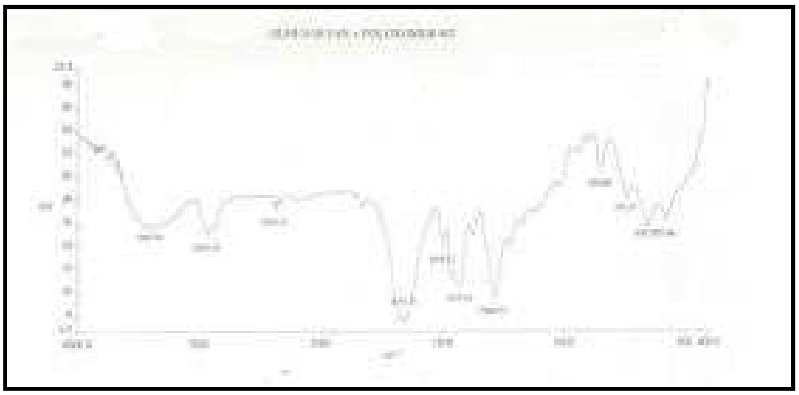

Figure No.2b: IR Olmesartan Medoxomil and Poloxamer 407

Figure No.2C: IR Olmesartan Medoxomil

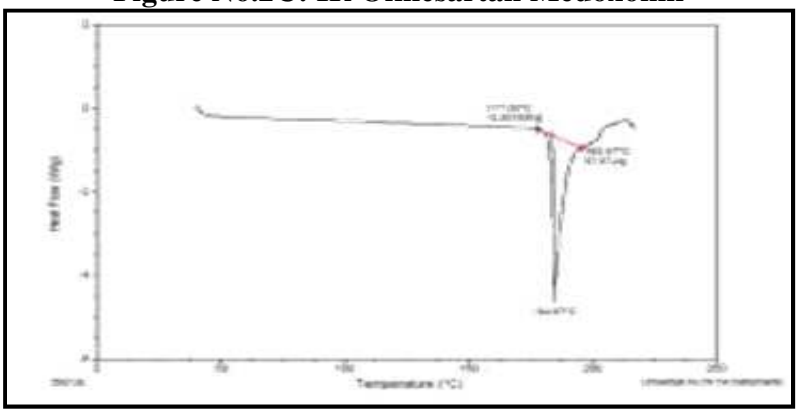

Figure No.3a: DSC of Olmesartan Medoxomil

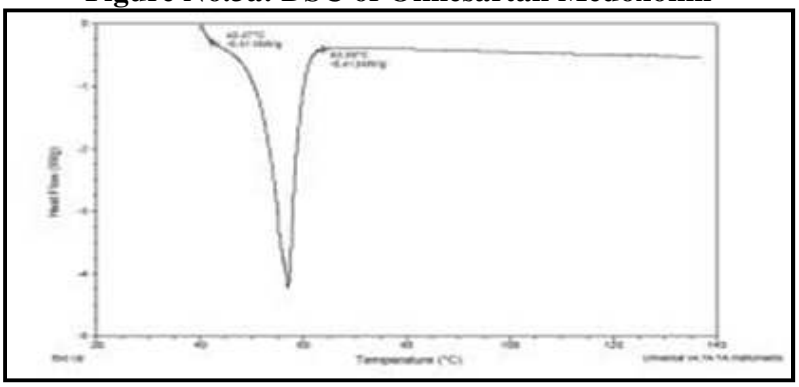

Figure No.3b: DSC of Poloxamer 407

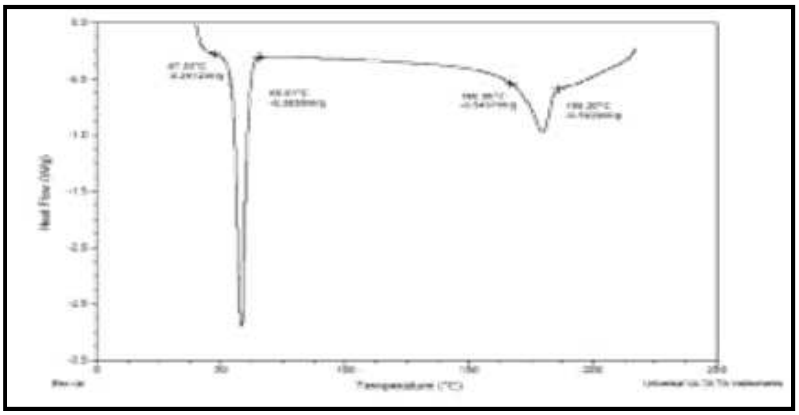

Figure No.3c: DSC of Olmesartan Medoxomil and Poloxamer 407

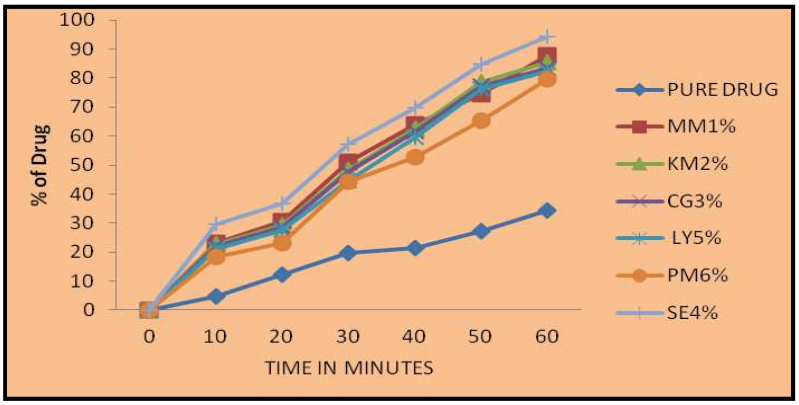

Figure No.4: *In vitro* drug release of solid dispersions, physical mixture and pure drug

CONCLUSION

The dissolution rate of Olmesartan medoxomil from solid dispersion by all the five methods were found to be significantly higher than pure drug but solvent evaporation method showed higher dissolution than other four methods. In conclusion, development of the solid dispersions could be a promising alternative method to attain fast dissolution rate and solubility which may lead to improvement in fast dissolution and better solubility.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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