WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 4, 683-705. Research Article ISSN 2277 – 7105

SOLUBILITY AND DISSOLUTION RATE ENHANCEMENT OF OLMESARTAN MEDOXOMIL BY SOLID DISPERSION AND DEVELOPMENT OF ORALLY DISINTEGRATING TABLETS

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Article Received on
12 March 2014,

Revised on 05 April 2014,
Accepted on 28 April 2014

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ABSTRACT

The main objective of the research work is to improve the solubility and dissolution rate of olmesartan medoxomil by solid dispersion with carriers like PVPK30,PEG6000 and sodium lauryl sulfate.The solid dispersion were prepared by kneading method. The prepared solid dispersion were characterized by Fourier Transform Infrared Spectroscopy (FTIR), X-RayDiffraction (XRD) and Differential Scanning Calorimetry (DSC). The FTIR and XRD spectra of olmesartan/carriers solid complexes showed that olmesartan medoxomil could form complex with carriers in solid state. The XRD spectra of olmesartan/ carriers solid complexes indicated olmesartan medoxomil existed in amorphous state, this could be explained the fact that the aqueous solubility of olmesartan medoxomil was increased. From the prepared solid dispersion, orally disintegrating tablets were formulated by using various superdisintegrants like sodium starch glycolate and croscarmellose sodium in various concentrations (5-15%).Prepared tablets were evaluated for physical parameters and drug release by invitro dissolution studies. Dissolution studies showed fast release of olmesartan medoxomil in tablets containing a high level of crosscarmellose sodium. Complexation of olmesartan medoxomil with carriers significantly improved the solubility of the drug and improved the mechanical properties of tablets produced by direct compression.

Key words:- Olmesartan Medoxomil Carriers, Sodium Starch Glycolate, Croscarmellose Sodium, Orally Disintegrating Tablets.

INTRODUCTION

Orally disintegrating tablets (ODT) are an emerging trend in formulation, gaining popularity due to ease of formulation and better patient compliance especially geriatric and pediatric patients [1]. Conventional tablets and capsules pose difficulty for swallowing in patient groups such as elderly, children and patients mentally retarded, uncooperative, or on reduced liquid intake diets [2,3]. To fulfill the above needs, formulators have developed ODT. Orally disintegrating tabletsare the solid dosage forms containing medicinal substances disintegrates rapidly, usually within a matter of seconds when placed upon the tongue. The performance of an ODT depends on the technology used in its manufacture. The disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation. Techniques, which have been used by various researchers to prepare ODT include freeze-drying, tablet moulding, spray drying, sublimation, direct compression, cotton candy process and mass-extrusion, however most of these techniques are patented. The direct compression process using Superdisintegrants is promising approach in the preparation of ODT [4-6]. Superdisintegrants are newer substances which are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch. It is effective at a concentration of 2-8%. It can take up more than 20 times its weight in water and the resulting high swelling capacity combined with rapid uptake of water accounts for its high disintegration rate and efficiency [7,8]. Croscarmellose Sodium is a white, free flowing powder with high absorption capacity. It has a high swelling capacity and thus provides rapid disintegration and drug dissolution at lower levels. It also has an outstanding water wicking capability and its cross-linked chemical structure creates an insoluble hydrophilic, highly absorbent material resulting in excellent swellingproperties [9,10]. The enhancement of solubility and dissolution rate ofpoorly water soluble drugs remains one of the most challenging aspects of drug development. Several approaches have been followed in improving solubility of such drugs, one being complexation using various carriers like PVPK30,PEG6000 and sodium lauryl sulfate. One of the most important characteristics of carriers is their ability to form complexes to improve pharmaceutical properties like solubility, dissolution rate, bioavailability, stability and even palatability without affecting

their intrinsic lipophilicity or pharmacological properties [11-14]. Olmesartan medoxomil is the latest angiotensin II receptor blocker approved by FDA for the treatment of hypertension. It is white to light yellowish-white powder or crystalline powder. It is practically insoluble in water and sparingly soluble in methanol. 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[15]. Based on the above physicochemical and biopharmaceutical properties, Olmesartan medoxomil was selected as a drug candidate. The aim of the present investigation is to enhance the solubility, dissolution rate and mask the taste of the olmesartan by preparing solid dispersion with carriers.The solid dispersion were characterized by x-ray diffractometry (XRD), differential scanning colorimetry (DSC), fourier transform infrared spectroscopy (FTIR) and by dissolution studies. Further these solid dispersion are used for the formulation of orally disintegrating tablets using sodium starch glycolate(SSG) and crosscaremellose sodium (CCS) as superdisintegrants.

MATERIALS AND METHODS

Olmesartan Medoxomil (OLM) was a gift sample from Lupin pharma Pvt Ltd, Pune, Sodium starch glycolate (SSG), Croscarmellosesodium(CCS), Microcrystalline cellulose, PVPK30,PEG6000 and sodium lauryl sulfate were gift samples obtained from Sankalp Pharma Pvt Ltd, Karad. All the chemicals were of analytical grade purchased from Loba Chemie, Mumbai, India. Distilled water was used throughout the experiment.

Preparation of solid dispersion of olmesertan medoximil

olmesertan medoximil solid dispersions were prepared by kneading methods using drug:PVP K30,drug:PEG 6000 and drug:sodium lauryl sulfate in proportion viz. 1:0.5, 1:1 and 1:2 ethanol: water(1:1) was selected as common solvent for solid dispersion. The product then was dried at 40°Cfor 24 hours and the resultant solids were pulverized and then sieved through 100 # and stored in desiccators overnight [16].

Saturation Solubility Studies

Solubility studies were carried out in distilled water according to the method reported by Higuchi and Connors. Excess quantity of olmesartan medoxomil and / or prepared solid dispersion were introduced in 20 mL of distilled water and shaken for 24 hours at room temperature. The content of each flask was then filtered through a Whatmann filter paper. The filtrate was then diluted and assayed spectrophotometrically at 256 nm. Each solubility

was determined in triplicate (n=3). The results obtained from saturation solubility studies were statistically analyzed. The saturation solubility studies were shown in Table.1

Table .1: Saturation solubility of olmesertan medoxiil

Sr. No.	Formulation Batches	Saturation Solubility (µg /ml)
1.	Pure Drug(olmeseratan medoximil)	281
2.	Drug: PVP K30(OP1)	536
3.	Drug: PVP K30(OP2)	579
4.	Drug: PVP K30(OP3)	518
5.	Drug: PEG 6000(OP4)	338
6.	Drug: PEG 6000(OP5)	290
7.	Drug: PEG 6000(OP6)	300
8.	Drug: Sodium lauryl sulfate (OP7)	385
9.	Drug: Sodium lauryl sulfate (OP8)	399
10.	Drug:Sodium lauryl sulfate (OP9)	528

Estimation of Drug Content for Inclusion Complexes

Solid dispersion of olmesartan equivalent to 20mg was weighed and transferred into a 100ml volumetric flask. To this small quantity of methanol was added to dissolve. It was shaken occasionally for about 15 minutes and the volume was made up to 100ml by adding 6.8 pH buffer. The solution was filtered by using a Whatman filter paper with a pore size 0.45 µm. The filtrate was subsequently diluted with 6.8 pH buffer and the absorbance was measured at 256nm using 6.8 pH buffer as blank. This test was repeated six times (N=6).

***In Vitro* Dissolution Studies for Solid dispersion**

Dissolution studies on prepared inclusion complexes were performed in a calibrated 8 station dissolution test apparatus (LABINDIA 8000) equipped with paddles (USP apparatus II method) employing 900 ml of 6.8pHbuffer as dissolution medium. The paddles were operated at 50 rpm and temperature was maintained at 37.0±0.5°C throughout the experiment. The samples (10 ml) were withdrawn at 5, 10, 15, 20, 30 and 45 minutes. and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of the drug dissolved was estimated by Shimadzu UV-1800 double beam U.V spectrophotometer at 256 nm. The dissolution profiles were show in Figure 1.

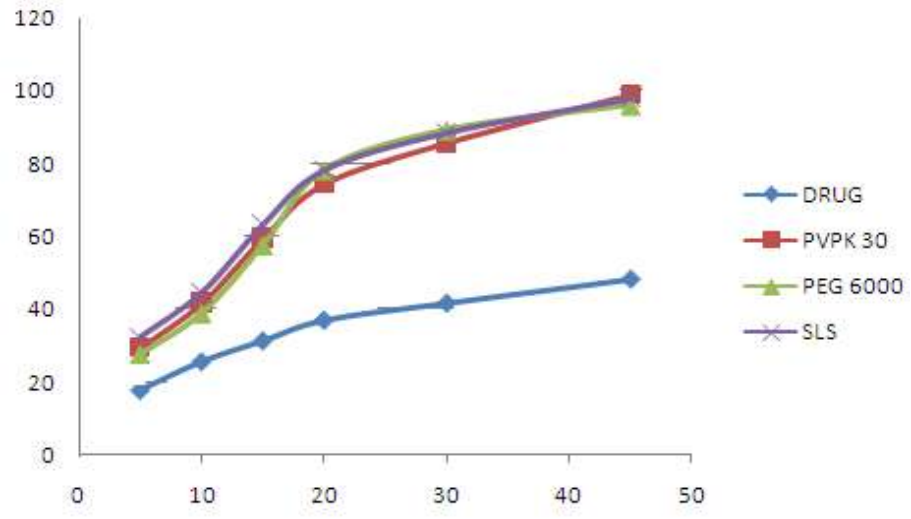
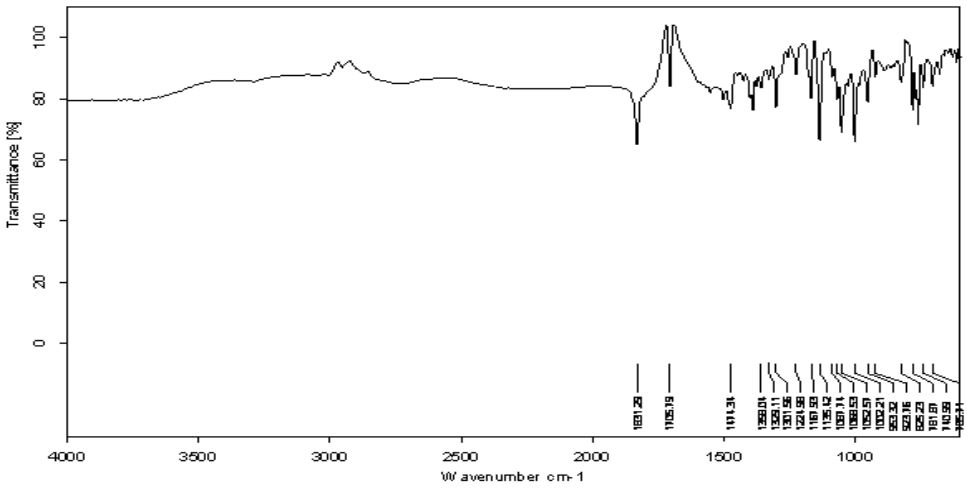


Fig. 1: Dissolution Profiles of Prepared solid dispersion by kneading Methods In Comparison With Pure Drug.

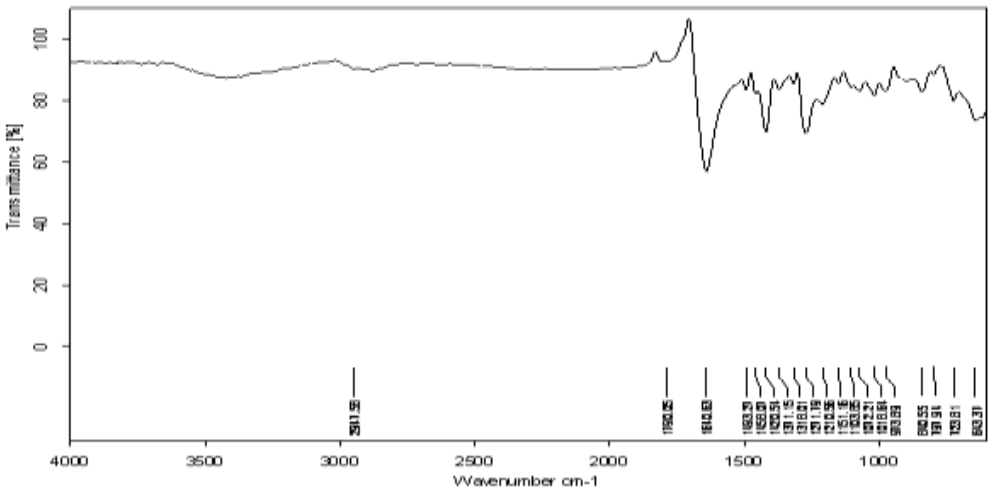
Characterization of Inclusion Complexes

FTIR Spectral Analysis

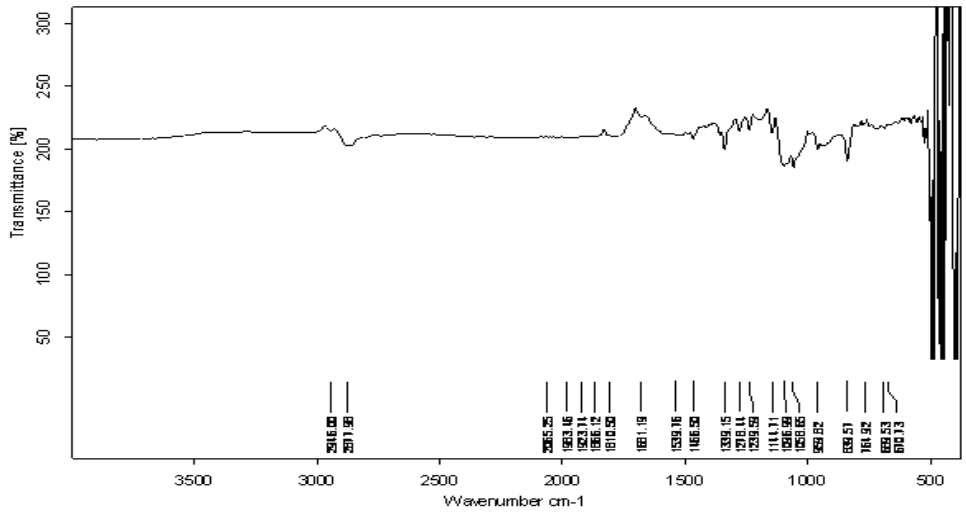
Infrared spectra of pure drug, PVPK30,PEG6000 ,sodium lauryl sulfate and its solid dispersion were recorded by KBr pellet method using Fourier Transform Infrared Spectrophotometer (BRUKER 8400S). A base line correction was made using dried potassium bromide and then spectra of dried mixtures of drug and solid dispersion with potassium bromide were recorded. The Samples were prepared by KBr pellet press method. The scanning range was 400 to4000 cm^{-1} . The spectra 1 were shown in Figures 2.



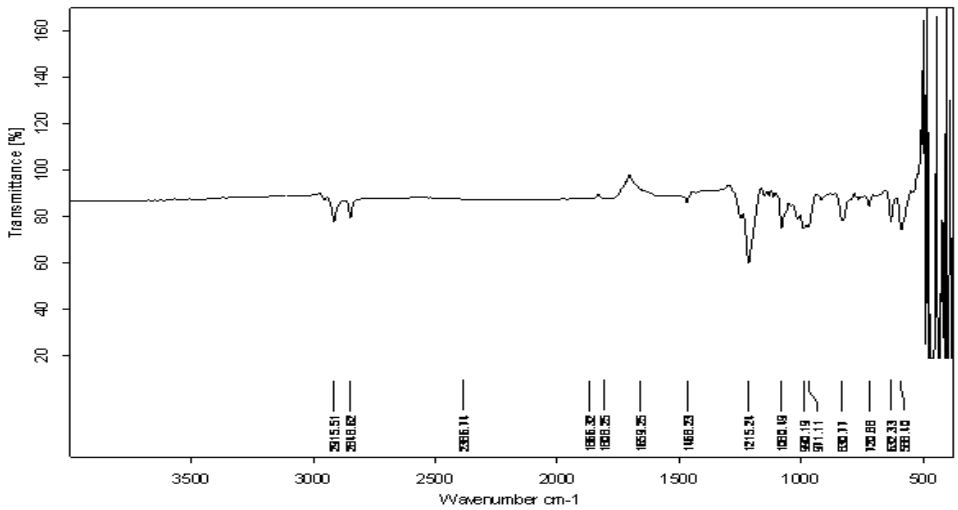
[A]


Transmittance [%]
Wavenumber cm-1

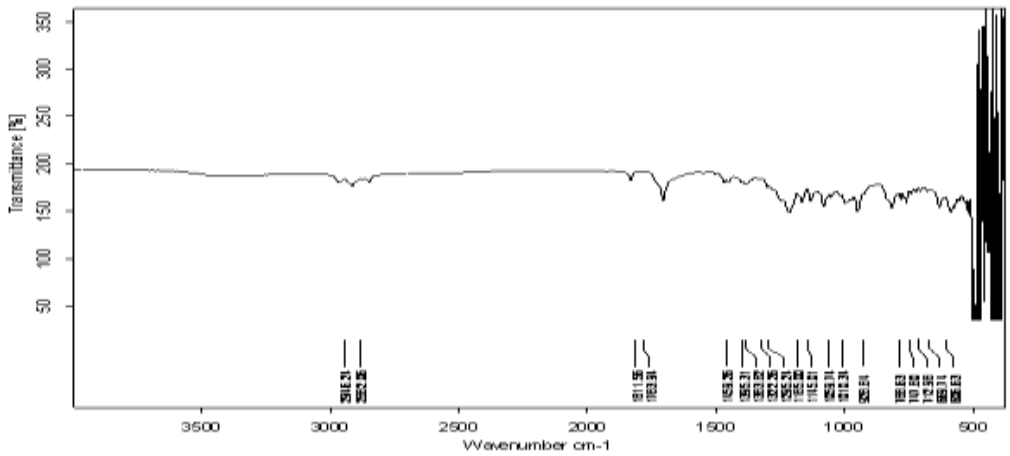
[B]


Transmittance [%]
Wavenumber cm-1

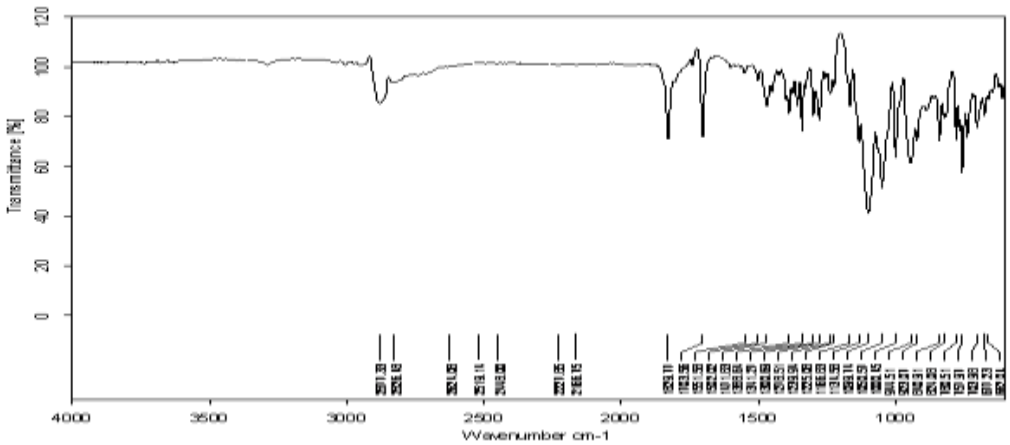
[C]


Transmittance [%]
Wavenumber cm-1

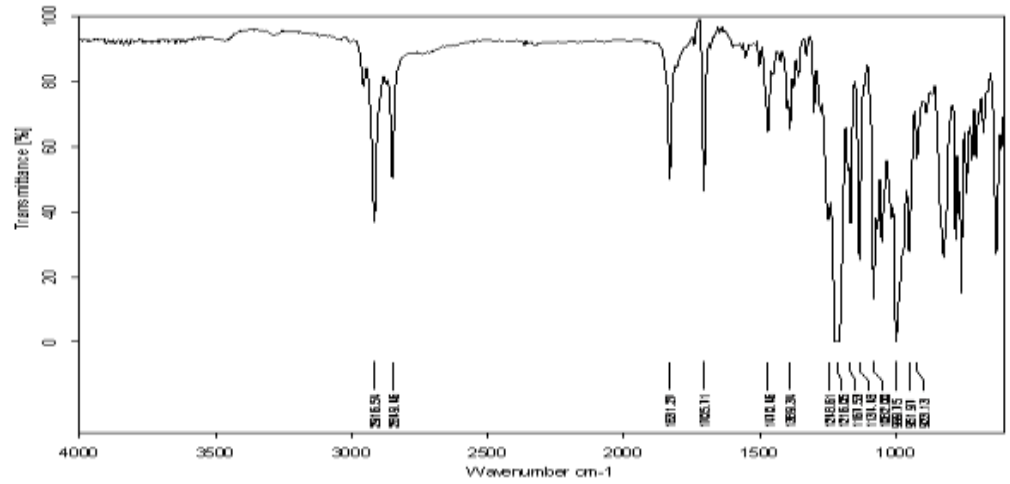
[D]



[E]



[F]

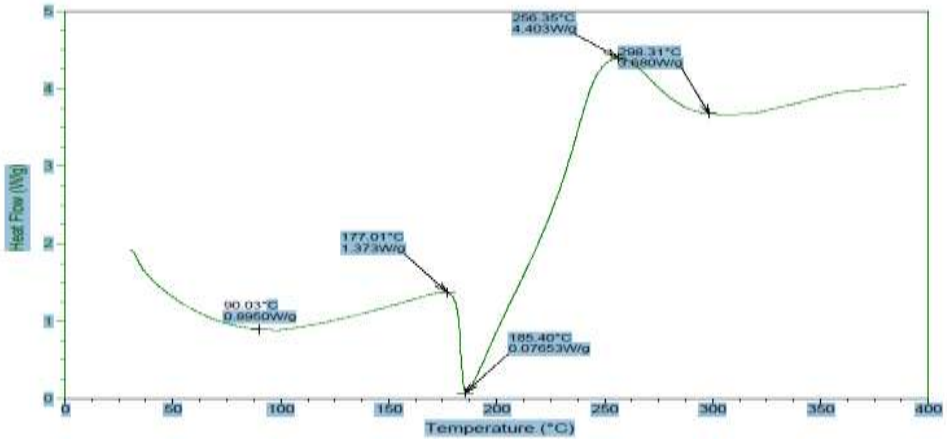


[G]

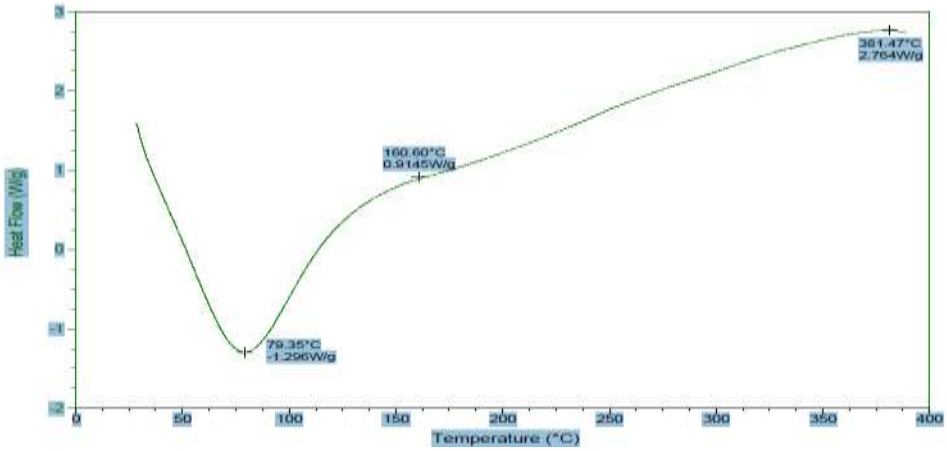
Fig.2:- FTIR spectra of pure olmesartan medoximil, polymer and solid dispersion A: Olmesartan medoxomil, B: PVPK30, C: PEG6000, D: Sodium Lauryl Sulfate, E:Olmesertan medoxomil + PVPK30 (1:1), F: Olmesartan medoxomil +PEG6000 (1:0.5), G: Olmesartan medoxomil + Sodium Lauryl Sulfate (1:2).

Differential Scanning Colorimetry (DSC)

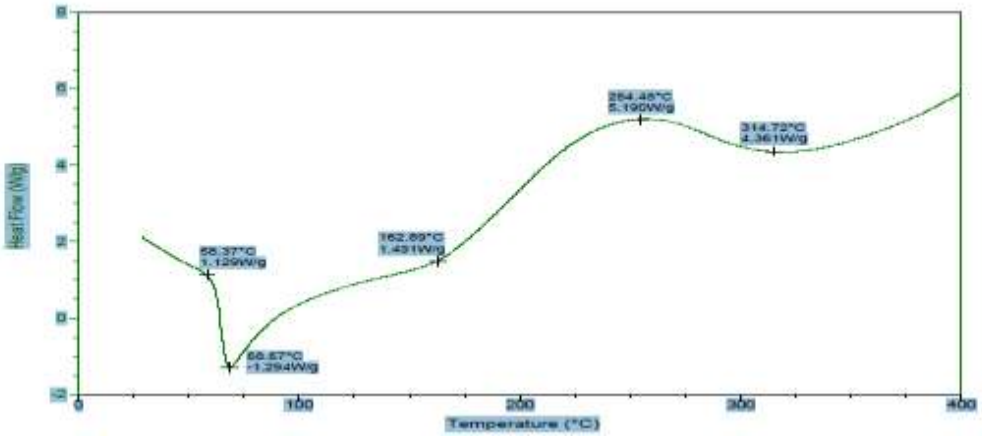
The DSC studies were performed for pure drug, PVPK30, PEG6000 and sodium lauryl sulfate and its solid dispersion were carried out in an open aluminum pans at 10° C/min heating range. The temperature range used was30–300°C.The thermograms were shown in Figures3.



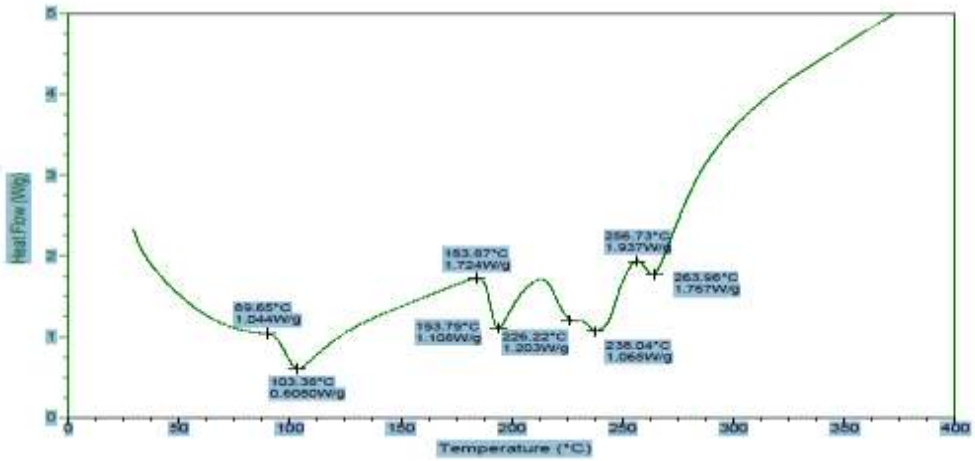
[A]



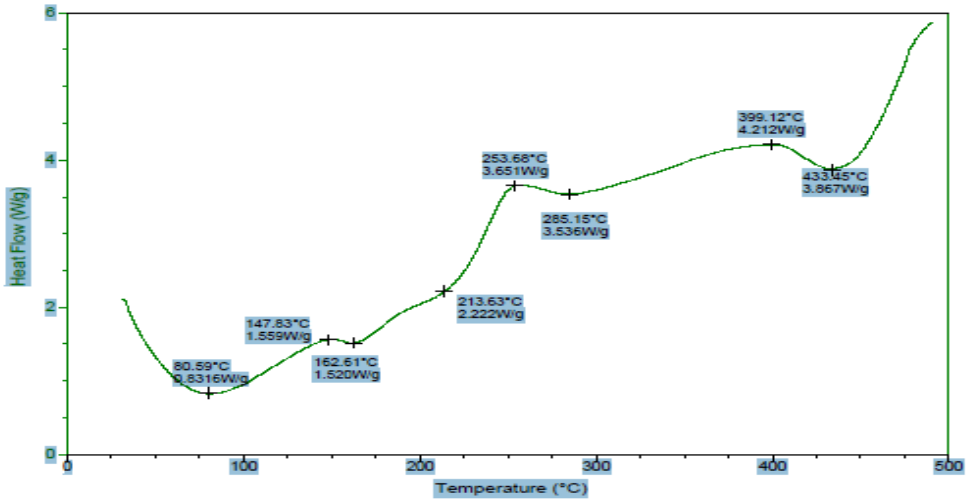
[B]



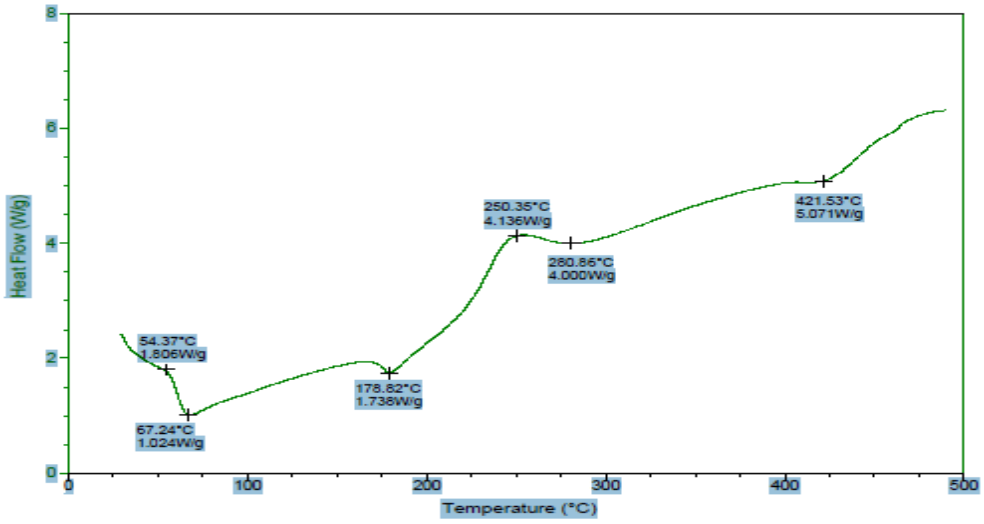
[C]


Heat Flow (W/g)
Temperature (°C)
89.65°C
1.044W/g
103.38°C
0.6060W/g
183.87°C
1.724W/g
193.79°C
1.106W/g
226.22°C
1.203W/g
236.04°C
1.069W/g
256.73°C
1.937W/g
263.96°C
1.767W/g

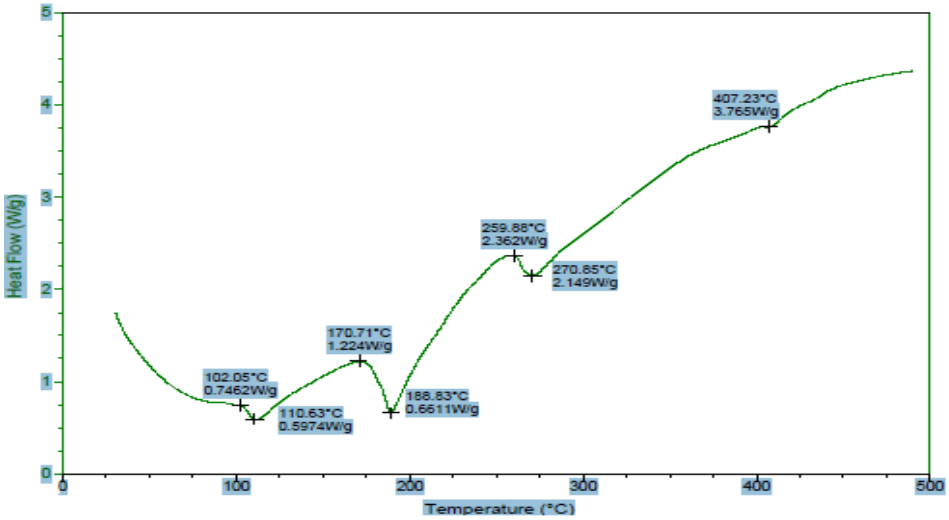
[D]


Heat Flow (W/g)
Temperature (°C)
80.59°C
0.8316W/g
147.83°C
1.559W/g
162.61°C
1.520W/g
213.63°C
2.222W/g
253.68°C
3.651W/g
285.15°C
3.536W/g
399.12°C
4.212W/g
433.45°C
3.867W/g

[E]


Heat Flow (W/g)
Temperature (°C)
54.37°C
1.806W/g
67.24°C
1.024W/g
178.82°C
1.738W/g
250.35°C
4.136W/g
260.86°C
4.000W/g
421.53°C
5.071W/g

[F]

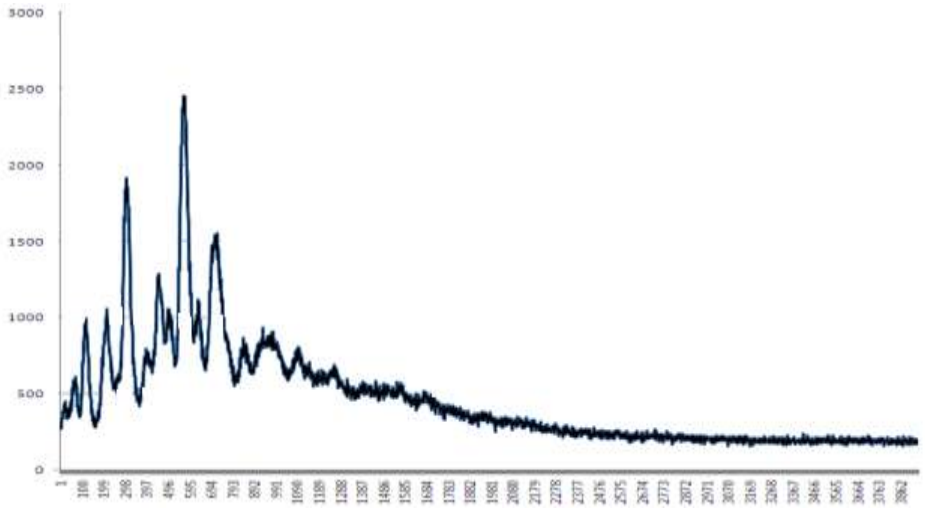


[G]

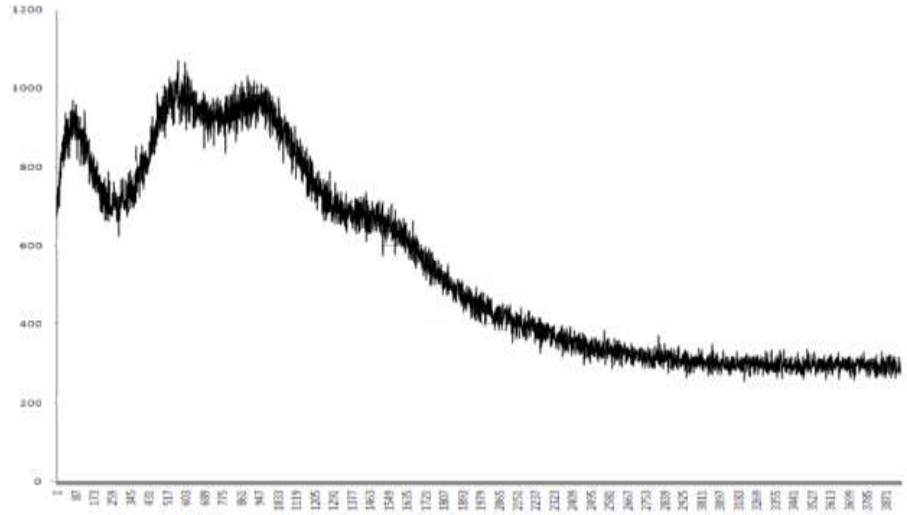
Figure.3:-DSC patterns of pure olmesartan medoximil, polymer and solid dispersion A: Olmesartan medoxomil, B: PVPK30, C: PEG6000, D: Sodium Lauryl Sulfate, E:Olmesertan medoxomil + PVPK30 (1:1), F: Olmesartan medoxomil +PEG6000 (1:0.5), G: Olmesartan medoxomil + Sodium Lauryl Sulfate (1:2)

X-Ray Powder Diffraction

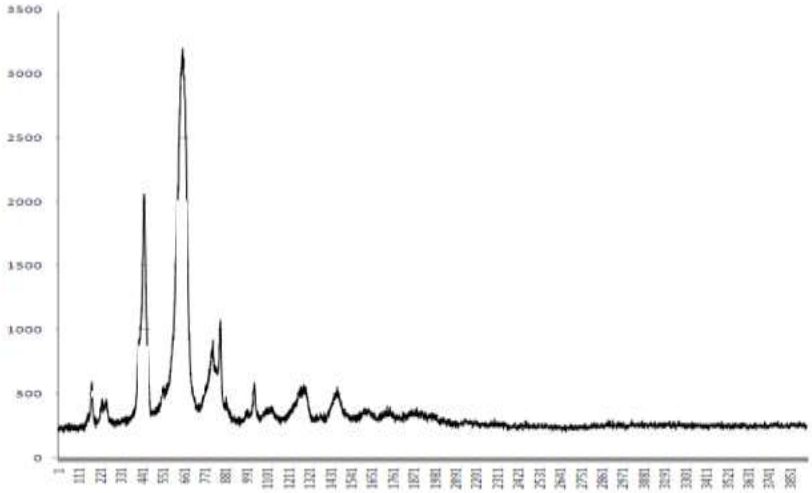
The XRPD data of pure olmesartan medoxomil,PVPK30, PEG6000,sodium lauryl sulfate and prepared solid dispersion were recorded on a Philips Analytical X-ray-PW 3710 (Phillips, Almedo, The Netherlands) diffractometer with tube anode Cr over the interval 10-70°/2Ɵ under following set of conditions: The generator tension (voltage): 40 kV and generator current: 30 mA. The XRPD were shown in Figures4.



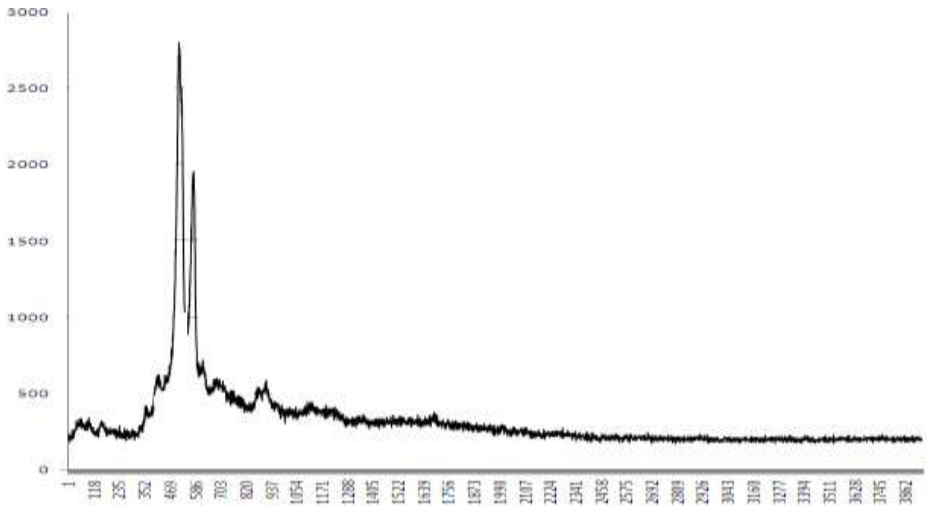
Position [2Ɵ] [A]



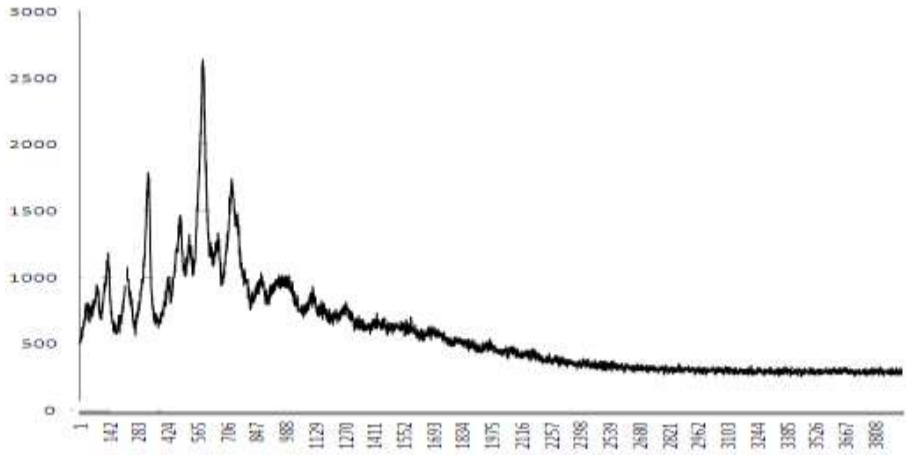
Position [2Θ] [B]



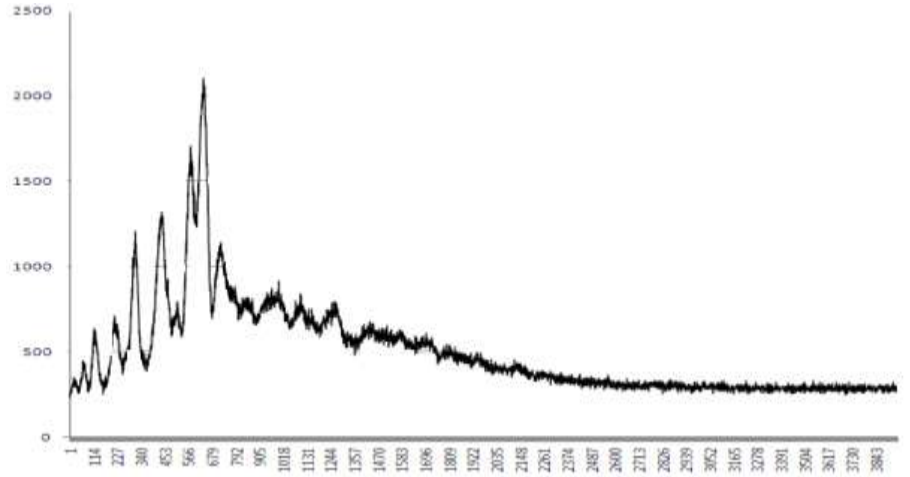
Position [2Θ] [C]



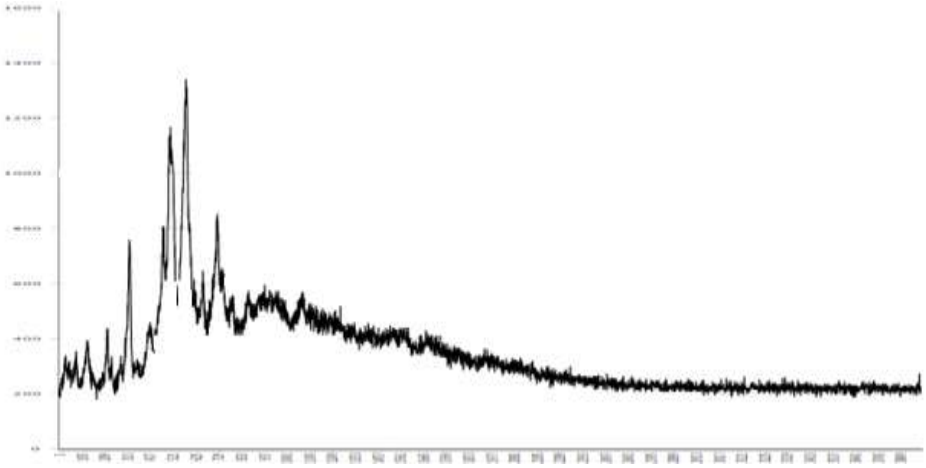
Position [2Θ] [D]



Position [2Θ] [E]



Position [2Θ] [F]



Position [2Θ] [G]

Figure 4.:- XRPD patterns of pure olmesartan medoximil, polymer and solid dispersion A: Olmesartan medoxomil, B: PVPK30, C: PEG6000, D: Sodium Lauryl Sulfate, E:Olmesertan medoxomil + PVPK30 (1:1), F: Olmesartan medoxomil +PEG6000 (1:0.5), G: Olmesartan medoxomil + Sodium Lauryl Sulfate (1:2)

Preparation of Olmesartan Medoxomil Orally DisintegratingTablets

Olmesartan medoxomil containing orally disintegrating tablets were prepared by direct compression process. All the ingredients were properly mixed and the blends were passed through sieve (#40) and compressed on rotary compression machine (Clit Mini press). The solid dispersion equivalent to 20mg of olmesartan prepared by different methods were blended with super disintegrants like SSG and CCS in varying concentration (5-15%) along with MCC as a diluent, mannitol as sweetener and 1% magnesium stearate as lubricant and then directly compressed. The compositions of various tablet formulations were given in Table 2.

Table.2: Composition of orally disintegrating tablets of batch F1-F5

Sr. No.	Ingredients (mg/tablet)	F1	F2	F3	F4	F5
1.	Solid dispersion(eq20mg)	30	30	30	30	30
2.	Sodium starch glycolate	---	10	20	---	---
3.	Croscarmellose Sodium	---	----	----	10	20
4.	Mannitol	20	20	20	20	20
5.	Microcrystalline cellulose(Avicel pH 102)	48	38	28	38	28
6.	Magnesium stearate	2	2	2	2	2
7.	Total wt.	100	100	100	100	100

Table.3: Composition of orally disintegrating tablets of batch F6-F10

Sr. No.	Ingredients (mg/tablet)	F6	F7	F8	F9	F10
1.	Solid dispersion(eq20mg)	40	40	40	40	40
2.	Sodium starch glycolate	---	10	20	---	---
3.	Croscarmellose Sodium	---	---	----	10	20
4.	Mannitol	20	20	20	20	20
5.	Microcrystalline cellulose(Avicel pH 102)	38	28	18	28	18
6.	Magnesium stearate	2	2	2	2	2
7.	Total wt.	100	100	100	100	100

Table.4: Composition of orally disintegrating tablets of batch F11-F15

Sr.No	Ingredients (mg/tablet)	F11	F12	F13	F14	F15
1.	Solid dispersion(eq20mg)	60	60	60	60	60
2.	Sodium starch glycolate	---	10	20	---	----
3.	Croscarmellose Sodium	---	----	----	10	20
4.	Mannitol	20	20	10	20	10
5.	Microcrystalline cellulose(Avicel pH 102)	18	08	08	08	08
6.	Magnesium stearate	2	2	2	2	2
7.	Total wt.	100	100	100	100	100

Evaluation of Tablets

Physical parameters such as weight variation, hardness, friability and disintegration were evaluated for prepared tablets. The prepared orally disintegrating tablets were further evaluated for physical parameters like drug content and *in-vitro* dissolution studies and their results were shown in Tables 3 & 4. Disintegration time of orally disintegrating tablets were carried out by the method given by Gohel *et al.* for this a Petri dish was filled with 10 ml of water and the tablet was carefully placed in the center of petri dish and the time taken for the tablet to completely disintegrate in to fine particles was noted [17].

Table.5: Physical parameter of orally disintegrating tablets of batch F1-F5

Blend Parameters	**Formulation Batches**				
	F1	**F2**	**F3**	**F4**	**F5**
Bulk Density(gm/ml)	0.46	0.472	0.465	0.498	0.471
Tapped Density(gm/ml)	0.571	0.583	0.573	0.593	0.581
Hausner's Ratio	1.24	1.23	1.22	1.19	1.23
Carr's(%) Compressibility Index	19.30	19.05	18.32	16.66	19.08
Angle of Repose	39.10	38.33	37.78	36.58	38.42
Tablet Parameters					
Weight Variation(mg)	±2	±2	±2	±2	±2
Thickness (mm)	5.27	5.26	5.29	5.24	5.26
Friability (%)	0.37	0.35	0.29	0.30	0.37
Drug Content	101.23	98.51	97.89	99.07	99.56
Disintegration Time (sec)	35	40	44	53	55
Hardness (kg/cm^3)	4.5	4.0	5.0	3.5	4.0

Table.6: Physical parameter of orally disintegrating tablets of batch F6-F10

Blend Parameters	**Formulation Batches**				
	F6	**F7**	**F8**	**F9**	**F10**
Bulk Density(gm/ml)	0.452	0.476	0.455	0.478	0.490
Tapped Density(gm/ml)	0.574	0.588	0.594	0.584	0.592
Hausner's Ratio	1.25	1.23	1.32	1.22	1.20
Carr's(%) Compressibility Index	20.12	19.06	23.51	18.30	17.30
Angle of Repose	40.29	38.35	43.11	38.47	36.22
Tablet Parameters					
Weight Variation(mg)	±2	±2	±2	±2	±2
Thickness (mm)	5.25	5.23	5.25	5.30	5.28
Friability (%)	0.49	0.39	0.56	0.34	0.27
Drug Content	102.59	101.84	99.39	98.92	99.54
Disintegration Time (sec)	45	48	50	36	45
Hardness (kg/cm^3)	4.9	3.9	4.8	5.0	4.3

Table.7: Physical parameter of orally disintegrating tablets of batch F11-F15

Blend Parameters	Formulation Batches				
	F11	F12	F13	F14	F15
Bulk Density(gm/ml)	0.473	0.471	0.483	0.469	0.489
Tapped Density(gm/ml)	0.577	0.574	0.58	0.569	0.591
Hausner's Ratio	1.21	1.22	1.21	1.23	1.20
Carr's (%) Compressibility Index	18.19	18.49	18.11	19.03	17.24
Angle of Repose	37.20	37.80	37.49	38.20	36.21
Tablet Parameters					
Weight Variation(mg)	±2	±2	±2	±2	±2
Thickness (mm)	5.24	5.25	5.24	5.22	5.25
Friability (%)	0.30	0.30	0.34	0.28	0.25
Drug Content	101.13	98.79	101.67	98.57	99.69
Disintegration Time (sec)	45	58	60	30	35
Hardness (kg/cm^3)	4.4	3.5	4.0	5.0	5.1

***In vitro* Dissolution Studies of orally disintegrating tablets**

Dissolution studies on each tablet formulation were performed in a calibrated 8 station dissolution test apparatus (LABINDIA8000) equipped with paddles (USP apparatus II method) employing 900 ml of 6.8 pH buffer as a dissolution medium. The paddles were operated at 50 rpm and temperature was maintained at 37° C ± 1° C throughout the experiment.

The samples (10 ml) were withdrawn at 5, 10, 15, 20, 30 and 45 minutes and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of the drug dissolved was estimated by Shimadzu UV-1800 double beam U.V spectrophotometer at 256 nm. The dissolution studies on each formulation were conducted in triplicate. The dissolution profiles for all formulations were shown in Figures 5-10 and the *In vitro* dissolution parameters were given in the Table 8-9.

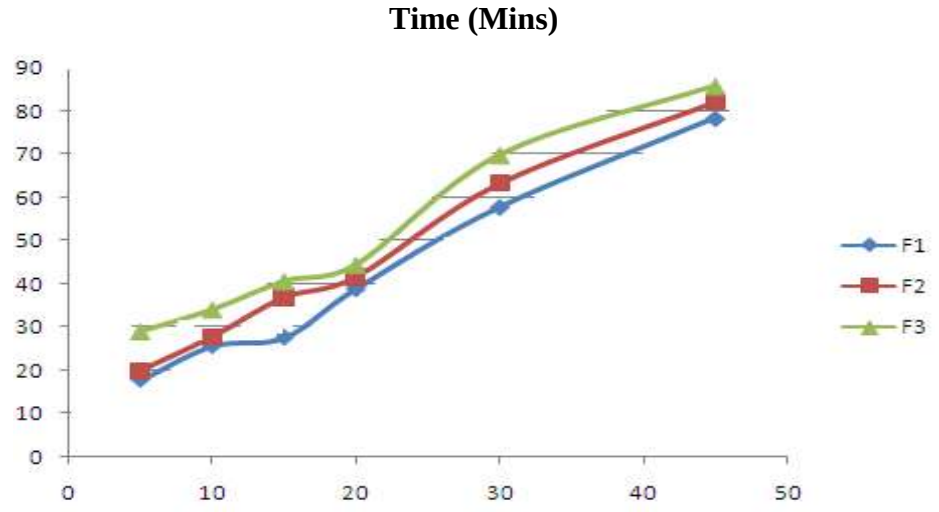


Figure.5:-Dissolution study of formulation Batches F1-F3

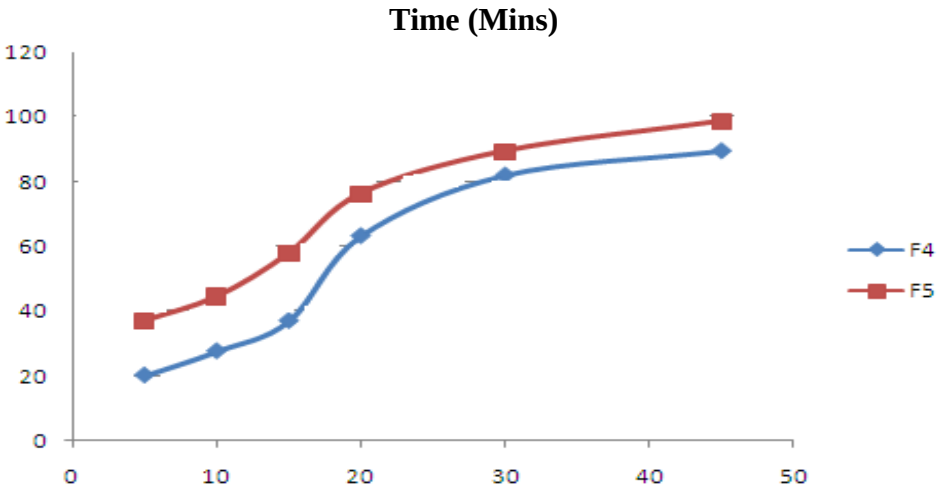


Figure.6:-Dissolution study of formulation Batches F4-F5

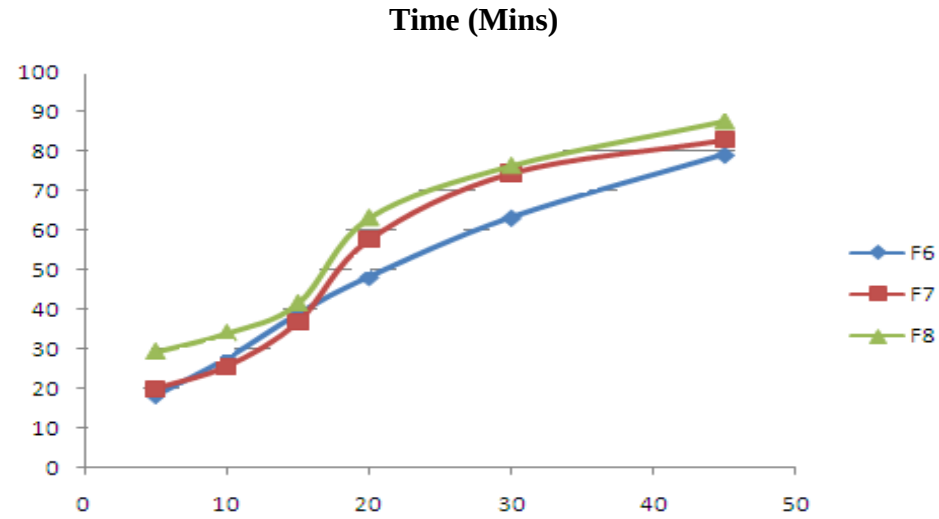


Figure.7:-Dissolution study of formulation Batches F6-F8

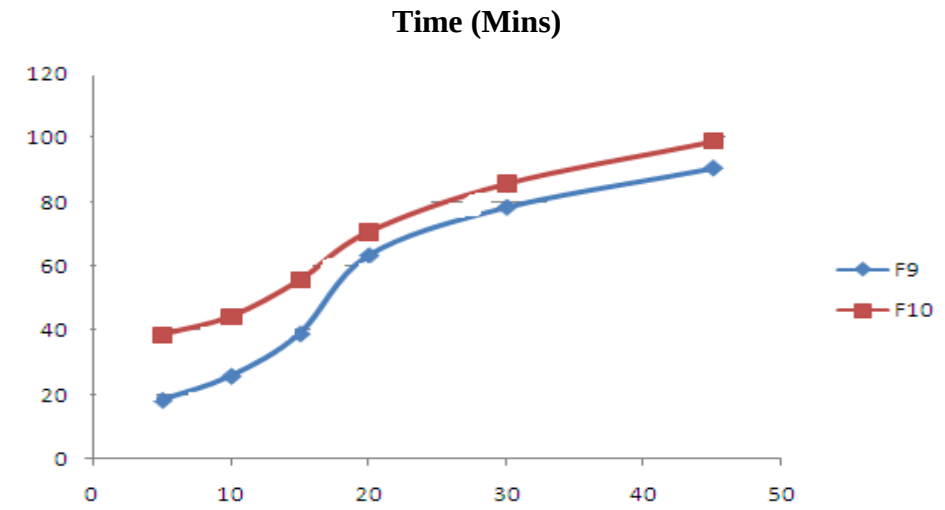


Figure.8:-Dissolution study of formulation Batches F9-F10

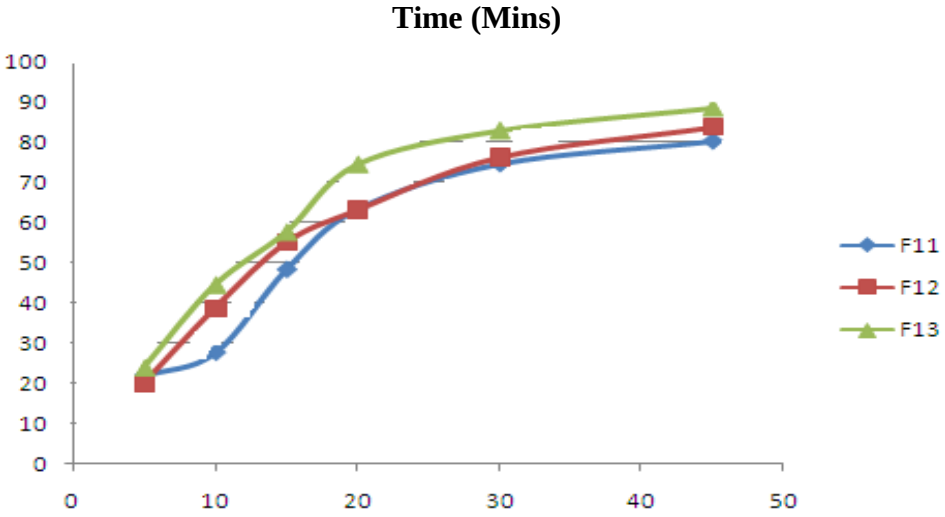


Figure.9:-Dissolution study of formulation Batches F11-F13

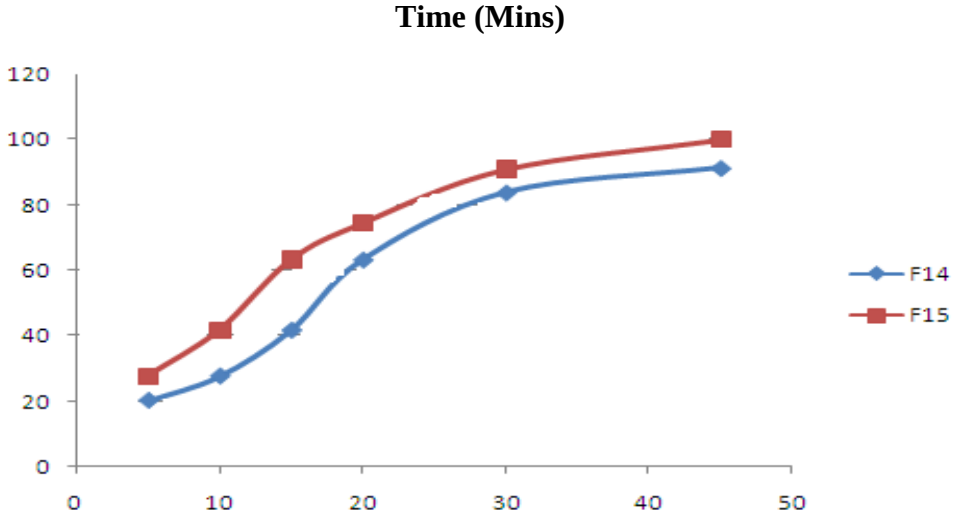


Figure.10:-Dissolution study of formulation Batches F14-F15

Table.8:- In vitro Dissolution study of formulations

Formulation code/Time in min	Cumulative % Drug Release								
	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
0	0	0	0	0	0	0	0	0	0
5	17.81	20.06	29.06	20.06	36.93	18.18	20.06	29.43	18.18
10	25.65	27.88	34.12	27.56	44.43	27.56	25.65	34.12	25.65
15	27.56	36.93	40.65	36.93	57.85	38.80	36.93	41.62	38.81
20	38.81	41.62	44.43	63.18	76.31	48.15	57.65	63.18	63.18
30	57.65	63.18	69.75	81.93	89.40	63.18	74.43	76.31	78.18
45	78.18	81.93	85.66	89.43	98.60	79.12	82.81	87.56	90.37

Table.9:- In vitro Dissolution study of formulations

Formulation code/Time in min	Cumulative % Drug Release					
	F 10	F 11	F12	F13	F14	F15
0	0	0	0	0	0	0
5	38.81	21.93	20.06	23.81	20.08	27.56
10	44.43	27.56	38.81	44.43	27.56	41.66
15	55.68	48.15	55.08	57.56	41.62	63.18
20	70.68	63.18	63.18	74.43	63.18	74.43
30	85.68	74.43	76.31	82.87	83.81	90.87
45	98.81	80.06	83.81	88.50	91.31	99.99

RESULTS

Saturation Solubility

Table.1 shows results of saturation solubility studies. The solubility of solid dispersion was found to be increased than pure olmesartan medoxomil. There was 2.060, 1.20 and 1.87 fold increase in solubility of solid dispersion with PVPK30,PEG6000 and Sodium Lauryl Sulfate of 1:1,1:0.5 and 1:2 ratios respectively. The improvement in solubility by solid dispersion was found to be extremely significant. This might be due to changes in crystal habit, structure and surface morphology. In addition to that, solvent included in crystal form solvates that might have changed the reactivity of drug particles, surface morphology and internal energy of the molecules which would be responsible for increasing solubility of solid dispersion. The solubility of sodium lauryl sulfate (1:2) and PVPK30 (1:1) was found to be greater than raw olmesartan medoximil and other ratios demonstrating that the incorporation of PVPK30,PEG6000 and sodium lauryl sulfate enhanced the drug solubility by improving wettability.

FTIR Study

The FTIR study of Olmesartan medoxomil , PVPK 30, PEG6000 and Sodium lauryl sulfate and its solid dispersion are shown in Fig.2. IR spectra of olmesartan medoximil showed characteristic peaks at 2974 cm-1 (Aliphatic C–H strech), 3039 cm-1 (Aromatic C–H strech), 3271 cm-1 (Broad, intermolecular hydrogen bonded, O-H strech), 1720 cm-1 (C=O of carboxylic group), 1504 cm-1(ring C=C stretch), 1483 cm-1 (C–N strech), 1371 cm-1(in plane O-H bend), 1053 cm-1 (ring C-O-C stretch) .The FTIR spectra of PEG 6000 and Sodium Lauryl sulfate displayed prominent peaks at 2,946 cm-1 (O-H), 2,930 cm-1 (C-H), 1,647 cm-1 (H-O-H bending) and 1,035 cm-1 (C-O-C). PVPK30 showed characteristic broad band at 3454cm-1(O-H, stretch, broad), 1666 cm-1 (C=O) owing to its oxygen functionalities. It was found that there were no considerable changes in the IR peaks of the agglomerates when compared to pure olmesartan Medoximil. In the FTIR study, the breakdown of the intermolecular hydrogen bond between the crystalline drug molecule and formation of hydrogen bond between the drug and the polymers might be related to the slight shift of the absorption band. However FTIR spectra of agglomerates showed that no changes have occurred in chemical structure. The strong interaction between drug and carrier, often leads to identifiable changes in the IR profile of the drug but the results of IR spectra indicated an absence of any well-defined interaction between olmesartan and PVPK30,PEG6000 and Sodium Lauryl Sulfate.

Differential Scanning Calorimetry(DSC)

The DSC thermograms of Olmesartan medoxomi , PVPK 30, PEG6000, Sodium lauryl sulfate and its solid dispersion are shown in Fig.3. The sharp melting point peak of pure Olmesartan medoxomil appeared at 185.40^{o}C, whereas no such peak was observed in solid dispersion prepared with PVPK 30, PEG 4000 and Sodium lauryl sulfate suggesting that Olmesartan medoximil may be molecularly dispersed and in amorphous form.

X-Ray Diffraction Study

The XRPD study of Olmesartan medoxomil , PVPK 30, PEG6000 and Sodium lauryl sulfate and its solid dispersion are shown in Fig.4.The presence of polymorphs, crystal habit modifications in drug crystals and / or generation of new crystal form during solid dispersion process can be elegantly examined using XRPD technique.(Figure.4). Examination of XRPD patterns of pure drug and solid dispersion confirmed formation of agglomerates. While studying the X-ray diffractograms of solid dispersion it was observed that some of the peaks

were appeared while some of them were disappeared when compared to diffractogram of pure olmesartan Medoximil. The formation of different polymorphic form was stated on the basis of changes in intensity of peaks in diffractograms of polymer indicating different rearrangement of molecules. Thus the agglomerates exhibited spectra with different peak positions (patterns) from their respective host and guest crystals which depicted that different internal structure might have formed with significant modification in crystals habit.

In –Vitro Release profiles of orally disintegrating tablets

The dissolution studies of orally disintegrating tablets were performed in pH 6.8 buffer by using USP-II paddle method. The drug release from all the tablet formulations were found to release the drug at a faster rate than compared to pure drug. It was found that the tablet formulation F15 with 15% CCS showed the rapid drug Release. when compared to the pure drug and other formulations. The drug release of tablet formulation in the presence of various Superdisintegrants were in the order of CCS >SSG. The rate of drug release of tablet formulations was found to be linear with Hixson-Crowell order rate constant. The R^2 values of all tablet formulations were in the range of 0.772 to 0.988. Hence suitable as orally disintegrating tablets.

DISCUSSION

From the saturation solubility studies it was observed that a linear increase in solubility with increasing concentration of carriers. Hence the solid dispersion were prepared by kneading method using carriers in 1:1 molar ratio and these combinations were found to be stable and suitable for masking the metallic taste of drug and enhances the dissolution rate of olmesartan. From the *in vitro* dissolution studies it was observed that the solid dispersion prepared by kneading method released the drug rapidly than the pure drug alone. The possible interaction between the drug and the carrier was studied by FTIR spectroscopy. In the FTIR study, the breakdown of the intermolecular hydrogen bond between the crystalline drug molecule and formation of hydrogen bond between the drug and the polymers might be related to the slight shift of the absorption band. However FTIR spectra of complexes showed that no changes have occurred in chemical structure. Broadening of peak indicates the formation of complex between the drug and carrier. DSC analysis was performed for the Pure drug, PVPK30, PEG6000,Sodium lauryl sulfate and for solid dispersion prepared by kneading method. From the DSC thermogram, it was observed that the drug was incorporated in the polymer, so the graph was extended. It indicated that there was no drug and polymer

interaction. The XRD patterns of olmesartan and complexes prepared by kneading method were studied. The powder diffraction patterns of pure olmesartan showed characteristic high diffraction peaks. On the other hand the diffraction patterns of complexes showed decrease in the peak intensity and finally absence of peaks was observed in solid dispersion which indicated the amorphous nature of olmesartan in solid dispersion and are considered to be the reason for the dissolution and solubility enhancement. From the prepared solid dispersion orally disintegrating tablets were prepared by using superdisintegrants such as SSG and CCS. The direct compression process was found to be suitable for compressing the tablet formulations as orally disintegrating tablets. Tablet formulations were further evaluated for physical parameters. All the tablet formulations were found to be stable within the I.P specified limits for weight uniformity, friability and drug content. The results indicated that tablets containing high concentration of Superdisintegrants i.e F15(CCS 15%) get softened and absorb more atmospheric moisture. The dissolution profiles were shown in Figure 5-10. The drug release of tablet formulations in the presence of various superdisintegrants were in the order of CCS>SSG. The rate of drug release of tablet formulations was found to be linear with Hixson-Crowell rate constant. The r^2 values of all tablet formulations were in the range of 0.772 to 0.988.

CONCLUSION

The present study has shown that it is possible to increase the solubility and dissolution rate of poorly soluble drug olmesartan medoxomil by preparing it as solid dispersion with carriers. The solid dispersion exhibited faster dissolution characteristics as compared to that of pure drug. This was due to solubilizing effect of the complexing agent. It was found that the solid dispersion prepared by the kneading method release the drug rapidly than the pure drug. The orally disintegrating tablets of olmesartan prepared with 15% crosscarmellose sodium (F15) as superdisintegrant showed rapid drug release when compared to pure drug and other tablet formulations.

ACKNOWLEDGEMENTS

The authors express their gratitude to Lupin Pharma PVT Ltd for providing the gift samples.

The authors are thankful to the Government College of Pharmacy, Karad. for providing the facilities to carry out the research work.

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