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Enhancement of solubility and dissolution rate of olmesartan medoxomil by solvent evaporation technique

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ABSTRACT

Ensuring sufficient drug solubility is a crucial problem in pharmaceutical-related research. For water-insoluble drugs, various formulation approaches are employed to enhance the solubility and bioavailability of lead compounds. The goal of this study was to prepare and characterize solid dispersions of the poorly water soluble antihypertensive agent Olmesartan with water soluble carriers such as Kolliphor P 407, Kolliphor P 188, Kolliwax GMS II, Kolliphor HS15, and Soluplus in proportions viz. 1:1, 1:3 & 1:5 (Drug: Carrier) to improving its aqueous solubility and rate of dissolution by solvent evaporation technique. All the formulations showed marked improvement in the solubility behavior and improved drug release. From all the formulations SD15 was found to be optimized formulation using Kolliwax GMS II as carrier based on the solubility and dissolution studies. The dissolution rate of the Olmesartan solid dispersion was greatly enhanced relative to the pure drug. The results obtained showed that the aqueous solubility and rate of dissolution was significantly improved when formulated in solid dispersion as compare to pure drug.

Keywords: Olmesartan, solid dispersions, Kolliwax GMS II, dissolution

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INTRODUCTION

Aqueous solubility and poor dissolution of insoluble drugs always remains a problem to the pharmaceutical industry. Low solubility and subsequent unsatisfactory dissolution rate often compromise oral bioavailability [1]. As a result, the improvement of solubility and dissolution rate of poorly soluble compounds is of great importance. There are many approaches for enhancing solubility like solubilization, complexation, particle size reduction, salt formation etc., but each of them has practical limitations [2, 3]. 1n 1961, Sekiguchi and Obi1 developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water soluble drugs can be overcome, the method is termed as “solid dispersion.[4]

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. Various preparation methods for solid dispersion have been reported in literature including solvent evaporation, kneading, melting or fusion method, melt extrusion method, co-precipitation method (co-evaporates), spray drying method, gel entrapment technique, supercritical fluid technology, lyophilization technique .[5]

Olmesartan Medoxomil is a novel drug recently approved by US Food and Drug Administration (FDA) for the treatment of hypertension, used alone or in combination with other agents [6]. Its oral bioavailability is 26% and having 99%plasma protein binding. It is metabolized in liver. Elimination half-life of Olmesartan Medoxomil is 13 hrs. [7] The lower bioavailability of Olmesartan Medoxomil arises from both its lower aqueous solubility and gastrointestinal efflux by drug resistance pumps. [8]

The aim of the present investigation is to enhance the solubility, dissolution rate and its bioavailability by preparing solid dispersion with water soluble carriers. The solid dispersion was characterized by X-ray diffractometry (XRD), Differential scanning colorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and by dissolution studies. Further this solid dispersion is used for the formulation of orally disintegrating tablets.

MATERIALS AND METHODS

Materials:

Olmesartan Medoxomil pure drug was generous gift from Aurobindo pharma limited, Hyderabad, India. Kolliphor P 407, Kolliphor P188 and Kolliphor HS -15 were obtained from BASF, Mumbai. Kolliwax GMS II obtained from Signet Chemical Corp. Pvt. Ltd, Mumbai. PEG and Soluplus were gifted from BASF, Germany. Mannitol and Sodium starch glycolate were gifted from Hetero drugs ltd, Hyderabad. All other chemicals used were of analytical grade.

Preliminary solubility studies of Olmesartan Medoxomil

Solubility measurement of Olmesartan Medoxomil was performed according to a published method. [9] An excess amount of Olmesartan Medoxomil was added to 25ml of aqueous solution of water soluble carriers like Kolliphor HS-15, Polaxomers (Kolliphor P 188 & Kolliphor P 407), Kolliwax GMS II, Soluplus, Mannitol, Sodium starch glycolate & PEG in various ratios (**Table 2**) in screw capped bottles. Samples were shaken for the 48 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solutions were analyzed for the Olmesartan Medoxomil by UV Visible spectrophotometer at 257 nm.

Preparation of solid dispersions of Olmesartan medoxomil by solvent evaporation method:

Olmesartan Medoxomil solid dispersions of fifteen formulations were prepared by using various carriers of Kolliphor P 407, Kolliphor P 188, Kolliwax GMS II, Kolliphor HS15, Kolliphor HS 15 and Soluplus in different ratios viz. 1:1, , 1:3, 1:5 (Drug: Carrier). The drug and carrier along was dissolved in methanol and triturated in dry mortar until the solvent is evaporated and a clear film of drug and carrier was obtained. Then the dispersion was subjected to methanol solvent evaporation by placing in 50 ^{0}C in hot air oven for 30min. The resultant solid dispersion was scraped out with a spatula. Solid dispersions were pulverized in a mortar and pestle and passed through a 45µm sieve before packing in an airtight container. [10]

Table 1: Formulation plan of Olmesartan Medoxomil solid dispersions

S. No	Ingredients (Units)	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8	SD9	SD10	SD11	SD12	SD13	SD14	SD15
1	Olmesartan Medoxomil (gm)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
2	Kolliphor HS 15	0.5	1.5	2.5	-	-	-	-	-	-	-	-	-	-	-	-
3	Kolliphor P 188 (gm)	-	-	-	0.5	1.5	2.5	-	-	-	-	-	-	-	-	-
4	Kolliphor P407 (gm)	-	-	-	-			0.5	1.5	2.5	-	-	-	-	-	-
6	Soluplus (gm)	-	-	-	-	-	-	-	-	-	0.5	1.5	2.5	-	-	-
7	Kolliwax GMS II (gm)	-	-	-	-	-	-	-	-	-	-	-	-	0.5	1.5	2.5
8	Methanol (mL)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Solubility studies of Olmesartan Medoxomil solid dispersion by solvent evaporation method:

Solubility measurements of Olmesartan Medoxomil were performed according to a published method [9]. Samples were shaken for the 48 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no 1. Filtered solutions were analyzed for the Olmesartan Medoxomil by using UV Visible spectrophotometer at 257 nm.

Evaluation of Olmesartan medoxomil solid dispersions:

Solid dispersions obtained from the above method were tested for their % Practical yield, drug content and in-vitro release studies.

% Practical Yield

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. SDs were collected and weighed to determine practical yield (PY) from the following equation [11].

$$\% \text{ Practical Yield} = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + Polymer)}} \times 100$$

Drug content

Solid dispersions equivalent to 50 mg of Olmesartan Medoxomil was weighed accurately and dissolved in 100 ml of methanol. The solution was filtered, diluted suitable and drug content was analyzed at λ_{max} 257 nm against blank by UV- Visible spectrophotometer. The actual drug content was calculated using the following equation as follows. [11]

$$\% \text{ Drug content} = \frac{\text{Actual amount of drug in solid dispersion}}{\text{Theoretical amount of drug in solid dispersion}} \times 100$$

***In vitro* release studies:**

In vitro dissolution studies of pure Olmesartan Medoxomil and solid dispersions were conducted with the USP type II apparatus (paddle type). The dissolution studies were performed using 900 ml phosphate buffer pH 6.8 as dissolution medium at 37±0.5^{0}C with 50rpm speed. The samples of 5 ml aliquots were withdrawn periodically at 5, 10, 15, 30, 45, 60 and 90 minutes time intervals and filtered through 0.45µ membrane filter. The withdrawn sample was replaced every time with same quantity of fresh dissolution medium. The filtered solutions were diluted suitably and the samples were analyzed for their drug content by using UV spectrophotometer at wavelength of 257 nm. [12]

Characterization:

Fourier Transform Infrared Spectroscopy (FTIR):

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons. [13]

Differential Scanning Calorimetry (DSC):

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. Accurately weighed samples were placed on aluminium plate, sealed with aluminium lids and heated at a constant rate of 5ºC/min, over a temperature range of 0 to 250ºC [14].

Powder X-ray diffraction:

A Bruker D8 diffractometer was used to perform powder X-ray diffraction (PXRD) of all samples. A Cu K-α 1 tube was the source, set at 40 KV and 50mA. A scan from 2 to 60^0 2 θ was carried out at a rate of 0.01220^0 2θ/s. The diffractometer was calibrated using powdered α-alumina. Hot-melt extruded samples were ground before analysis [15].

Scanning electron microscopy:

The shape and surface morphology of the Olmesartan Medoxomil and optimized formulation of solid dispersion prepared by solvent evaporation was examined using XL 30 model JEOL 6800 scanning electron microscope. [16]

Stability studies:

Prepared solid dispersions were placed inside sealed 40cc HDPE container with child resistant cap under controlled temperature environment inside stability chamber (Thermo Lab, India) with relative humidity of 75%±5%RH and temperature of 40 ^{0}C±2^{0}C for stability studies. Samples were removed after 1, 2, 4 and 6 months, evaluated for % drug content and in vitro dissolution study and compared with those SD tested immediately after preparation. [17]

RESULTS AND DISCUSSION

Preliminary solubility studies of Olmesartan Medoxomil

In case of solid dispersions initially preliminary solubility analysis was carried out to select the appropriate water soluble carriers for the preparation of solid dispersion in which pure drug solubility was found to be 0.025 mg/ml (**Table 2**). From this study, drug and Kolliwax GMS II in the ratio of 1:1 shown highest drug solubility i.e. 0.52 mg/ml, almost 20 fold increased compared to that of pure drug. For all the water soluble carriers used in preliminary solubility studies, PEG, Mannitol and SSG shown low solubility when compared with other carriers and excluded from the preparation of Olmesartan medoxomil solid dispersions. The graphical representation of solubility studies was shown in **Figure 1**.

Table 2: Preliminary Solubility studies of Olmesartan Medoxomil in different polymers

Sample (Physical mixtures)	Drug & Polymer ratios	Solubility(mg/ml)*
Pure drug	-	0.025±0.04
Drug: PEG 6000	1:1	0.22±0.03
Drug: Kolliphor HS-15	1:1	0.30±0.04
Drug : Kolliphor P188	1:1	0.35±0.03
Drug : Kolliphor P 407	1:1	0.42±0.06
Drug : Soluplus	1:1	0.40±0.05
Drug : Kolliwax GMS II	1:1	0.52±0.01
Drug : Mannitol	1:1	0.26±0.02
Drug: Sodium starch glycolate	1:1	0.28±0.04

**Mean±SD, n=3*

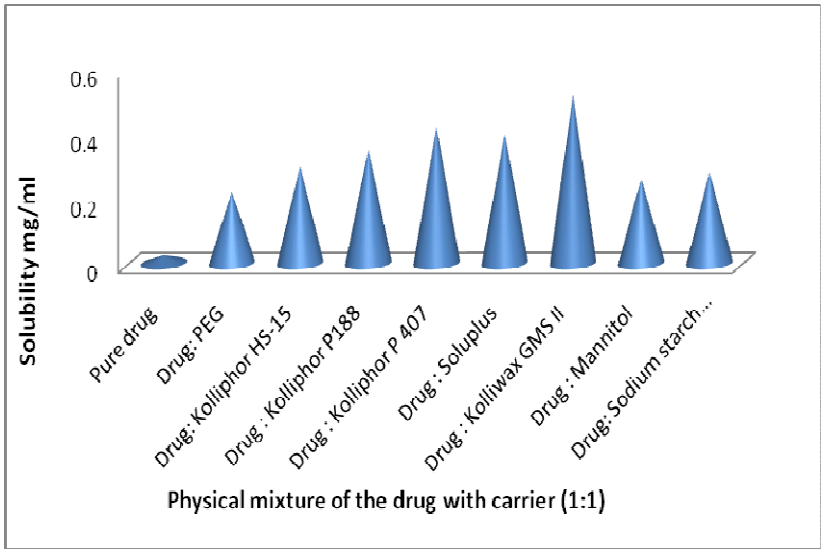

Figure 1: Solubility studies of Olmesartan medoxomil physical mixture

Preparation of Olmesartan Medoxomil solid dispersions

Solid dispersions of Olmesartan medoxomil were prepared by using Kolliphor P407, Kolliphor P 188, Kolliphor HS15, Kolliwax GMS II and Soluplus in different drug carrier ratios of 1:1, 1:3 and 1:5. In the present investigation 15 formulations were prepared and their complete composition was shown in **Table 1.** For all the water soluble carriers used in preliminary solubility studies, PEG 6000, Mannitol and Sodium starch glycolate shown low solubility when compared with other carriers and excluded from the preparation of Olmesartan solid dispersions. All the solid dispersions prepared were found to be fine and free flowing powders.

Figure 2: Olmesartan Medoxomil Solid Dispersions

Evaluation parameters:

Solubility studies of Olmesartan medoxomil solid dispersions:

Fifteen formulations of solid dispersions were prepared by solvent evaporation method with their respective carriers. After preparation of solid dispersion solubility analysis was carried out, this is compared with physical mixtures of the same drug to carrier ratio. The formulation (SD 15) with Kolliwax GMS II in the ratio of 1:5 (drug: carrier) shown highest solubility i.e. 1.22±0.04 mg/ml, almost 49 fold compared to that of the pure drug (Pure drug solubility is 0.025±0.04 /ml). The results are tabulated in **Table 3** and graphical representation was shown in **Figure 3.**

Table 3: Solubility studies of solid dispersions prepared by solvent evaporation method:

S. No.	Formulation code	Solubility (mg/ml)*
1	Pure drug (Olmesartan medoxomil)	0.025±0.04
2	SD1	0.55±0.02
3	SD2	0.62±0.03
4	SD3	0.67±0.03
5	SD4	0.56±0.02
6	SD5	0.61±0.03
7	SD6	0.68±0.03
8	SD7	0.75±0.04
9	SD8	0.82±0.03
10	SD9	0.90±0.02
11	SD10	0.71±0.04
12	SD11	0.76±0.01
13	SD12	0.84±0.02
14	SD13	0.83±0.01
15	SD14	1.02±0.03
16	SD15	1.22±0.04

**Mean±SD, n=3*

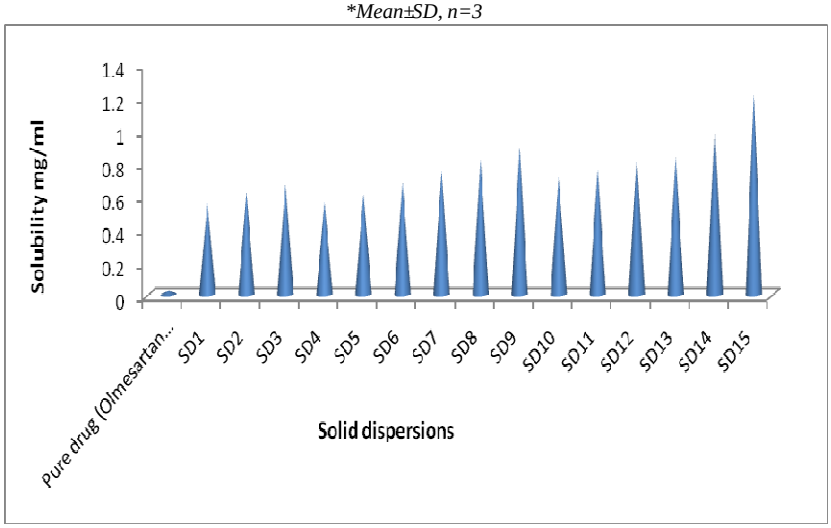

Figure 3: Solubility studies of Olmesartan Medoxomil solid dispersion

% Practical yield and Drug content:

The results of % practical yield for all formulations of solid dispersions found to be 89.98% - 98.78%. The results of % practical yield studies are shown in **Table 4**. Maximum yield was found to be 98.78% in formulation SD 15. Actual drug content of all 15 formulations are shown in **Table 4**. The drug content of the prepared solid dispersions was found to be in the range of 87.08 – 98.62 %. Maximum % drug content i.e. 98.62% was found in the formulation SD 15.

Table 4: % Practical yield and drug content for Olmesartan medoxomil solid dispersions

S. No	Formulation	% Yield	% Drug content
1	SD1	95.21%	93.47
2	SD2	96.16%	95.77
3	SD3	93.78%	92.62
4	SD4	92.88%	87.08
5	SD5	93.56%	89.47
6	SD6	94.68%	91.92
7	SD7	89.98%	92.50
8	SD8	90.22%	93.52
9	SD9	91.87%	91.53
10	SD10	94.26%	90.56
11	SD11	93.99%	91.57
12	SD12	92.12%	92.64
13	SD13	91.87%	93.43
14	SD14	92.12%	92.37
15	SD15	98.78%	98.62

In vitro dissolution studies

The drug release data obtained for formulations SD 1-SD 15 are tabulated in **Table 5 & 6**. It shows the cumulative percent drug released as a function of time for all formulations. In vitro studies reveal that there is marked increase in the dissolution rate of Olmesartan medoxomil from all the solid dispersions when compared to pure Olmesartan medoxomil itself. From the in vitro drug release profile, it can be seen that formulation SD 15 containing 1:5 ratio of drug: Kolliwax GMS II shows higher dissolution rate i.e. 99.1±2.9% compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier. The graphical representation SD 1-SD 7 & SD 8-SD 15 were depicted in **Figures 4 & 5.**

Table 5: In vitro dissolution profile of pure drug and different formulations of Olmesartan Medoxomil solid dispersions (SD1–SD7)

Time in Min	Cumulative % drug release							
	Pure drug	SD1	SD2	SD3	SD 4	SD 5	SD6	SD7
0	0	0	0	0	0	0	0	0
5	11.6±2.6	28.2±2.9	29.1±1.9	31.1±1.9	25.4±3.7	26.6±2.9	26.6±2.9	21.5±1.3
10	17.5±2.5	36.8±3.0	35.6±2.5	37.6±2.5	31.9±1.9	36.7±3.9	37.5±3.9	31.0±2.4
20	23.9±1.5	48.2±2.6	47.8±2.7	47.8±2.7	44.1±2.8	58.8±2.0	60.5±2.0	32.5±3.3
30	27.8±1.3	58.4±2.3	58.2±2.4	59.2±2.4	56.4±1.4	63.4±1.4	64.4±1.4	33.1±2.6
45	30.2±1.6	66.2±2.8	65.6±3.4	68.6±3.4	67.5±2.7	77.7±3.8	78.7±3.8	36.0±2.4
60	34.4±1.8	75.2±2.4	78.2±2.0	79.2±2.0	79.3±2.9	84.4±2.2	85.4±2.2	40.2±4.3
90	38.6±0.5	80.2±2.8	84.2±2.2	86.2±2.2	82.4±3.8	87.6±1.7	88.6±1.7	55.8±3.4

Table 6: In vitro dissolution profile of pure drug and different formulations of Olmesartan Medoxomil solid dispersions (SD 8- SD15)

Time in Min	Cumulative % drug release								
	Pure drug	SD 8	SD 9	SD 10	SD 11	SD 12	SD 13	SD 14	SD 15
0	0	0	0	0	0	0	0	0	0
5	13.6±2.8	23.4±2.9	23.4±2.9	26.8±2.0	30.3±2.5	31.3±2.5	22.2±3.4	40.7±2.1	41.7±2.1
10	20.5±2.5	27.8±2.3	28.8±2.3	30.3±2.9	36.9±1.5	38.9±1.5	35.8±1.4	59.8±2.1	59.8±2.1
20	26.9±2.5	31.5±1.6	32.5±1.6	46.5±3.3	46.5±2.7	47.5±2.7	45.2±2.4	68.1±2.8	68.9±2.8
30	29.8±1.7	32.8±1.8	35.8±1.8	59.5±3.8	58.2±2.6	59.2±2.6	73.1±2.4	77.1±2.6	79.1±2.6
45	30.2±1.9	37.5±1.7	39.5±1.7	64.5±1.9	64.5±2.2	65.5±2.2	84.4±1.7	89.1±3.3	90.1±3.3
60	33.6±1.8	42.9±1.8	45.9±1.8	70.9±3.3	77.3±2.9	79.3±2.9	88.2±3.1	95.3±1.4	97.3±1.4
90	37.6±0.5	61.2±1.2	64.2±1.2	72.4±3.1	79.5±2.8	80.5±2.8	92.5±3.9	96.9±2.9	99.1±2.9

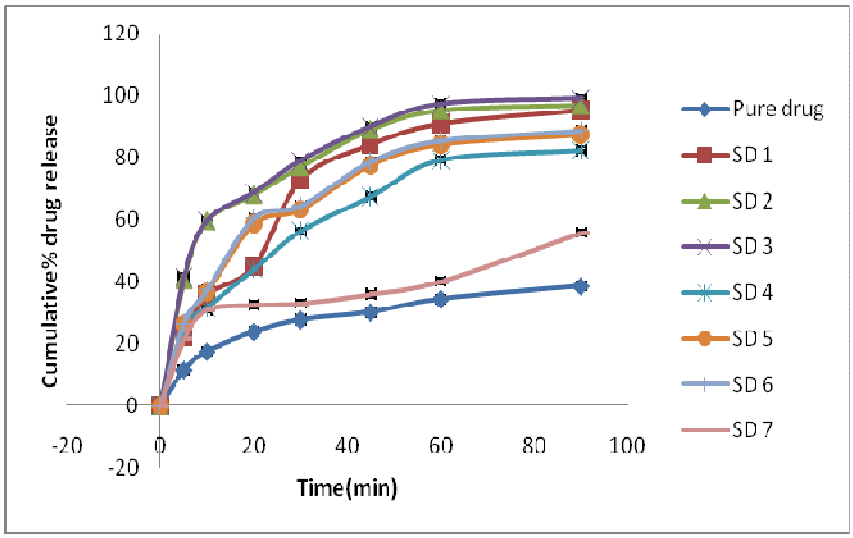

Figure 4: In vitro dissolution profile of pure drug, Olmesartan Medoxomil solid dispersions (SD 1-SD 7)

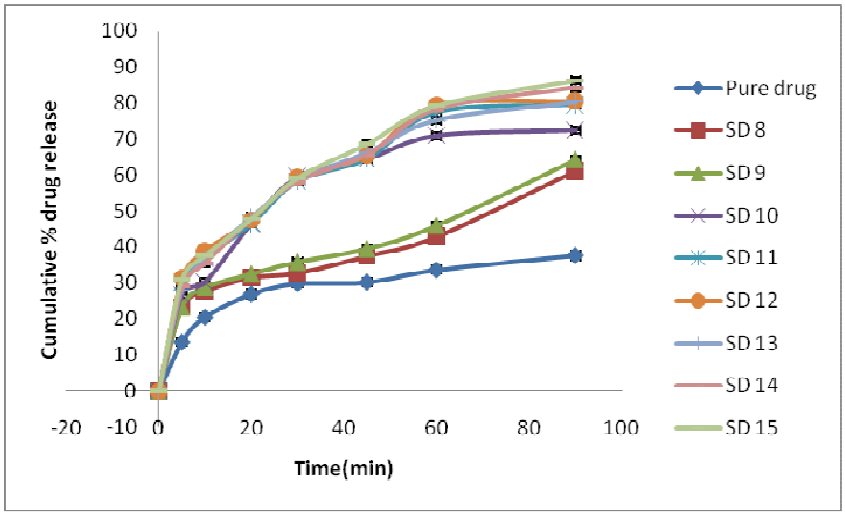

Figure 5: In vitro dissolution profile of pure drug, Olmesartan Medoxomil solid dispersions (SD 8-SD 15)

FTIR studies:

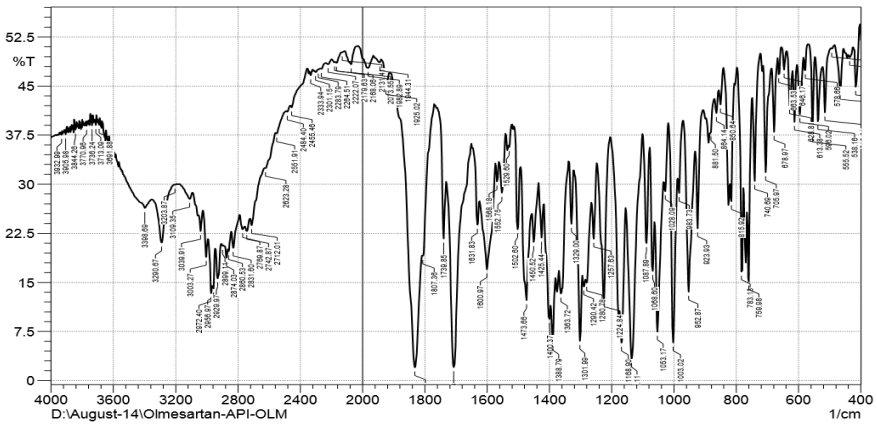

Figure 6: FTIR Spectrum of Olmesartan medoxomil pure drug

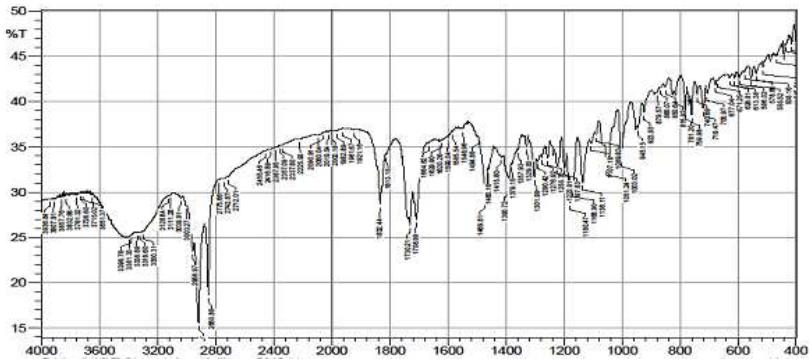

Figure 7: FTIR Spectrum of Kolliwax GMS II

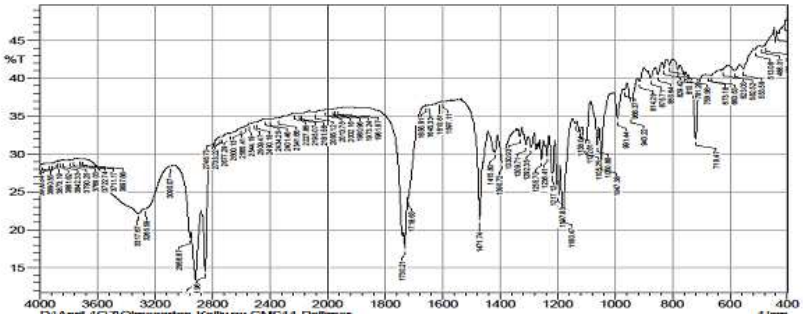

Figure 8: FTIR Spectrum of Olmesartan medoxomil optimized formulation SD15

FT-IR spectrums are mainly used to determine if there is any interaction between the drug and any of the excipient used **(Figure 6,&7)**. The FTIR spectra of pure Olmesartan displayed bands at 3398 cm^{-1} due to N-H stretch, at 1707 cm^{-1} due to C=O stretching, at 1631 cm^{-1} due to heterocyclic C=C stretching **(Figure 6)**. The spectra also showed bands at 1224 cm^{-1} due to C-N bending. The FTIR spectrum of solid dispersion containing Olmesartan exhibited characteristic bands consistent with the molecular structure of Olmesartan such as bands at 3396 cm^{-1} due to N-H stretch, at 1710 cm^{-1} due to C=O stretching, at 1631 cm^{-1} due to heterocyclic C=C stretching, at 1251 cm^{-1} due to C-N bending **(Figure 8)**. Thus, the presence of characteristic absorption bands of Olmesartan and the solid dispersion containing Olmesartan suggest that there was no interaction between the drug and excipients used in the formulation.

Differential Scanning Calorimetry:

The DSC thermogram of Olmesartan pure drug was shown sharp endothermic peak (**Figure 9**) at melting point 175 ^0C, indicating that the drug is highly crystalline. The absence of drug peak in the solid dispersion formulation SD15 indicating the drug was converted into an amorphous form. As the intensity of the endotherm was markedly decreased in the drug – Kolliwax GMS II solid dispersion, the faster dissolution rate of the drug from the solid dispersion is attributed to the reduction in the crystallinity of the drug. Crystallization inhibition is attributed to the entrapment of the drug molecules in the polymer matrix during solvent evaporation.

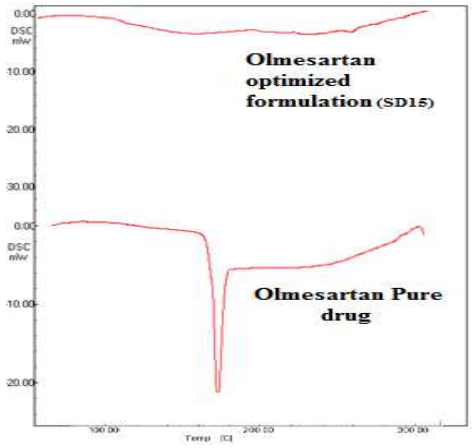

Figure 9: DSC thermograms of Olmesartan medoxomil pure drug and optimized formulation SD15

X-Ray Diffraction patterns:

The Olmesartan medoxomil solid dispersions were analyzed in Bruker D8 advanced PXRD instrument to find out whether the solid dispersions of various drug polymer ratios are crystalline or amorphous. The presence of numerous distinct peaks in the XRD spectrum of pure Olmesartan medoxomil indicates that Olmesartan medoxomil was present as a crystalline material (**Figure 10**). On the other hand, the spectrum of optimized formulation SD15 of solid dispersion was characterized by the complete absence of any diffraction peak, which is characteristic of an amorphous compound (**Figure 11**). The enhancement in the dissolution rate of the drug from the drug-Kolliwax GMS II solid dispersion is ascribed to the marked reduction in the crystallinity of the drug.

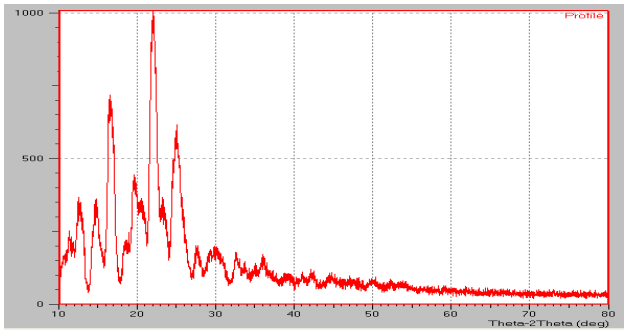

Figure 10: X-Ray powder diffractogram of Olmesartan pure drug

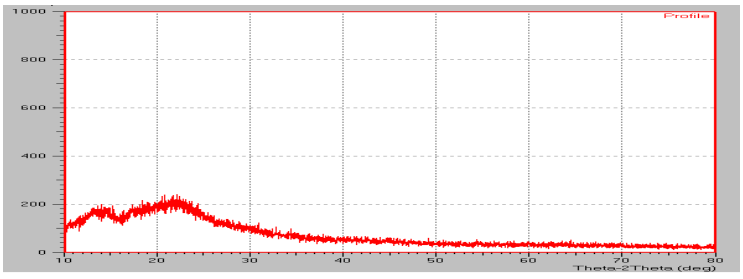

Figure 11: X-Ray powder diffractogram of Olmesartan optimized formulation SD15 SEM Studies

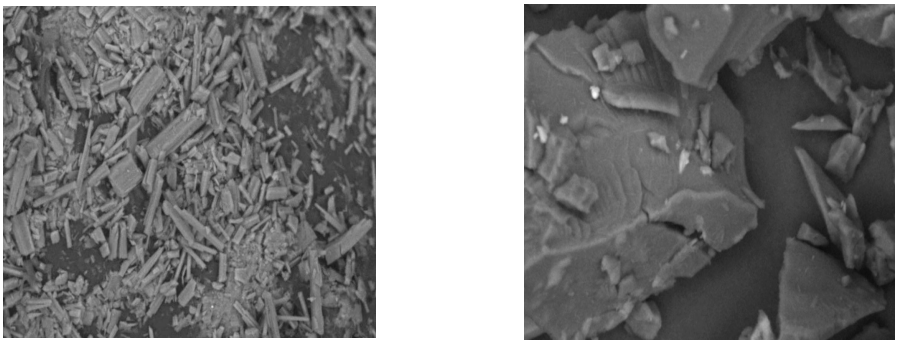

Figure 12: Pure drug of Olmesartan and Olmesartan optimized formulation SD15

SEM photographs for pure drug and optimized formulation SD 15 are shown in **Figures 12** the drug crystals seemed to be smooth-surfaced, irregular in shape and size. In case of Solid dispersions, it was difficult to distinguish the presence of drug crystals. The drug surface in solid dispersion seems to be more porous in nature. Solid dispersions appeared as uniform and homogeneously mixed mass with wrinkled surface. Drug crystals appeared to be incorporated into the particles of the polymers. The solid dispersion looked like a matrix particle. The results could be attributed to dispersion of the drug in the molten mass of the polymer.

Stability studies:

Optimized formulation (SD 15) was selected for stability studies on the basis of % drug content and cumulative % drug release. Stability studies were conducted for 6 months at accelerated stability conditions according to ICH guidelines. The systems were stable during a 6-month period. From these results it was concluded that, optimized formulation is stable and retained their original properties with minor differences which depicted in **Table 7.**

Table 7: Evaluation parameters of optimized formulation (SD15) stored at 40 ±2^{0}C /75 ±5%RH

Retest time for optimized formulation (SD 15)	% Drug content	*In-vitro* drug release (%)
0 days	98.62	99.1
30 days	97.26	988
60 days	96.74	97.2
120 days	95.85	96.4
180 days	95.02	95.9

CONCLUSION

In the present study it was clearly demonstrated that Olmesartan Medoxomil solid dispersion formulation can be effectively produced by processing via solvent evaporation method with enhanced solubility and dissolution rate. Novel drug- polymer combinations were optimized and stable SD systems were developed successfully. Utilization of Kolliwax GMS II offers excellent possibilities to develop stable amorphous solid dispersion. Furthermore, this Olmesartan medoxomil incorporated solid dispersion gave higher dissolution and solubility values compared to the pure Olmesartan Medoxomil drug. I*n vitro* drug release studies exhibited a cumulative release of 99.1 % as compared to 37.6% for the pure drug. Analysis by differential scanning calorimetry and powder X-ray diffraction showed that Olmesartan Medoxomil existed in the amorphous form within the solid dispersion formulation fabricated using the solvent evaporation process. Additionally, scanning electron microscopy studies suggested the conversion of crystalline Olmesartan Medoxomil to an amorphous form. The dissolution rate and solubility of Olmesartan solid dispersions was improved significantly using Kolliwax GMS II**.**

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