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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF OLMESARTAN MEDOXOMIL BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Olmesartan Medoxomil crystalline substance is a novel drug for the treatment of the hypertension, it is a specific angiotensin II type 1 antagonist. Olmesartan Medoxomil is a novel antihypertensive drug having low aqueous solubility and poor bioavailability. Solid dispersions were prepared by Melting method using mannitol, polyethylene glycol (PEG) 4000 and polyethylene glycol (PEG 6000) as carriers. Drug : carrier weight ratios were 1:1, 1:2, 1:3 and 1:4. This Solid dispersion technology can be used to improve the dissolution properties of poorly soluble drugs and evaluated for the enhancement of solubility and dissolution rate of Olmesartan Medoxomil. The prepared Solid dispersions were subjected for solubility, drug content, stability studies and percent drug release. The study shows that all the polymers enhanced the release profile of Olmesartan Medoxomil. *In vitro* release profiles of all solid dispersions were comparatively evaluated and also studied against pure Olmesartan medoxomil. Faster dissolution was exhibited by solid dispersion containing 1:4 ratio of Olmesartan Medoxomil: PEG 6000 by Fusion/Melting method. The solid dispersions were also characterized by Fourier transform infrared spectroscopy (FTIR), X-Ray Diffraction (XRD) as well as Differential Scanning Calorimetry (DSC).

KEY WORDS: Olmesartan medoxomil, Solid dispersion, bioavailability, dissolution.

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. As a result, the improvement of solubility and dissolution rate of poorly soluble compounds is of great importance. These poorly water soluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. Therefore, the improvement of drug solubility thereby its oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system.

Oral formulation has been the preferred and most common route of drug delivery around the globe. The popularity of this dosage form is owing to its ease of administration and good patient compliance. From drug development and formulation perspective, a solid dosage form offers superior stability compared to intravenous formulations. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used in a solid dosage form that originate an effective and reproducible in vivo plasma concentration after oral administration (Kumar N, 2008).

The method was termed as "solid dispersion". 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. Olmesartan is a specific angiotensin II type I antagonist used alone or with other anti-hypertensive agents to treat hypertension. Olmesartan has poor aqueous solubility and low bioavailability of 26%. In the present study, an attempt was made to increase the solubility and dissolution rate of Olmesartan by solid dispersion technique using water soluble carrier's mannitlo, peg4000 and peg6000. The prepared solid dispersions were evaluated for drug content, *in vitro* dissolution rate studies, solubility studies, crystallinity studies and interactions between drug and carriers using IR, DSC and Powder X-ray diffraction study.

MATERIALS AND METHODS

Olmesartan Medoxomil was obtained as a gift sample from CTX life science Laboratories Ltd. Surat Gujarat India. PEG-6000- Qualikems fine chem. Pvt.Ltd.,Vadodara, PEG-4000- Qualikems fine chem. Pvt.Ltd.,Vadodara, Mannitol- Merck specialities. Pvt.Ltd., Mumbai. Methanol- Finar chemicals limited ,Ahmedabad. Hydrochloric acid- Finar chemicals limited, Ahmedabad. Sodium hydroxide- Merck specialities. Pvt.Ltd., Mumbai. Di-sodium hydrogen phosphate- Merck specialities. Pvt.Ltd., Mumbai. Anhydrous Potasium dihydrogen phosphate- Merck specialities. Pvt.Ltd., Mumbai.

Method of preparation of solid dispersion:

Melting method: The solid dispersion of drug with polymers like Mannitol, PEG4000 and PEG6000 were prepared. Olmesartan Medoxomil: Polymers mixtures containing 1:1, 1:2, 1:3 and 1:4 ratios taken. First polymer ratio taken into china dish and heated directly until it melted. Now 100mg of Olmesartan is added to china dish which was maintained at 40^0c .The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved. The solidified masses were often found to require storage for one or more days in desiccators at ambient temperatures for hardening and ease of powdering (Das, 2002).

Table1: Various solid dispersions prepared by Melting method

Formulation code	Solid dispersions	Drug : carrier ratio
F1	Olmesartan - Mannitol	1:1
F2	Olmesartan - Mannitol	1:2
F3	Olmesartan - Mannitol	1:3
F4	Olmesartan - Mannitol	1:4
F5	Olmesartan - PEG 6000	1:1
F6	Olmesartan - PEG 6000	1:2
F7	Olmesartan - PEG 6000	1:3
F8	Olmesartan - PEG 6000	1:4
F9	Olmesartan - PEG 4000	1:1
F10	Olmesartan - PEG 4000	1:2
F11	Olmesartan - PEG 4000	1:3
F12	Olmesartan - PEG4000	1:4

CHARACTERIZATION OF PREPARED SOLID DISPERSION

Fourier Transform Infrared spectroscopy (FTIR): Infrared spectra were recorded on a Fourier transform Infrared (FTIR) spectrophotometer using KBr dispersion method (B. Kapoor, 2012). All samples were recorded in the range of 4000-400 cm^{-1}.

Differential scanning calorimetry: DSC studies were performed on a Seiko, DSC 220C Differential scanning calorimeter. The samples heated on sealed aluminum pans at a rate of 10^0C/min from 30^0 to 300^0C. Approximately 2 mg of Olmesartan Medoxomil or drug-carrier mixture was taken in aluminium pan, sealed with aluminium cap and kept under nitrogen purging (atmosphere) (A. Kalia, 2011).

X-Ray diffraction: The powder XRD of the Olmesartan Medoxomil and carriers were recorded using an X-ray diffractometer , Using Philips PW 1729 X-ray generator (Computer 1710). Target Cu, Filter Ni, Voltage 35 kv, Current 20 mA receiving slit 0.2 inches, X-axis: 10mm = 10 2q; y-axis 2000. CPS using Cu,Ka radiation as source. Decrease in crystallinity of the drug is often a predominant mechanism responsible for increased dissolution rates (Jain CP, 2009).

Solubility studies: Excess amount of the drug Olmesartan medoxomil (20mg) was added to stoppered conical flask containing 100ml of solvent media and subjected to shaking for nearly 6 hrs ,then the flasks were removed and kept aside for 24 hrs at a constant temperature to attain equilibrium condition and filtered.The filtrate was suitably diluted and analyzed on a uv-spectrophotometer at 255nm.The studies were carried out in triplicate and the average value was noted (Choudhary D, 2010; Sucheta B, 2011).

Drug content: An accurately weighed amount of solid dispersions equivalent to 20mg of Olmesartan was dissolved in methanol, volume was made upto 100ml ,the drug was then extracted by using methanol by subjecting to continuous shaking on a rotary shaker for 24hrs.The concentration of Olmesartan in the extracted fluid was determined using uv-visible spectrophotometer against phosphate buffer pH6.8 solutions as blank at 255nm. (Bhowmik D, 2009; M. Ratnaparkhi, 2012).

***In vitro* dissolution studies of solid dispersion of olmesartan medoxomil:** The quantity of solid dispersion equivalent to 20 mg of Olmesartan Medoxomil was placed in dissolution medium. The dissolution study of solid

dispersion was conducted using dissolution testing apparatus II (paddle method) in 900 ml of phosphate buffer solution of pH 6.8 at 37±0.5 ºC and at a speed of 50 rpm. Aliquots of 10 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 255 nm against suitable blank using UV-visible spectrophotometer.[10,11]

Stability studies: Stability studies on prepared solid dispersions containing optimized batch F8 was carried out by storing 1gm of solid dispersions in an amber colored screw capped bottle at different temperatures for a period of 3 months .The solid dispersions visually examined for any physical change ,drug release and drug content was estimated at the end of 3 months (Rawat, 2011).

RESULTS AND DISCUSSION

Solubility studies:

Table.2.Solubility of Olmesartan solid dispersion at room temperature

Solvent medium	Saturation solubility (gm/100ml)*
Distilled Water	0.0037
0.1NHCL	0.0013
Methanol	0.0073
P^H6.8 phosphate buffer	0.0071

Characterization of olmesartan medoxomil and its solid dispersion:

Fourier Transform Infrared (FTIR) Spectroscopy:

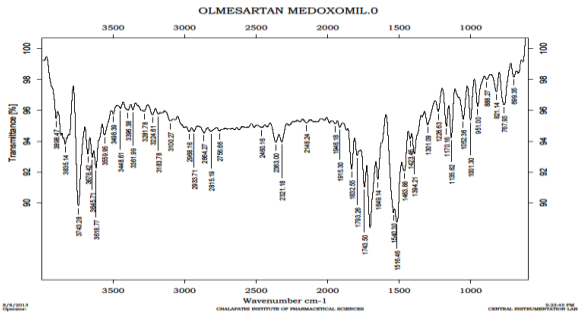

Figure.1.IR Spectra of Olmesartan medoxomil (Pure drug)

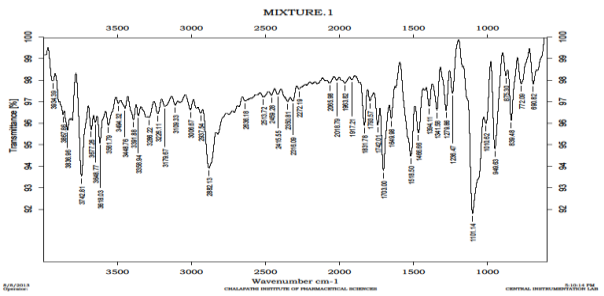

Figure.2.IR Spectra of Physical Mixture

Differential scanning calorimetry:

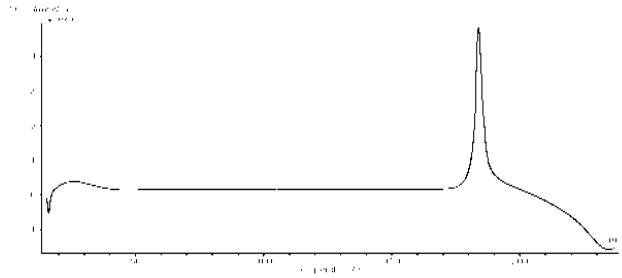

Figure.3.DSC Thermogram of Pure drug (Olmesartan medoxomil)

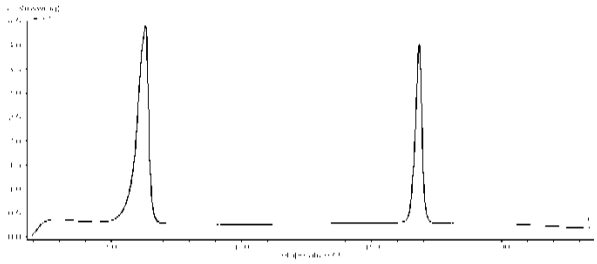

Figure.4.DSC Thermogram of Physical Mixture

X-Ray Diffraction:

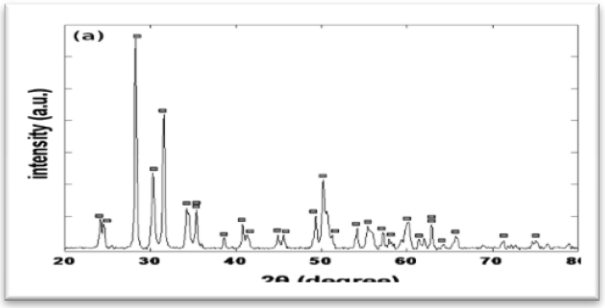

Figure.5.XRD of Olmesartan medoxomil (Pure drug)

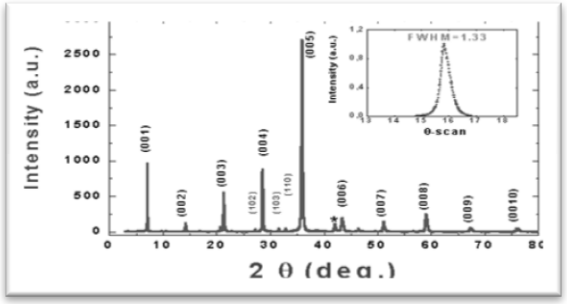

Figure.6.XRD of Physical Mixture

***In vitro* dissolution studies of olm and its solid dispersions:**

Table 3: *In Vitro* % Drug release study of Formulations F1-F12

Time (min)	Cumulative percent drug released												
	PD	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	10.7	5.1	4.8	5.5	5.6	6.81	7.05	8.35	9.6	5.7	6.3	7.7	5.8
10	21.9	10.4	9.9	11.3	11.7	14.5	15.05	19.2	21.1	11.8	12.9	15.7	12.6
15	33.6	16.3	15.2	17.2	18.4	23.1	23.4	31.4	33.3	18.8	21.5	23.9	20.5
20	47.2	23.1	20.6	23.3	25.7	33.25	32.6	44.6	48.6	26.4	30.5	32.6	29.7
30	62.2	30.7	26.3	29.7	34.7	44.4	44.1	59.7	66.2	35.9	40.2	41.5	39.9
45	79.1	39.5	32.9	43.1	47.8	56.85	58.1	77.1	87.1	50.5	51.3	58.1	61.3

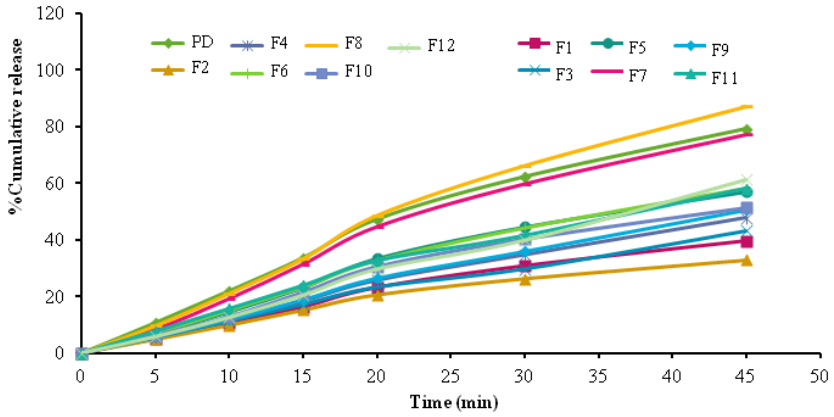

Figure.7.*In Vitro* % Drug release plots of Formulation F1-F12

Drug content:

Table.4: % Drug content studied on formulation F1-F12

Formulation code	Percent drug content (%)	Formulation code	Percent drug content (%)
F1	95.68	F7	99.12
F2	95.73	F8	99.73
F3	96.29	F9	96.44
F4	96.87	F10	96.47
F5	98.34	F11	97.28
F6	98.52	F12	97.86

Comparative studies for optimized and pure drug:

Table.5.Comparative study of %Drug Release

Time(min)	% Drug release of F8	%Drug release of pure drug
5	9.6	10.7
10	21.1	21.9
15	33.3	33.6
20	48.6	47.2
30	66.2	62.2
45	87.1	79.1

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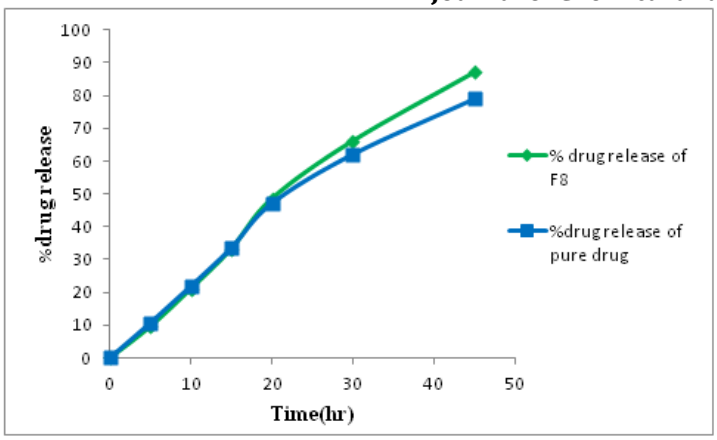

Figure.8.Comparative study of %Drug Release

Stability studies:

Table 6: *In vitro* drug release data of stability for optimized batch F8 under 30ºC± 2ºC/65%RH±5%RH

Characteristics	1month	2month	3month
Physical appearance	Smooth & white color	Smooth &white color	Smooth &white color
Drug content (%)	99.73%	99.62%	99.51%
In vitro drug release upto 24hours (%)	87.1%	87.05%	87%

Solubility studies: The solubility and dissolution rate of Olmesartan Medoxomil was significantly increased. The solubility results show that Olmesartan pure drug and its formulations were more soluble in methanol than in ph6.8 phosphate buffer, 0.1NHCl and distilled water.

Characterization of Olmesartan Medoxomil and its solid dispersion: FTIR and DSC study revealed no drug-polymer interactions. XPRD studies of solid dispersions conformed that conversion of crystalline drug into the amorphous form.

***In vitro* dissolution studies of Olmesartan and its solid dispersions:** *In vitro* dissolution test results indicate complete dissolution of drug (OLM) from its solid dispersion within 45 minutes. Among from F1 to F12 batches the formulation F8 showed maximum release of 87.1%, in 45 min. Hence the F8 can be considered as good formulation because of its better release profile for the entire drug comprised within the solid dispersion by melting method.

Drug content: The drug content results suggest that the drug was uniformly dispersed throughout the formulations prepared.

Comparative studies for optimized and pure drug: The comparative study shows optimized batch F8 formulation shows maximum drug release compared to pure drug.

Stability studies: The prepared solid dispersion containing Olmesartan F8 batch was selected for stability studies under 30ºC±2ºC/65%RH±5%RH storage condition. There are no significant changes in their physico-chemical properties and their drug release studies.

CONCLUSION

Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the *in vivo* absorption of drug. Currently only 8% of new drug candidates have both high solubility and permeability. Because of solubility problem of many drugs the bio availability of them gets affected and hence solubility enhancement becomes necessary. Solid dispersion technology is one of the possible modes that increase the solubility of poorly soluble drugs. The solubility study of Olmesartan Medoxomil was carried in different media, from the results more solubility is seen in methanol. The percent drug content study shows the uniform

dispersion of Olmesartan throughout the formulations prepared. Drug –polymer interactions: The studies revealed no significant interactions between Olmesartan Medoxomil and polymers. The *in vitro* release study was carried out on pure drug and various solid dispersion formulations by employing pH 6.8 phosphate buffer as a dissolution medium. The Olmesartan Medoxomil containing polymer PEG-6000(1:4) ratio showed more percent drug release 87.1% within 45min. The results of present study showed that the polymer ratio used in the formulation F8 showed optimized result. This shows an increased release of the drug from the dispersions in comparison to pure Olmesartan Medoxomil drug.

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