



Enhancement of Aqueous Solubility and Oral Bioavailability of Bcs Class II Drug by Dry Emulsion

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Abstract

Liquid emulsions have distinct advantages over other dosage forms by improving oral bioavailability as well as by reducing the side effects. On contrary, liquid emulsion exhibit lack of physicochemical stability and compliance issues. To overcome these problems, dry emulsion formulation recommended. Dry emulsions are formulated by spray drying, evaporation and rotary evaporation. The aim of the present investigation is to improve the dissolution and oral bioavailability of poorly water soluble drug Olmesartan medoxomil by preparing dry emulsion. Olmesartan medoxomil is poorly soluble drug used for treatment of high blood pressure, showing absorption window at stomach and upper part of small intestine. Dry emulsion was ready by victimisation purgative during which drug is very soluble, using poloxamer188 as water soluble carrier and aerosil 200 as an adsorbent. The preferred oils were castor oil, olive oil, soybean oil and isopropyl myristate and polymers were PEG400, Eudragit EPO and Poloxamer 188. Dry emulsion was prepared by spray drying. Dry emulsion was evaluated for drug content, percentage moisture content, aqueous solubility, dissolution study and in-vivo bioavailability study. In vitro drug release of dry emulsion was studied by using USP type II paddle dissolution apparatus. The solubility of the drug was increased with surfactant and polymer at 1:1 ratio. Probable mechanisms of improved solubility were characterized by particle size determination, Differential Scanning Calorimetry (DSC), Powder X-ray Diffractometry (PXRD) and Scanning Electron Microscopy (SEM). This study revealed that solid dry emulsion technique could prove promising for improvement of solubility, dissolution rate and oral bioavailability of Olmesartan medoxomil.

Keywords: Dry Emulsion; Lab Spray Dryer; Olmesartan Medoxomil; Castor Oil; Poloxamer 188; Bioavailability

Introduction

Dry emulsion is of interest as a result of their stability and sustained unharness result [1]. Dry emulsions gift a

possible oral drug delivery system for lyophilic and low soluble drug substances and for drug substances needing protection against light. Solid carrier, binary compound and lyophilic solvent can be used for the preparation

of dry emulsions. The solid carrier could endure partial or complete transformation into an amorphous state.

Dissolution rate is the limiting issue for drug absorption for each class II and IV medication consistent with the biopharmaceutics organization. Emulsion has been reported to be one amongst the economic strategies to boost the dissolution rate and increase bioavailability of poorly soluble medication [2,3].

Spray drying involves the organization of a liquid feedstock into spray of droplets and containing the droplets with hot air in drying chamber. The house are manufacture by either rotary (wheel or nozzle) atomises. Evaporation of wet from droplets and formulation of dry particles. Proceed underneath controlled temperature and air flow conditions.

Powder is discharged unceasingly from drying chamber. Operational condition appliance style is chosen consistent with drying characteristics of the merchandise and powder specification. The technology has been well-tried in human trials and has been scaled to industrial levels.

This organized repetitious approach permits one to quickly slender in on the formulation approaches possibly to yield the specified results [4,5]. Olmesartan medoxomilis, BCS-II class drug, an angiotensin II type 1 (AT (1)) receptor antagonist (angiotensin receptor blocker [ARB]) that inhibits the actions of angiotensin II on the renin-angiotensin-aldosterone system, which plays a key role in the pathogenesis of hypertension [6].

Preformulation Study

a. Physical Appearance

Physical appearance of pure drug Olmesartan medoxomil (OLM) was checked by visual inspection [7].

b. Melting Point

The Melting point of OLM was determined by capillary method using programmable melting point apparatus.

c. Selection of Oils and Surfactant

The selection of the oils and surfactant for the further study was governed by the emulsification efficiency rather than the ability to solubilize OLM. Selection is carried out by using visible spectrophotometer to measure the drug solubility in oils and surfactants.

Preparation of Dry Emulsion

d. Preparation of Dry Emulsion with Carriers (PEG 400, Poloxamer188, Eudragit EPO) By O/W Type

Tween 80 and carriers were measured accurately in various ratios (1:0.25, 1:0.50 and 1:1), transferred to beaker and stirred on magnetic stirrer. The emulsion was prepared by dissolving the drug in castor oil in which drug dissolves to maximum extent and then specified quantity of aqueous phase was added to the oil. Then specified quantity of surfactant and adsorbent (aerosil 200) was added. This emulsion is then homogenized at 5,000 rpm to obtain stable milky white emulsion. The stability of emulsion was checked by keeping it for 48 hrs (Tables 1 & 2). These milky emulsions were dried by using lab spray dryer LU 222 Advanced, underfollowing conditions: 150°C inlet temperature, 120°C outlet temperature, 80°C cool temperature, 50Nm³/hr aspirator flow rate, 1mL/min feed pump flow rate [8,9].

Sr. No.	Surfactant: Polymer	Ratio	Method	Formulation code	Oil
1	Tween80 PEG-400	1:0.25	O/W type by using spray dryer	Q1	Castor oil
2		01:00.5		Q2	Castor oil
3		1:01		Q3	Castor oil
4	Tween80 Poloxamer188	01:00.3	O/W type by using spray dryer	R1	Castor oil
5		1:50		R2	Castor oil
6		1:01		R3	Castor oil
7	Tween80 Eudragit EPO	01:00.3	O/W type by using spray dryer	S1	Castor oil
8		01:00.5		S2	Castor oil
9		1:01		S3	Castor oil

Table 1: Method and formulation code of dry emulsion using castor oil.

Sr. No.	Surfactant: Polymer	Ratio	Method	Formulation code	Oil
1	Tween80 PEG-400	1:0.25	O/W type by using spray dryer	T1	Olive oil
2		01:00.5		T2	Olive oil
3		1:01		T3	Olive oil
4	Tween80 Poloxamer188	01:00.3	O/W type by using spray dryer	P1	Olive oil
5		1:50		P2	Olive oil
6		1:01		P3	Olive oil
7	Tween80 Eudragit EPO	01:00.3	O/W type by using spray dryer	E1	Olive oil
8		01:00.5		E2	Olive oil
9		1:01		E3	Olive oil

Table 2: Method and formulation code of dry emulsion using olive oil.

Characterization of Dry Emulsion

e. Drug content

Dry emulsion equivalent to 10 mg of OLM were weighed accurately and dissolved in suitable quantity of methanol, filtered through filter paper no. 41. The stock solutions were diluted fittingly in distilled water. The drug content was analysed at 257 nm by UV spectrophotometer [10-12].

f. Solubility of OLM in Distilled water

An excess quantity of drug and dry emulsion was taken in 5 mL screw cap vials separately. Sealed vials were kept on mechanical shaker at $37 \pm 0.5^\circ\text{C}$ for 48 hours. After equilibrium, each test tube was centrifuged at 6000 rpm for 20 min using a centrifuge (OSCAR OPTIK model-OS-2304, India). Supernatant was filtered through membrane filter using $0.45 \mu\text{m}$ filter disk. Filtered solution was appropriately diluted with methanol and UV absorbance was measured at 257.4 nm. Concentration of dissolved drug was decided by normal equation.

g. Moisture Content

Moisture content studies were carried out to determine how much % moisture to be present in dry emulsion. Moisture content was determined by following formula-

$$\text{MC} = \times 100$$

h. Particle Size Determination

Particle size of OLM and dry emulsions was determined by using Delsa TM Nano instrument.

i. Drug Carrier Compatibility by FTIR Spectroscopy

Infra-red studies was carried out to rule out interaction between drug and carrier used in formulation of dry emulsion by potassium bromide disc method using Infra-red spectrophotometer. The scanning range was 400 to 4000cm^{-1} .

Differential Scanning Calorimetry (DSC)

The DSC of OLM and dry emulsions was recorded by differential scanning measuring instrument (DSC823e Make-MettlerF Toledo). Approximately 2-5 mg of every sample was heated in associate open aluminium pan from 30°C to 150°C at a heating rate of $10^\circ\text{C}/\text{min}$ underneath the stream of nitrogen at 50 mL/min.

Powder X-ray Diffraction (PXRD)

As a consequence of the importance of solid drug substance characterization, analytical tools such as X-ray Diffractometry are usually employed in the pharmaceutical field. The detection of crystalline phases in mixed systems was analysed by powder diffraction. However, too much crystallinity causes brittleness. The crystallinity elements provide sharp slim optical phenomenon peaks and also the amorphous part offers a really broad peak.

Scanning Electron Microscopy (SEM)

The pure drug (OLM) and solid dry emulsions (2mg) were mounted on to the stubs separately using double sided adhesive tape and then coated with gold metal alloy mistreatment fine coat particle sputter. The samples were subsequently analysed under the scanning electron microscopy.

Dissolution Studies

The in-vitro dissolution studies were meted out for OLM and dry emulsions by USP type II paddle equipment. The sample equivalent to 40 mg of OLM was added to 900 mL of 0.1N HCL at $37 \pm 0.5^\circ\text{C}$ and stirred at 50 rpm. An aliquot of 5 mL was withdrawn at specified time intervals and filtered through Whatman filter paper no. 41. An equal volume of fresh dissolution medium was replaced to take care of the

quantity of dissolution medium. The filtered samples were analysed spectrophotometric ally at 257nm.

In Vivo Study (Pharmacokinetics Parameter)

The In Vivo study was conducted in New Zealand white male rabbits which weighed 900gm–1500gm following oral administration. The research protocol of the animal experimentation was approved by the Institutional Animal Ethics Committee, MESCO, Sona and Maharashtra, India. The animals were housed in animal house, Faculty of Pharmacy, MESCO, Sona and Maharashtra, India. The animals were housed in polypropylene cages with free access to standard laboratory diet and water. The routine animal handling was performed according to Good Laboratory Practices. The animal dose was calculated as 2.09 mg/kg for rabbit for current study. The dry emulsion and OLM were dissolved in 1 ml of gum acacia solution (2% w/v) and given orally using oral feeding sonde. The blood samples (1–1.5 ml) were withdrawn from the ear vein at predetermined time intervals. The samples were collected in micro centrifuge tubes which were first rinsed with EDTA followed by addition of small quantity (4–8 mg) of powdered EDTA to the tube. Blood collected was mixed with anticoagulant properly by shaking and then centrifuged at 4,000 rpm for 20 min (Tables 3 & 4). The plasma was separated and holds on at –20°C till drug analysis by HPLC. Pharmacokinetic parameters such as AUC, Cmax and Tmax were calculated from plasma profile curve. All pharmacokinetic parameters were calculated individually for each subject. The area under concentration time curve was calculated according to log trapezoidal method [13,14].

Results and Discussion

Physical Appearance

Sr. No.	Description	Observation
1	Colour	White
2	Odour	Odourless

Table 3: Physical Appearance.

Melting point

The reported melting point of OLM was 175-180°C and observed melting point of OLM was 175.66°C. So it was concluded that the given sample of OLM was in pure form [15-20].

Sr. No.	Melting point (OC)	Average M. P.(OC)
1	176	175.66
2	176	
3	175	

Table 4: Melting point of OLM.

Solubility of OLM in Distilled Water

The Solubility of OLM in distilled water was found to be 204.71, 204.42, 204.19 µg/mL. The OLM is BCS class II drug i.e. practically insoluble (hydrophobic) in distilled water (Table 5).

Sr. No	Solubility	Absorbance at 257.4nm	Solubility in µg/mL
1	Solubility1	1.4535	204.71
2	Solubility2	1.4514	204.42
3	Solubility 3	1.4498	204.19

Table 5: Solubility of OLM in distilled water.

Solubility of OLM in different oils

The solubility of OLM in different oils was found to be 1230, 1100, 1080, 3910 µg/mL. The OLM was more soluble

in Castor oil (3910 µg/mL) and Olive oil (1230 µg/mL) as compared to other oils. Therefore Castor oil and Olive oil was used for the preparation of dry emulsion (Table 6).

Sr.No.	Name of oils	Absorbance at 257(nm)	Solubility of OLM in oils (µg/mL)
1	Olive oil	0.0967	1230 µg/mL
2	Soybean oil	0.0859	1100 µg/mL
3	Isopropyl myristate	0.0847	1080 µg/mL
4	Castor oil	0.3052	3910 µg/mL

Table 6: Absorbance and solubility of drug in given oils.

Evaluation Of Dry Emulsion Powder

Drug Content

Drug content of prepared dry emulsion was found in the range of 72.4 to 96.2%. The drug content of dry emulsion

with PEG 400 (T3) was found low as compared to dry emulsion with Eudragit EPO (S3) and Poloxamer 188 (R3). This may be due to the interaction between the drug and carrier (Table 7).

Sr. No	Formulation code	Absorbance in duplicate at 257 nm	Drug content in ($\mu\text{g}/\text{mL}$)	% drug content
1	T3 0.5231	0.5214	7.24	72.40%
		7.69	76.90%	
2	S3 0.8786	0.8989	9.56	95.60%
		9.44	94.40%	
3	R3 0.9144	0.9145	9.62	96.20%
		9.62	96.20%	

Table 7: %Drug content of formulation.

T3: Dry Emulsion with PEG 400.**S3:** Dry Emulsion with Eudragit EPO.**R3:** Dry Emulsion with Poloxamer 188.

Solubility of Dry Emulsion in Distilled Water

The solubility of OLM was enhanced in dry emulsions prepared with Poloxamer 188 and Eudragit EPO as compared

to PEG 400. The solubility of OLM in dry emulsions was enhanced due to conversion of drug from crystalline to amorphous form, decreased in drug particle size (Table 8).

Sr. No	Formulation code	Absorbance in triplicate at 257.4 (nm)	Solubility in $\mu\text{g}/\text{mL}$
1	T3	1.5569	219.2
		1.5689	220.9
		1.5597	219.6
2	S3	1.7998	253.4
		1.7889	251.9
		1.7829	251.1
3	R3	1.892	266.4
		1.8889	266
		1.8879	265.9

Table 8: Solubility of dry emulsion in distilled water.

Moisture Content

The present moisture content of R3 (0.10 to 1.47%) was

found very less as compared to T3 (0.20 to 9.82%), S3 0.10 to 4.16% (Table 9).

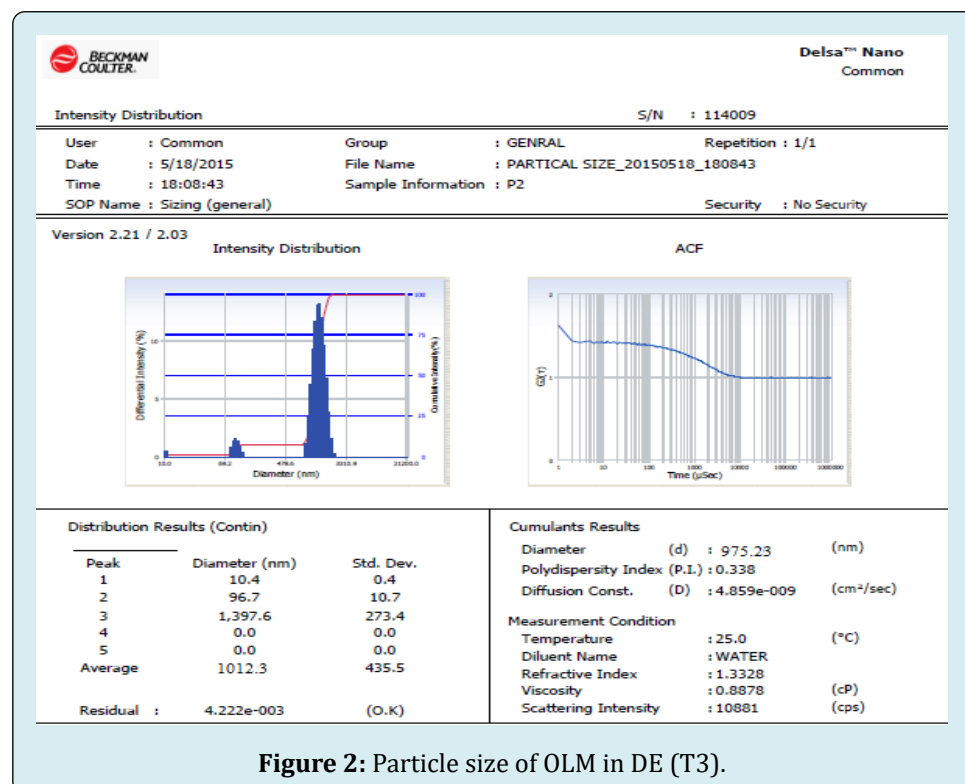
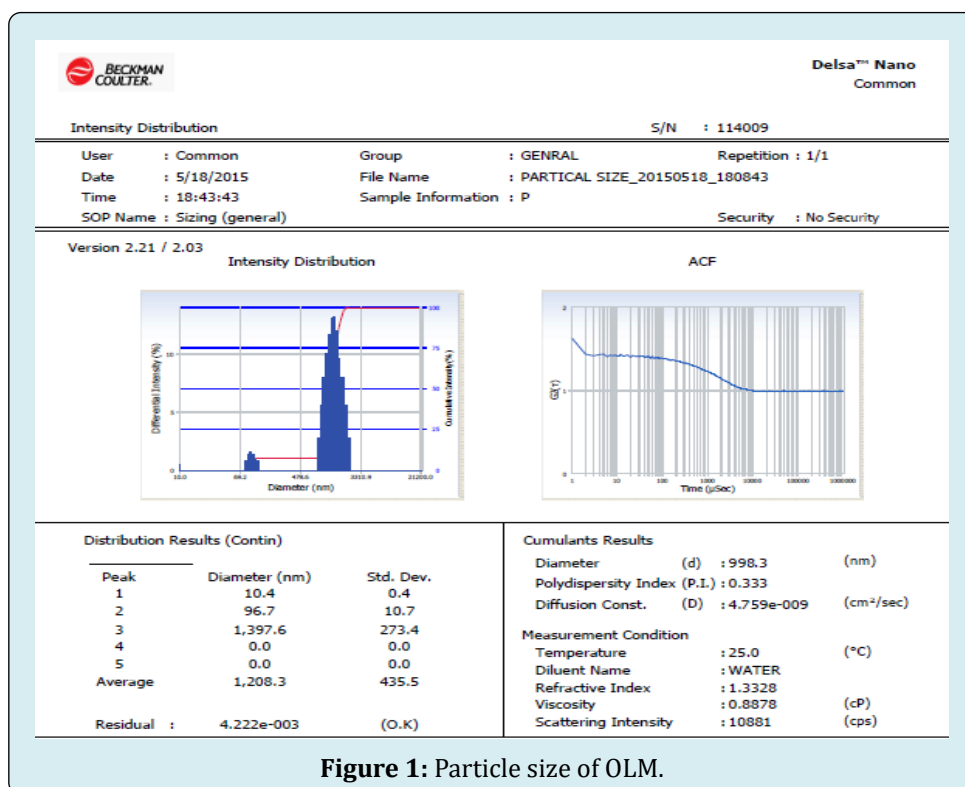
Sr. No	Storage temp. (0C)	Initial weight (gm) T3, S3 and R3	Oven dry weight (gm)			% Moisture content (%)		
			T3	S3	R3	T3	S3	R3
1	50	20	19.96	19.98	19.98	0.2	0.1	0.1
2	60	20	19.91	19.93	19.96	0.45	0.35	0.2
3	70	20	19.52	19.85	19.95	2.45	0.75	0.25
4	80	20	18.92	19.81	19.9	5.7	0.95	0.5
5	90	20	18.63	19.53	19.85	7.35	2.4	0.75
6	100	20	18.52	19.39	19.75	7.99	3.14	1.26
7	110	20	18.42	19.28	19.73	8.57	3.73	1.36
8	120	20	18.21	19.2	19.71	9.82	4.16	1.47

Table 9: % Moisture content.

Particle size of OLM and dry emulsions

The particle size of OLM, T3, S3, R3 was found to be 998.30 nm, 975.23 nm, 797.18 nm, 676.6 nm respectively.

The particle size of OLM in R3 was decreased more as compared to other formulations (T3, S3) (Figures 1-6).



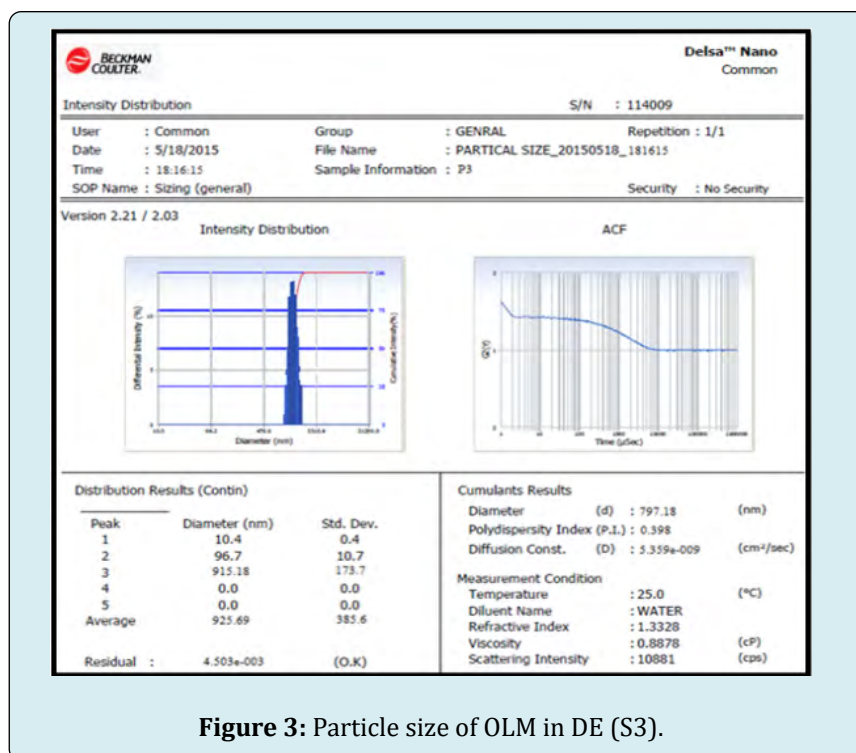


Figure 3: Particle size of OLM in DE (S3).

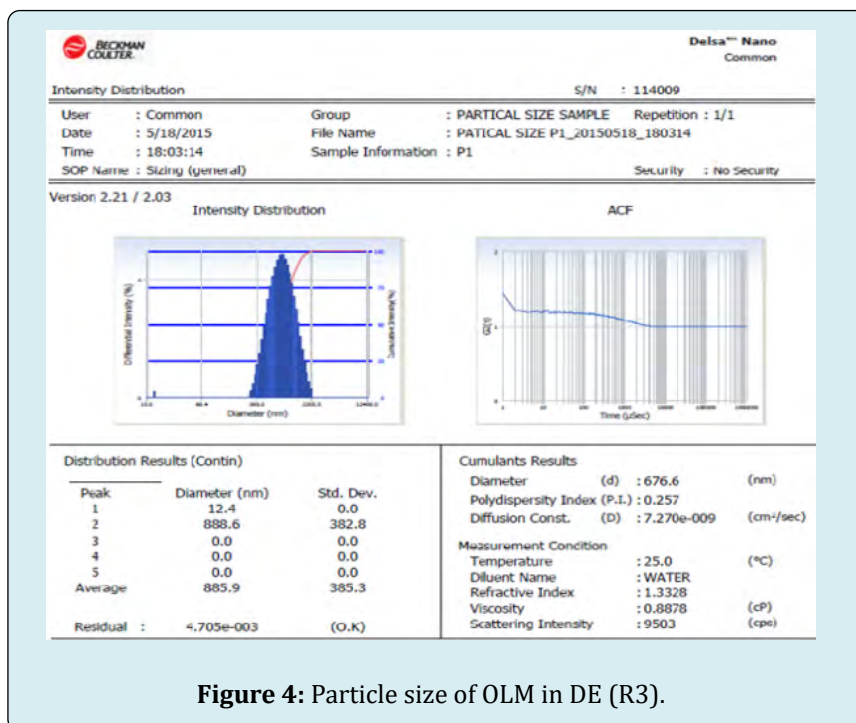


Figure 4: Particle size of OLM in DE (R3).

Fourier Transform Infra-Red (FTIR) Spectroscopy

The IR spectra of Dry emulsion showed there was no significant change in principle peaks in pure drug because

of its frequencies close to the standard frequencies. So these spectra are in full support of the given structures of drugs. In dry emulsion with PEG 400 showed absence of some frequencies, So S3 and R3 was selected for further investigation (Table 10).

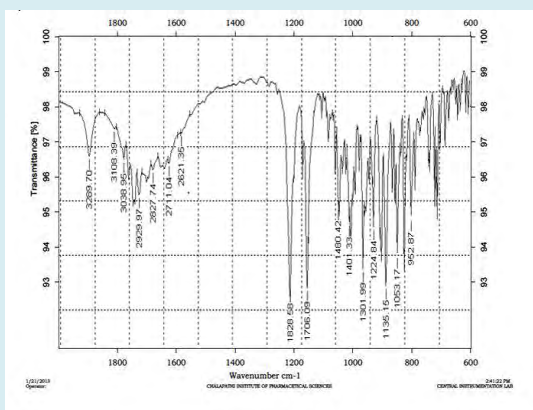


Figure 5: FTIR of OLM.

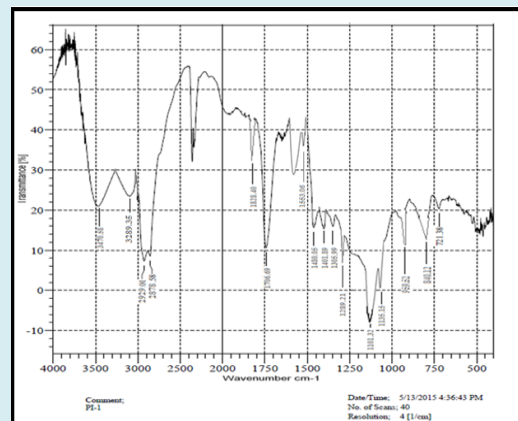


Figure 6: FTIR of DE with Poloxamer 188.

Sr. No.	Compound	Frequency (cm-1)				Type of vibration
		standard	T3	S3	R3	
1	OLM	3286.81	Absent	3289.23	3289.35	O-H group
2		1282.71	1348.24	1245.01	1289.21	C-N stretching
3		1707.06	Absent	1708.93	1706.69	Diaryl ketone
4		1737.2	1741.72	1741.72	1828.4	Ester carbonyl group
5		1552.75	Absent	1465.9	1553.05	C=C aromatic stretching

Table 10: Comparisons of interpretation of IR spectrum of drug and dry emulsions.

Differential Scanning Calorimetry (DSC)

The solid state characteristics of dry emulsion were investigated using DSC to find out crystallinity of Olmesartan medoxomil. The Olmesartan medoxomil, dry emulsion of OLM with Poloxamer188 and dry emulsion of OLM with Eudragit EPO showed endotherm at 178.52°C, 56.12 °C and 97.75°C respectively. The peak gradually shifted to the lower temperature and near to the melting point of carriers. Melting endotherm of drug was not found in the thermo grams of dry emulsions. It seems that during the formation of dry emulsion, the drug dissolved in carriers. This phenomenon may be responsible for higher solubility observed with dry emulsion with respect to pure drug (Figures 7-12).

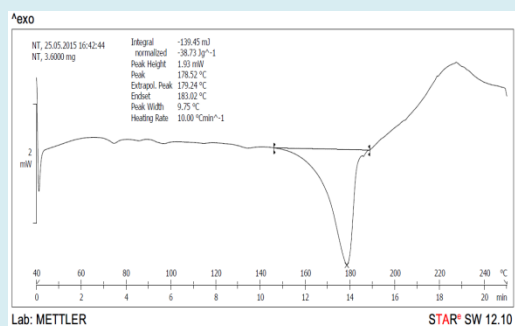


Figure 7: DSC of OLM.

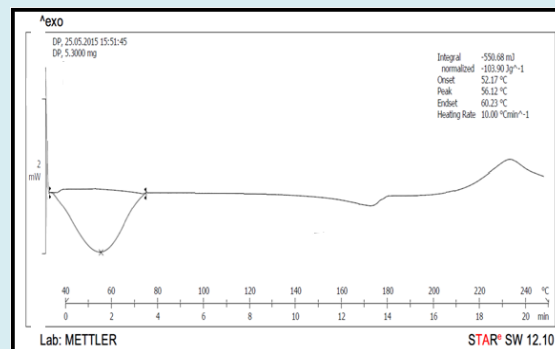


Figure8: DSC of DE with Poloxamer188.

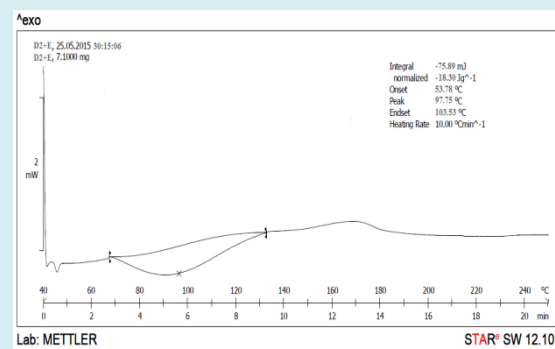


Figure 9: DSC of DE with Eudragit EPO.

Powder X-ray Diffraction (PXRD)

The XRPD pattern for the OLM and dry emulsion are shown in figure 10, 11, 12. The dry emulsion did not show any similarity with that of the initial crystalline material which means that drug may be presented in the more amorphous form than the crystalline form. Dry emulsion technique may have presented the drug in the amorphous form. The XRPD of the OLM showed sharp peaks at a diffraction angle of 19.24° , 23.37° , 26.32° , 27.00° , 36.32° , 39.83° , 83.15° , 44.06° , 10.2° , 22.7° . A sharp and intense peak of OLM was observed in the diffraction spectra due to high crystallinity. Dry emulsion with Eudragit EPO showed peaks at a diffraction angle of 19.32° , 23.30° , 24.48° , 55.0° . But in case of the dry emulsion with Poloxamer 188 showed less intense and broad peaks. The amorphous solid state has the advantage of the increased solubility and therefore faster dissolution rate as compared to the crystalline material.

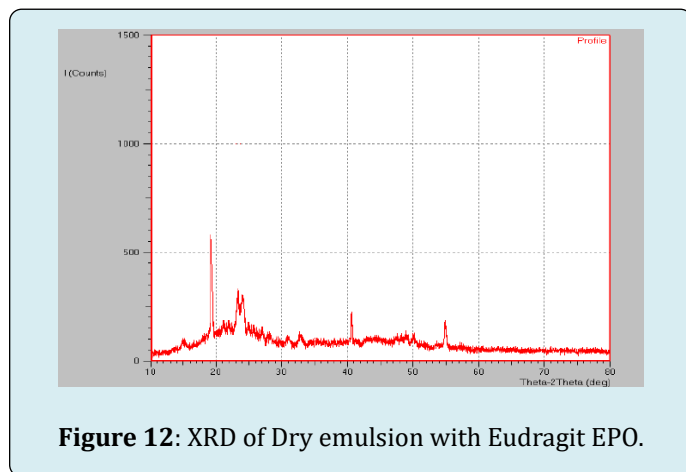


Figure 12: XRD of Dry emulsion with Eudragit EPO.

Scanning Electron Microscopy (SEM)

The SEM of OLM and dry emulsion is shown in Figure 13, 14, 15. The characteristic crystals of the OLM showed prominent changes in the surface morphology of dry emulsion with Poloxamer 188, but in case of dry emulsion with Eudragit EPO there were no significant changes in crystallinity. The SEM of dry emulsion with Poloxamer 188 showed that the loss of crystallinity and particle size of drug, converting into amorphous form which help to increase the dissolution rate (Figures 13-15).

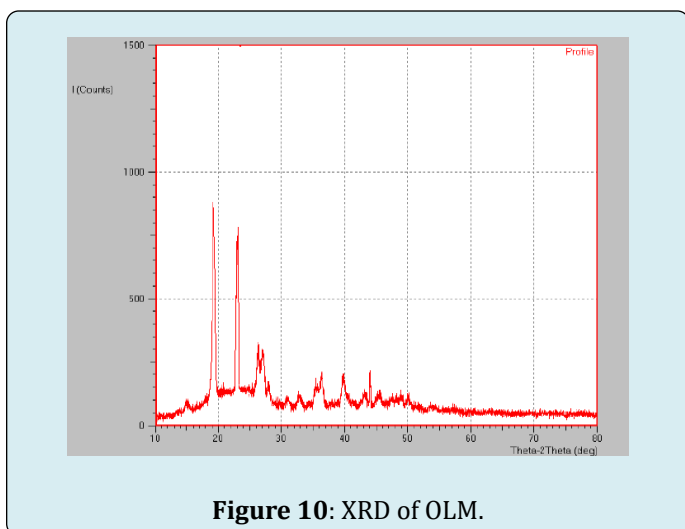


Figure 10: XRD of OLM.

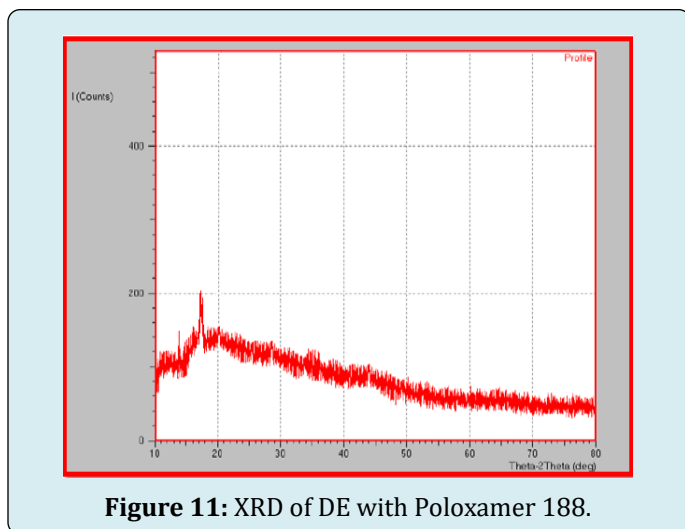


Figure 11: XRD of DE with Poloxamer 188.

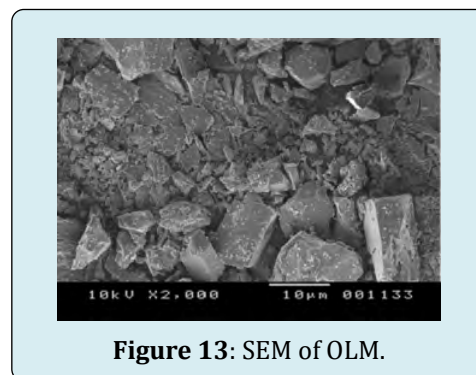


Figure 13: SEM of OLM.

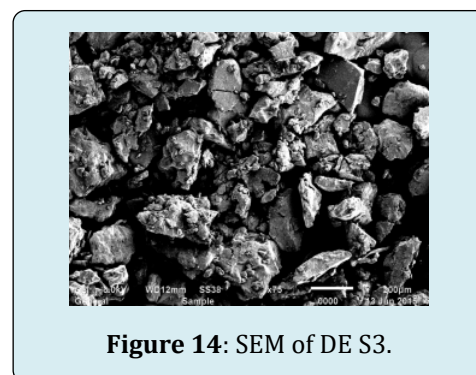


Figure 14: SEM of DE S3.

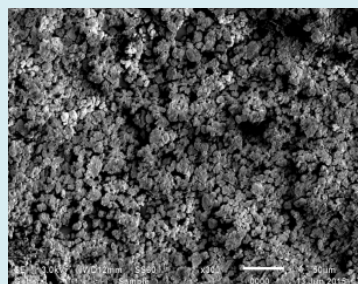


Figure 15: SEM of DE R3.

In-Vitro Dissolution Studies

The % cumulative drug release for OLM and dry emulsions (T3, S3) was found 39.83, 58.49, 80.32 at the end of 8 hrs and R3 showed 97.01% cumulative drug release at end of 4 hrs, The dry emulsion with Poloxamer188 using castor oil showed maximum drug release as compared to OLM and other dry emulsions. This study indicated that dissolution rate of dry emulsion was increased as compared to OLM. The dissolution rate of dry emulsion (R3) with Poloxamer188 (1:1) was increased more as compared to other dry emulsions (T3 and S3) (Table 11 & Figure 16).

Sr.No.	Time (Min)	%Cumulative Drug Release+SD (n =3)			
		OLM	T3	S3	R3
1	15	17.9536 ± 0.03147	19.2376 ± 0.2168	20.1466 ± 0.0335	23.4036 ± 0.003
2	30	17.7643 ± 0.05687	26.8856 ± 0.3851	39.402 ± 0.0640	47.8233 ± 0.0638
3	45	17.9536 ± 0.03147	48.5996 ± 0.5278	48.143 ± 0.1639	67.4076 ± 0.377
4	60	18.0776 ± 0.03139	50.91 ± 0.5481	61.23 ± 0.5403	73.903 ± 0.6843
5	120	18.6983 ± 0.1588	52.3743 ± 0.7145	64.2213 ± 0.3394	79.7746 ± 0.1691
6	180	19.6053 ± 0.04712	52.8263 ± 0.3651	70.773 ± 0.4031	80.178 ± 0.05024
7	240	20.2846±0.008963	53.8333 ± 0.4966	76.7533 ± 0.6506	97.0183 ± 0.2746
8	300	23.495 ± 0.05766	55.5806 ± 0.3044	77.3713 ± 0.1673	-
9	360	26.661 ± 0.01000	56.3676 ± 0.2233	78.4856 ± 0.2081	-
10	420	36.186 ± 0.1333	57.259 ± 0.2234	79.3496 ± 0.07596	-
11	480	39.8343 ± 0.2561	58.4983 ± 0.2951	80.3223 ± 0.2015	-

Table 11: Dissolution study of drug and dry emulsion powder.

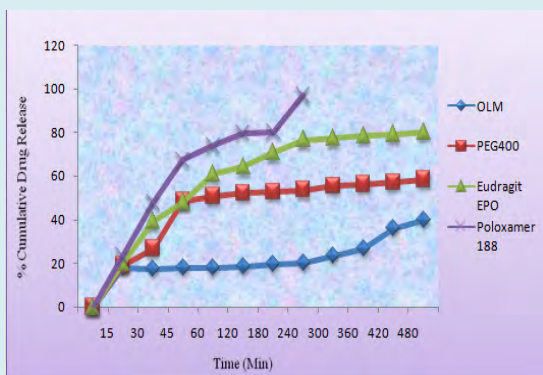


Figure 16: In-Vitro Dissolution profile of dry emulsions and OLM in 0.01 N HCL at 37 ± 0.5°C.

In-Vivo Bioavailability study

The DE (R3) produced a maximum plasma concentration (C_{max} =74.81 µg/ml) as compared to Std. Olmesartan Medoxomil (58.26 µg/ml). The time to reach C_{max} (T_{max})

for the DE (R3) was 6 hr which was lower as compared to pure Olmesartan Medoxomil (9 hr.). The extent of absorption (AUC) of Std. Olmesartan Medoxomil (153.99 µg.hr/ml) from the DE (R3) was also higher as compared to Std. Olmesartan Medoxomil (132.11 µg.hr/ml) (Tables 12, 13 & Figure 17).

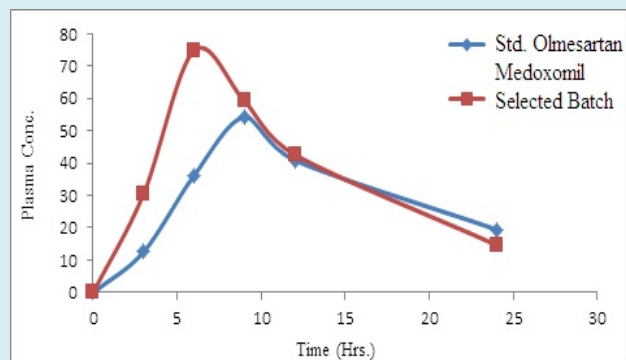


Figure 17: Plasma drug profile of std. Olmesartan Medoxomil and selected batch (R3).

Sr. No.	Time interval (Hrs)	Std. Olmesartan Medoxomil	Selected Batch (R3)		
		Peak area +SD (n=3)	Conc. µg/ml	Peak area +SD (n=3)	Conc. µg/ml
1	3	43897+0.65	12.54	109557.26+0.67	30.45
2	6	1351487+0.89	36.17	271093+0.52	74.81
3	9	197857+0.46	54.26	216127+0.34	59.27
4	12	146561+0.82	40.91	153842+0.11	42.65
5	24	69173+0.58	19.47	51282+0.39	14.67

Table 12: *In-Vivo* Bioavailability study data

Sr. No.	Pharmacokinetic Parameter	Std. Olmesartan Medoxomil	Selected batch (R3)
1	T max	9 Hrs	6 Hrs
2	C max	54.26 µg/ml	74.81µg/ml
3	[AUC]	132.11 µg.hr/ml	153.99 µg.hr/ml

Table 13: Comparative Study of the Pharmacokinetic Parameters.

Conclusion

Enhancement of solubility of Olmesartan Medoxomil is important to improve its bioavailability. This study developed a simple formulation with enhanced solubility of Olmesartan Medoxomil which was helpful to improve its bioavailability.

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