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Research Article

MODIFICATION OF PHYSIOCHEMICAL PROPERTIES OF OLMESARTAN MEDOXIMIL USING VARIOUS CARRIERS & VITAMIN E TPGS AS A SOLUBLISER

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ABSTRACT
The Prime objectives of present investigation were to enhance the solubility of water insoluble drug olmesartan medoxomil using vitamin E-TPGS as a solubliser and screening ofvarious adsorbents like aerosol 200, aeroperl 300 and neusilin with aspects of further formulation development. Total 9 batches (F1-F9) were prepared by varying the concentration of vitamin E-TPGS and using aforesaid different adsorbents. Melt dispersions were prepared by melting vitamin E-TPGS and addition of drug to melt followed by adsorption of molten mass on various carriers in a ratio of olmesartan, vitamin E-TPGS & Carriers as 1:0.5:1,1:1:1 &1:2:1. Pure drug and prepared melt dispersions were evaluated for saturation solubility study, micromeritic properties, drug content and in vitro dissolution study. PXRD, FTIR and DSC analysis were carried out to determine incompatibility between drug and various carriers. DSC, XRD and FTIR studies showed no incompatibilities between drug and excipients. Mixtures of drug with Vitamin E-TPGS and carriers like Aeroperl 300, Aerosil 200 & Neusilin showed increase in dissolution rate as compared to the pure drug. Solid dispersions with Aeroperl 300 showed more solubility along with good flow properties as compared to Aerosil & Neusilin. Based upon results formulation F2 containing API: Vitamin E-TPGS: Aeroperl 300 (1:1:1) ratio can be finalized for further formulation development with other excipients like diluents, disintegrants, lubricants to form tablet dosage form. So, it can be concluded that melt dispersion technique using E-TPGS and Aeroperl 300 can be used to increase bioavailability of poorly soluble drugs.

Keywords: *Melt Dispersions, Vitamin E-TPGS, Neusilin, Aeroperl 300, Olmesartan Medoxomil*

INTRODUCTION
Approximately more than 40% new drug candidates are poorly water soluble. So, for the BCS class-II (low soluble and high permeable) drugs solubility is rate determining step for the absorption of drug from the site of administration to the systemic circulation (Sharma *et al.,* 2009). Bioavailability of drug depends upon the solubility/dissolution rate therefore, to increase to bioavailability it is essential to increase the water solubility/dissolution rate of poorly soluble drugs (Khadka *et al.,* 2014). Various method are listed in literature for the solubility enhancement of poorly water soluble drugs as micronisation (Muller *et al.,* 2000; Jinno *et al.,* 2000), solid dispersion (Urbanetz, 2006) nanonisation (Hu *et al.,* 2004; Liversidge *et al.,*1995), inclusion complexation etc (Brewster *et al.,* 2007). Melt dispersion is one the method used for the solubility enhancement which involves the adsorption of drug and polymer molten mass on the carriers which produces the free flowing material which can be either filled in to the capsule or compressed in to tablet along with other excipients (Ahn *et al.,* 2011).
Olmesartan medoxomil is described chemically as 2, 3-dihydroxy-2-butenyl4-(1-hydroxy-1-methylethyl)-2-propyl-1-[p-(o-1H-tetrazol-5-ylphenyl) benzyl] imidazole-5-carboxylate, cyclic 2, 3-carbonate (Ganesh *et al.,* 2014). It is a prodrug and hydrolyzed to olmesartan during absorption from the gastrointestinal tract, used for the treatment of hypertension (Gregory and Blair, 2002; Fiese and Hagen, 1987).
Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively receptor in vascular smooth muscle blocking the binding of angiotensin II to the AT_1 therefore, its action is independent of the

pathways for angiotensin II synthesis (Fiese and Hagen, 1987). It is practically insoluble in water and sparingly soluble in methanol. Absolute bioavailability is 26% because of low aqueous solubility and C_{max} reached after 1to 2 hrs. Elimination of Olmesartan is in a biphasic manner with a terminal elimination half-life of approximately 13 hours (Benicar).

Vitamin E-TPGS (water-soluble derivative of natural Vitamin E) is polyethylene glycol 1000 ester of d-alpha-tocopheryl succinate having polar hydrophilic head (polyethylene glycol 1000 succinate) end and lipophilic tail (Phytyl chain of d-α- tocopherol) (Zhang *et al.,* 2012; Guo *et al.,* 2013). Due to its amphiphile properties it is widely used as solubliser for ample poorly soluble drugs (Varmaand Panchagnula, 2005; Yu *et al.,* 1999). So, keeping this in point of view attempt has been made to improve solubility of olmesartan by melt adsorption technique using vitamin E-TPGS and various adsorbents like aerosol 200, aeroperl 300 and neusilin.

MATERIALS AND METHODS

Materials

Olmesartan Medoximil obtained as a gift sample from the Lupin Ltd. Pune, NeusilinUS-2 was gifted by Fuji chemicals Japan, Aeroperl 300 pharma and Aerosil were obtained from Evonik Chemicals, Vitamin E-TPGS obtained from BASF Pharma BASF (Mount Olive, NJ, USA). All other chemicals are of analytical reagent grade.

Methods

Preparation of Melt Dispersion of Olmesartan Medoxomil

Melt dispersions of olmesartan were prepared in different ratios of Vitamin E-TPGS, Aerosil 200, Aeroperl 300 pharma and Neusilin as shown in table 1. First Vitamin E-TPGS was melted on water bath at constant temperature (40°C). Further to the molten mass olmesartan was added with stirring so that paste formed. Then to that paste various carriers are added and triturated in mortar for uniform mixing. The prepared mixture were passed through sieve no.20 and then transferred to the glass bottles, sealed and stored in desiccators until further use.

Table 1: Formulation Trials

Formulation Code	Olmesartan	Vitamin E-TPGS	Aeroperl 300	Aerosil	Neusilin
F1	1	0.5	1	-	-
F2	1	1	1	-	-
F3	1	2	1	-	-
F4	1	0.5	-	1	-
F5	1	1	-	1	-
F6	1	2	-	1	-
F7	1	0.5	-	-	1
F8	1	1	-	-	1
F9	1	2	-	-	1

Note: All the excipients and Olmesartan taken in ratio as shown in table 1

Evaluation of Melt Dispersions

Saturation Solubility study

The saturation solubility studies of pure drug and melt adsorptions were carried out to determine the solubility. Weighed quantity of pure drug and melt adsorptions added to 100 ml volumetric flask containing 10 ml of distilled water. Stoppard flasks were shaken for 24 hours on vibratory shaker. Aliquots were filtered through HDPE 0.45µm filter and concentration of olmesartan determined at 256 nm using UV-spectrophotometer.

Micromeritics

Bulk Density & Tap Density

Accurately weighed melt dispersion of mass 'M' of all batches were passed through sieve no.18 to break agglomerates and further transferred separately in 100 ml graduated cylinder. The volume occupied by each sample, before tapping (Vo) were determined. Further the cylinder was mechanically tapped and final volume after tapping (Vt) were determined in triplicate using bulk density apparatus (Lab Hosp, Mumbai, Maharashtra, India). The bulk density (ρb) and tap density (ρt) was calculated using the formulas (Killedar *et al.,* 2014),

$$\rho b = \frac{M}{Vo} \qquad Eq.1$$

$$\rho t = \frac{M}{Vt} \qquad Eq.2$$

Carr's Compressibility Index (CCI) and Hausner's Ratio (HR)

Carr's compressibility index (CCI) and Hausner's ratio (HR) was calculated using the following formula (Jadhav *et al.,* 2014),

$$CCI = \frac{\rho t - \rho b}{\rho t} X\ 100 \qquad Eq.3$$

$$Hausner's\ Ratio = \frac{\rho t}{\rho b} \qquad Eq.4$$

Drug Content

Melt adsorptions equivalent to 10 mg of Olmesartan was dissolved in 50ml volumetric flasks containing phosphate buffer pH 6.8 and sonicated for 15 min. Solutions were filtered through HDPE 0.45µm filter and then 1ml of above solution diluted in 10ml volumetric flask with phosphate buffer pH 6.8. Drug content was analyzed by UV-spectrophotometer at 256 nm. Each sample analyzed in triplicate. Drug content determined from following formula (Singh and Singh, 2012),

$$\%\ Drug\ Content = \frac{Practical\ Drug\ Content}{Therotical\ Drug\ Content} \times 100 \qquad Eq.5$$

FTIR Study

Interaction between functional groups and polymer were studied by infrared spectroscopy. The FTIR spectra was recorded using FTIR spectrometer- 430(JASCO, Japan). The samples (Pure drug, F2, F5 and F8) were previously ground and mixed thoroughly with potassium bromide at 0.5:50 (sample: KBr) ratio, respectively and scanned over a range of 4000-400 cm^{-1} (Patel and Patel, 2011; Punita and Devi, 2009).

XRD Study

X-ray diffraction studies were carried out to study the change in crystallinity of olmesartan. XRD spectra of pure drug and formulations (F2, F5 & F8) was obtained by using Philips analytical X-ray-PW-3710 diffractometer with tube anode Cr over interval 10-70º/2θ operated at generator tension (voltage) 40 kV and generator tension 25 mA (Panchal and Tiwari, 2013; Choudhary *et al.,* 2010).

DSC Analysis

The drug-polymer and carriers interaction were investigated by Differential scanning calorimetric analysis (Universal V4.7A TA Instrument). The DSC thermogram of pure drug and the formulations were recorded to study the interactions between them. The samples were separately sealed in aluminium cells and set in a thermal analyzer. The thermal analysis was performed at a scanning rate of 10°C over a temperature range of 25-500° C (Rawat *et al.,* 2011).

In-Vitro Dissolution Study

In-Vitro dissolution study of pure drug and melt adsorptions of Olmesartan medoxomil (n=3) were performed as per US-FDA dissolution database in USP type-II Paddle apparatus (Electrolab, Mumbai, India) in phosphate buffer pH 6.8 (37 ± 0.5°C and 50 rpm). Melt adsorptions equivalent to 40mg of olmesartan medoxomil was added to the dissolution media and 5ml of aliquots was withdrawn at intervals of 10, 20, 30, 45& 60 min (Yadav *et al.,* 2012). Sink condition was maintained by replacing with same volume of dissolution media. Absorbances of filtered aliquots were measured by UV-spectrophotometer at 256nm using blank. Cumulative % drug release was calculated from absorbances and graph of % drug release versus time plotted.

RESULTS AND DISCUSSION

Total nine batches of melt dispersions were successfully prepared.

Micromeritics

Melt dispersion of batch F1-F3 showed good flow properties as compare to other batches. This might be due to excellent flow properties of Aeroperl 300. While Melt dispersion of batch F4-F6 showed very poor flow which can be assigned to very poor flow of Aerosil 200. Batch F7-F9 showed good to passable flow despite of excellent flow properties of neusilin. Results of flow properties are shown in Table 2.

Table 2: Flow Properties Analysis

Trial	BD(gm/ml)	TD(gm/ml)	CI	HR	Conclusion
Olmesartan	0.303	0.522	41	1.7	Very poor flow
Aeroperl	0.2	0.236	15	1.2	Excellent
Aerosil	0.034	0.05	32	1.47	Very poor flow
Neusilin	0.319	0.376	13.1	1.2	Excellent
F1	0.393	0.47	16.4	1.2	Good
F2	0.37	0.447	17.2	1.2	Good
F3	0.305	0.372	18.0	1.2	Passable
F4	0.178	0.285	37.5	1.6	Very poor flow
F5	0.28	0.45	37.8	1.61	Very poor flow
F6	0.186	0.267	30.3	1.44	Poor flow
F7	0.495	0.593	16.5	1.2	Good
F8	0.4325	0.5568	22.3	1.27	Passable
F9	0.378	0.621	39.1	1.27	Very poor flow

CI: Carr's Index, HR: Hausner's Ratio

Solubility Study

Batch F3 and F9 showed highest solubility of olmesartan. Detailed results of solubility are shown in Table 3 and Figure 1.

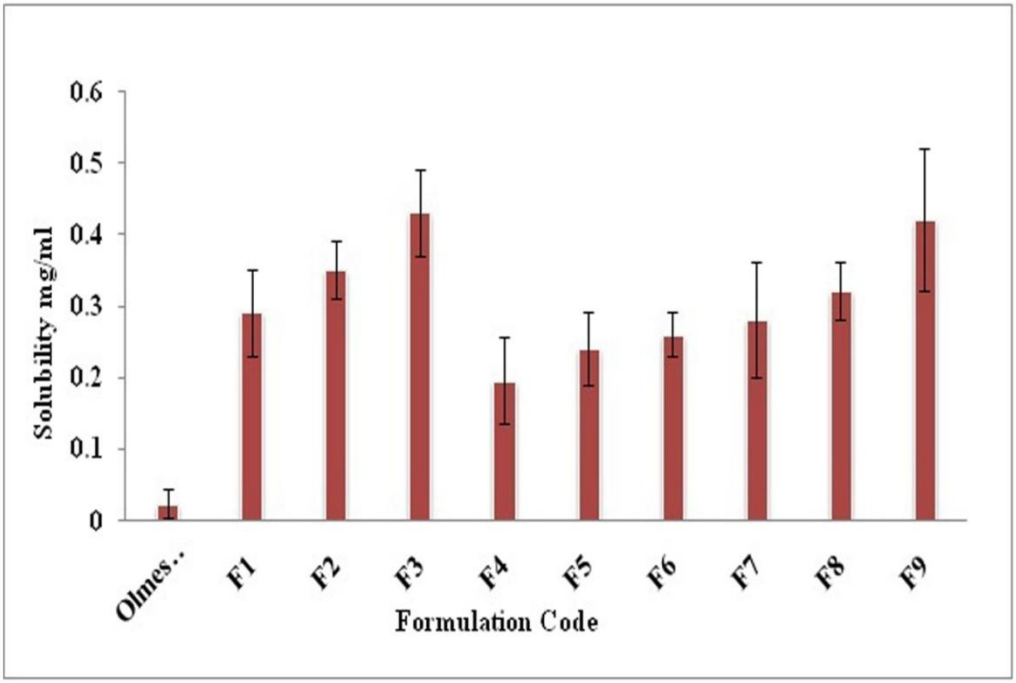

Figure 1: Solubility of Pure Drug and Melt Dispersions in mg/ml

Table 3: Solubility Study of Pure Drug and Melt Dispersions

Formulation code	Solubility mg/ml ± SD
Olmesartan	0.023±0.02
F1	0.290±0.06
F2	0.350±0.04
F3	0.430±0.03
F4	0.195±0.04
F5	0.240±0.005
F6	0.260±0.003
F7	0.280±0.008
F8	0.320±0.004
F9	0.420±0.01

Drug Content

For all batches (F1-F9) drug content was found to be in the range of 93.1±3.2 to 100.9±2.9 which is an acceptable limit. Detailed result is shown in Table 4.

Table 4: Drug Content of Melt Dispersions

Formulation Code	%Drug Content ± SD (n=3)
F1	98±6.1
F2	99±5.05
F3	96±4.1
F4	93.1±3.2
F5	95.1±4.2
F6	96.7±6.2
F7	100.3±1.9
F8	99.1±4.0
F9	100.9±2.9

FTIR Study

Drug and all formulations showed presence of O-H stretching, C=O Carboxylic group stretching, C-N Stretching and O-H in plane Bend. From the IR study of Olmesartan and formulations it was found that there were no considerable changes in the IR peaks of the melt dispersions when compared to pure Olmesartan. 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 melt dispersions showed that no changes have occurred in the 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 absence of any well-defined interaction between olmesartan, vitamin E TPGS and carriers (Aeroperl, Aerosil & Neusilin). FT-IR Spectra of drug and melt dispersion are depicted in Figure 2.

DSC Analysis

The results obtained from Differential Scanning Colorimetry (DSC) showed that olmesartan exhibited a sharp endothermic peak at 188.83°C corresponding to its melting point showing crystalline nature and an exothermic peak at 254.31°C. In case of melt dispersions F2, F5 & F9 broad endothermic peaks were observed at 184.27°C, 181.73°C & 180.71°C and exothermic peaks at 251.27°C, 251.27°C & 247.72°C respectively. In case of melt dispersions broad, disappearing endothermic and exothermic peaks were observed and also decrease in melting point was observed as compared to pure drug. Reduction in intensity and shifting of sharp melting peak of olmesartan could be attributed to complete solublization and decrease in crystallinity of olmesartan in melt dispersion with Vitamin E TPGS as compared to pure Olmesartan. Melt dispersions with Neusilin showed more decrease in intensity and shifting of

endothermic peak which might be due to its porous nature than that of aeroperl 300 pharma and aerosil 200. DSC thermogram of pure drug and melt dispersions are shown in Figure 3.

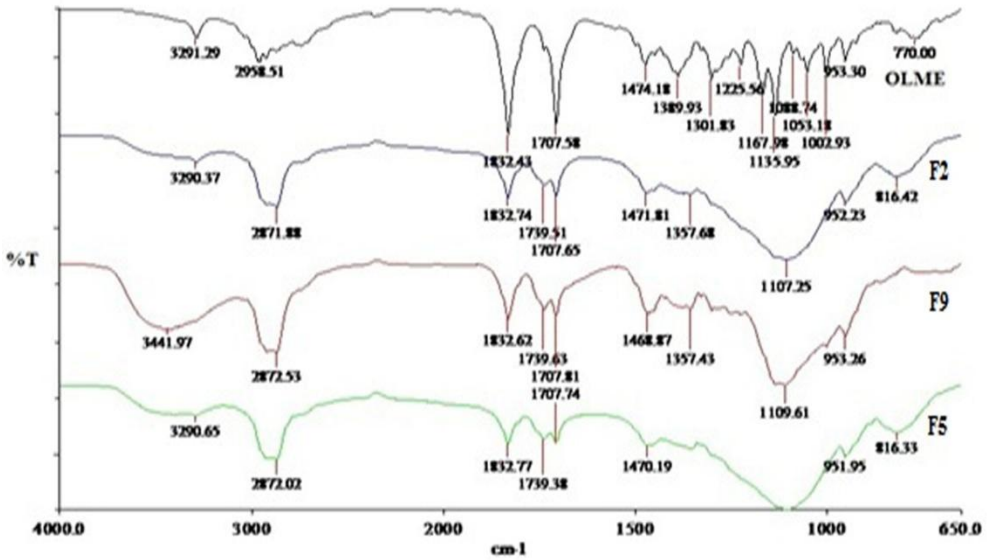

Figure 2: FT-IR spectrum of Pure Drug and Melt Dispersions

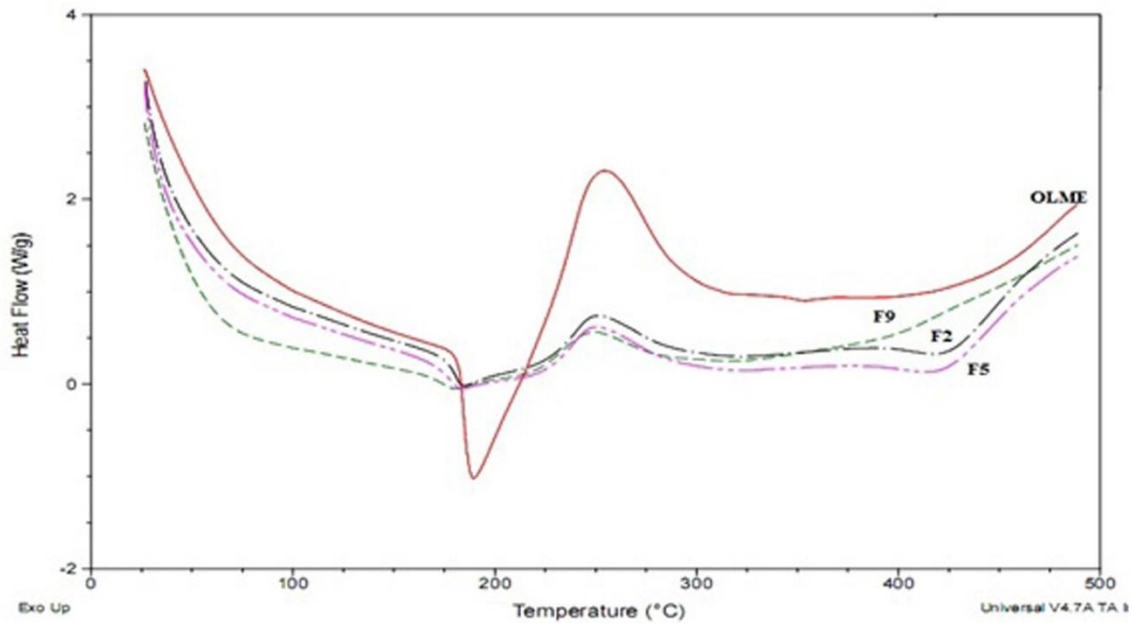

Figure 3: Overlay DSC Thermogram of Pure Drug and Melt Dispersions

XRD Study

From the XRD spectra of olmesartan and formulations, it is clear that the peak intensities are decreased, indicating the change in crystallinity of drug in formulations i.e. amorphous nature of drug. Melt dispersion of batch F9 showed more amorphous nature compare to pure drug, batch F5 and F2 which might be due more porous nature of neusilin molten paste remained as it is in to the pores of carrier. XRD graphs of formulations and pure drug shown in Figure 4.

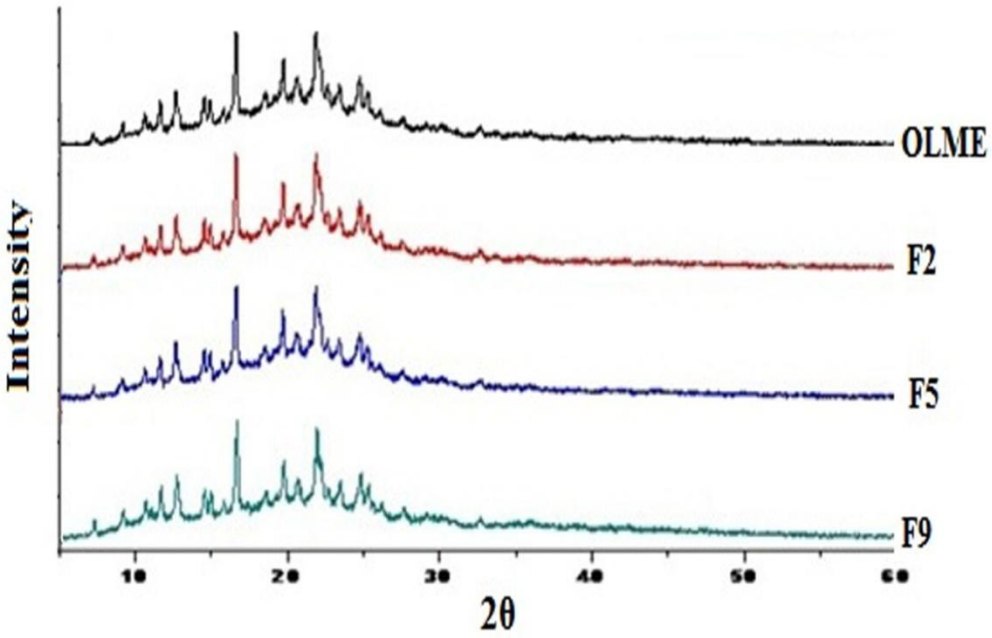

Figure 4: XRD of Pure Drug and Melt Dispersions

In Vitro Dissolution Study

From the in-vitro dissolution study of the pure olmesartan API and melt dispersion formulations it was observed that melt dispersions showed more dissolution rate than pure API. For trial batches F1 to F3 with Aeroperl 300 and Vitamin E TPGS it was observed that the rate of dissolution increased with increase in concentration of Vitamin E TPGS due to increase in solubility. For trials F4 to F6 with aerosil and Vitamin E TPGS it was observed that decrease in dissolution rate with increasing Vitamin E TPGS concentration it may because of the higher concentration. Pure drug showed only 27.1±6.2 % cumulative drug release compared to batch F1 (100.1±4.06). All batches except F3 and F4 showed more than 90% of drug release as compare to pure drug (27.1%) at the end of 60 min (Figure 5).

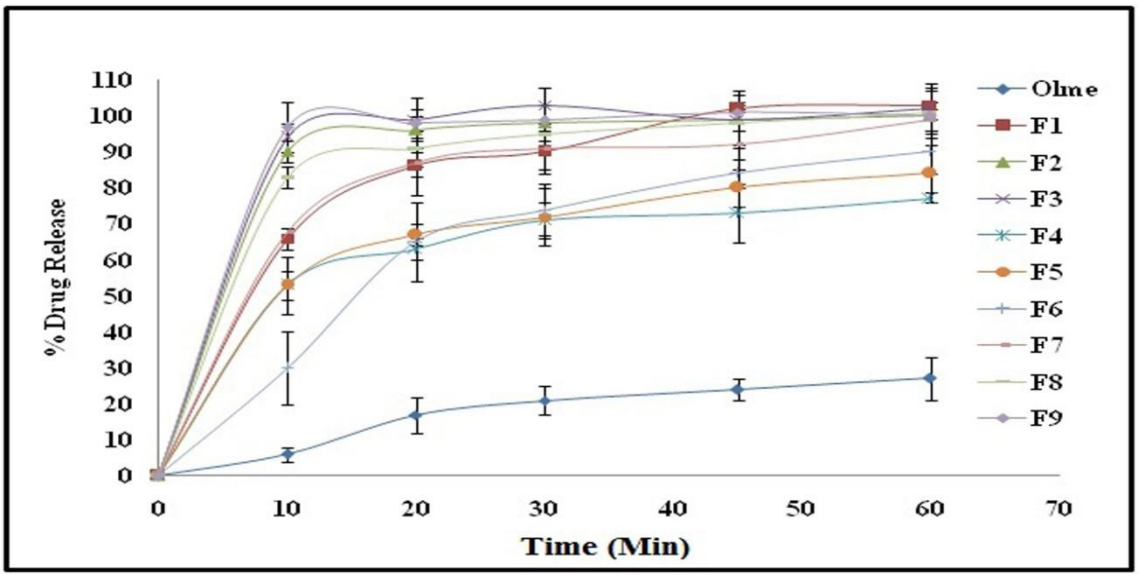

Figure 5: In-Vitro Dissolution of Pure Olmesartan and its Melt Dispersions

Conclusion

In present investigation melt dispersion method for solubility enhancement of olmesartanmedoximil was studied. It was found that the melt dispersions of olmesartan have significantly more solubility and dissolution rate compared to the pure Olmesartanmedoximil. From melt dispersions of olmesartan it was concluded that the formulation F2 containing Aeroperl 300 shows good flow properties and along with good solubility and dissolution rate compared to other formulations. Other formulations like F9 shown highest solubility and dissolution rate but poor flow properties, which may cause content uniformity problem during further development.

Formulation F2 containing API: Vitamin E-TPGS: Aeroperl 300 (1:1:1) ratio can be finalized for further formulation development with other excipients like diluents, disintegrants, lubricants to form tablet dosage form. Melt dispersions prepared with Vitamin E-TPGS has more solubility and dissolution rate than pure drug. So, melt dispersion technique using E-TPGS and Aeroperl 300 can be used to increase bioavailability of poorly soluble drugs.

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