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ENHANCEMENT OF OLMESARTAN MEDOXOMIL DISSOLUTION BY SURFACE SOLID DISPERSION

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ABSTRACT
Olmesartan Medoxomil (OM) is an angiotensin-receptor blocker. Based on the solubility and permeability, (OM) is classified as class II drug according to the biopharmaceutics classification system (BSC), meaning that the drug is poor soluble. This is believed to be responsible for its low bioavailability. Therefore, the objective of this study was to enhance Olmesartan Medoxomil dissolution by surface solid dispersion (solvent evaporation). The drug was precipitated from its ethanolic solution in presence of Aerosil and hydrophilic polymer. The selected polymer was Polyvinyl Pyrrolidone 40T (PVP). Thermal behavior results confirmed reduced drug crystallinity. FTIR spectroscopy indicated drug-excipient compatibility. All formulations showed improvement in drug dissolution compared to pure drug. Surface solid dispersion (solvent evaporation) in presence of hydrophilic polymer is a promising approach for enhancing dissolution rate of poorly soluble drugs.

KEYWORDS: Olmesartan Medoxomil, Polyvinyl Pyrrolidone 40T (PVP), Aerosil 200, enhance dissolution rate.

INTRODUCTION
Oral drug administration has been one of the most convenient and widely accepted routes of delivery for most therapeutic agent.[1,2] Traditionally, oral dosage forms refer to tablets, capsules, and liquid preparations taken orally, swallowed, and transiting the gastrointestinal tract (GIT) for post buccal absorption.[3]

The conventional dosage forms (tablet and capsule) have a wide acceptance of up to 50-60% of total dosage forms.[4] Tablet is still the most popular conventional dosage forms existing today because of ease of self-administration, compact in nature, easy to manufacture and it can be delivered in an accurate dose.[5]

One important drawback of solid dosage forms is the difficulty in swallowing (dysphagia) or chewing in some patients particularly pediatric and geriatric patients.[6]

The Fast Dissolving Tablets were solving this problem due to their disintegration in the oral cavity without the need for water.[7] The time for the disintegration of fast disintegrating tablets is generally considered to be less than one minute resulting in rapid absorption, reduced first-pass metabolism, and also increased bioavailability.

Optimizing the drug dissolution rate is the limiting factor in the formulation of this system.[8, 9]

Olmesartan Medoxomil (OM) is an angiotensin receptor blocker which is employed as an anti-hypertensive agent.[10,11] Based on the solubility and permeability, OM is classified as class II drug according to the biopharmaceutics classification system, meaning that the drug is poor permeable and poor soluble.[12] This is believed to be responsible for its low bioavailability after oral administration with the reported values being as low as 26%.[13,14] Accordingly, researchers utilized different strategies to enhance the dissolution rate of OM as the main tool to improve its oral bioavailability.

The aim of this work is to enhance dissolution rate via Surface Solid Dispersion technique. This was conducted in the presence and absence of hydrophilic polymer.

MATERIALS AND METHODS

Materials

Olmesartan medoxomil was a Gift sample from Apex Pharmaceutical Chemical Company (Cairo, Egypt). Ethanol was purchased from Al Gomhoria Co.(Tanta, Egypt) Polyvinyl pyrrolidone (PVP 40T) and Aerosil were kindly supplied by the Sigma Pharmaceutical industries (Quesna, Egypt).

Methodology

Preparation of drug crystals by surface solid dispersion technique

Table (1) represents the composition of the prepared formulations and their physical mixture. The aim was to prepare drug crystals by surface solid dispersion technique. The precipitation process was done by evaporation of solvent on a water bath in the presence or absence of hydrophilic polymer. The selected polymer was PVP.

The drug/Aerosil/polymer solid dispersion were prepared according to composition of formulations presented in table (1).

The drug was dissolved in the least amount of ethanol (about 30 ml). The resultant liquid was sonicated for 10 min, then Aerosil was added with continuous mixing using glass rode and sonicated for another 10 min. After that PVP was added and the mixture sonicated for another 10 min. The evaporation of solvent occurred on a water bath. The obtained dry powder product was stored in a tightly closed container. The drug/Aerosil/polymer co-precipitate was prepared according to composition of formulation presented in Table (1).

Preparation of physical mixtures

This was achieved by a geometric dry blending of the drug, Aerosil, and polymer as revealed in Table (1).

Table 1: Composition of the prepared formulations and the dissolution parameters.

Formula	Drug (gm)	Aerosil (gm)	PVP (gm)	$\%Q_5$ *	$\%DE_{10}$**	$\%DE_{60}$ ***
Negative Control	0.3	–	–	5.5±1.4	5.86±0.5	22.5±1.4
Positive Control	0.3	–	–	16.5±3.3	15.9±1.8	41.9±3.9
F1	0.3	0.1	_	22.2±3.04	19.9±1.1	49.9±2.3
F2	0.3	0.2	_	55.9±1.4	42.3±0.9	65.7±0.7
F3	0.3	0.1	0.1	31.4±2.1	28.1±1.03	58.6±0.8
F4	0.3	0.1	0.2	43.9±3.4	37.5±3.3	69.7±1.8
PM 1	0.3	0.1	_	10.7±0.2	9.9±0.2	26.6±0.2
PM 2	0.3	0.1	0.1	7.7±0.6	7.1±0.34	23.9±0.8

Negative control: pure unprocessed drug.
Positive control: drug crystals prepared with no additives
*Percentage drug released after 5 minutes
**Dissolution Efficiency after 10 minutes
*** Dissolution Efficiency after 60 minutes

Differential Scanning calorimetry (DSC)

Olmesartan medoxomil, Aerosil 200, PVP and physical mixture of selected formulations were subjected to thermal analysis using differential thermal analyzer (Shimadzu DSC-60-Japan) at the microanalytical unit, Cairo University, to evaluate any possible drug-polymer interaction.

Fourier–transform infrared spectroscopy

For further investigation of the drug physical characteristics, FTIR spectroscopy was used to study the possible interaction between the drug and other components in the formulation. Structural changes and lack of a crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy. Since not all peaks in the IR spectrum are sensitive to crystalline changes, it is possible to differentiate between those that are sensitive to changes in crystallinity and those are not.[8]

Estimation of Drug content

The drug content was determined for all formulations by dissolving an amount equivalent to 50 mg of the drug in a 50 ml volumetric flask using ethanol as solvent, mixed thoroughly, and sonicated for 10 min. The resultant liquid was filtered. The 1 ml of clear solution was suitably diluted to 10 ml ethanol before the spectrophotometric determination of the drug concentration at λ_{max} 258 nm.

In vitro drug release from prepared formulation

Dissolution tests are one of the tests most used in the characterization of drugs and in the quality control of dosage forms.[15]

The dissolution rate of Olmesartan from different formulations (precipitated drug crystals and physical mixtures) was determined using the USP II dissolution apparatus (Copley, NG 42 JY, Nottingham, UK). The unprocessed pure drug was used as a control. The paddle rotation was adjusted at 50 rpm and the dissolution

medium (900 ml phosphate buffer pH (6.8 ± 0.5) was maintained at 37 ºC ±0.5 ºC. After loading the drug (40 mg) or an equivalent amount of all tested formulations, an aliquot of 5 ml each were collected at predetermined time intervals as 5, 10, 15, 30, 45, and 60 minutes and replaced with fresh dissolution medium. The samples were immediately filtered through a 0.45 µm Whatman membrane filter before being suitably diluted with the fresh dissolution medium and analyzed spectrophotometrically at λ_{max} 258 nm.[16]

Statistical analysis

All experiments were conducted in triplicates and statistical analysis employed Student t-test. Results were quoted as significant where P-value is less than 0.05.

RESULTS AND DISCUSSION

Differential Scanning calorimetry (DSC)

Figure (1) shows The DSC thermograms of pure Olmesartan Medoxomil, processed drug, Aerosil 200, PVP, F2 and F4. The DSC thermograms of pure olmesartan medoxomil which displays a two-peak, the first of which was a sharp endothermic peak having an onset of 175.09ºC, end of 186.61 ºC and a T_m of 181.36 ºC[17] This sharp peak can be attributed to the melting transition of the drug and reflects its crystalline nature.[13]

High phase transition temperature (Tm) and peak sharpening would indicate a high degree of the crystalline structure of a substance.[18]

The second exothermic peak was very broad and had a Tm of 234.77ºC and can be explained on the base of drug decomposition.

The DSC thermogram of Olmesartan Medoxomil was typical of crystalline substance, exhibiting a sharp endothermic peak at 181.36 ºC this result was close to the result obtained by Kamble et al.,2014; Ghadage et al., 2016.[19,20]

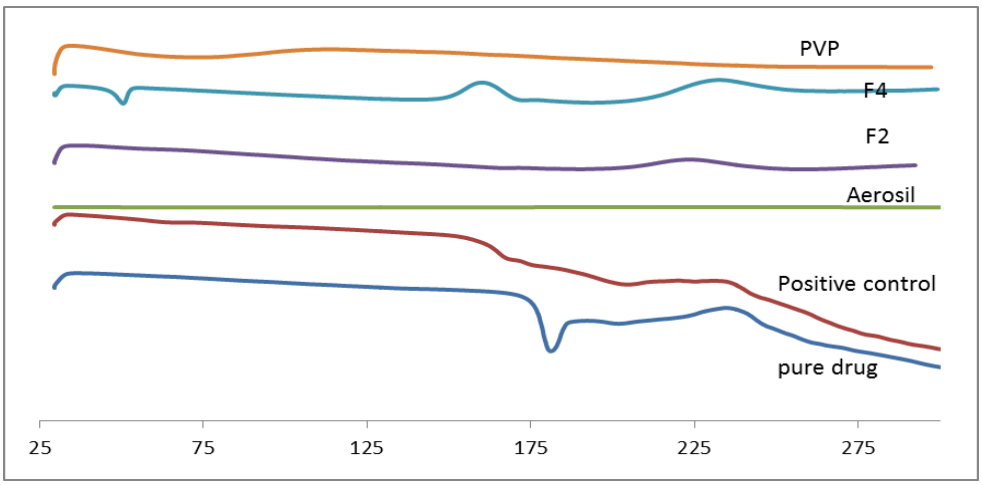

Figure 1: DSC of pure Olmesartan Medoxomil, processed drug (positive control), Aerosil, F2, F4 and PVP.

The DSC thermograms of drug crystal which was prepared by surface solid dispersion in absence of any additives using ethanol as a solvent, showed that the characteristic peak of Olmesartan was abolished, indicating a reduction in drug crystallinity. A second peak showed T_m 236.18C due to the decomposition of the drug. This pattern is in agreement with Ghadage et al., 2016.[20]

The thermogram of aerosil 200 showed the characteristic pattern of an amorphous chemical with no endothermic or exothermic peak being recorded. This pattern is in agreement with El-Gizawy et al., 2015.[21]

The DSC thermograms of pure PVP showed a broad endothermic peak starting at 38.46 ºC and ending at 115.54 ºC. This broad endotherm can be attributed to the evaporation of water and is characteristic of the amorphous PVP. This was in agreement with El Maghraby et al., 2014.[22]

Precipitation of the drug ethanolic solution in presence of Aerosil 200 as a carrier produced drug crystal showing the main endothermic peak at 175.92 ºC . The peaks are shifted to lower T_m with a reduction in intensity and showed some broadening The exothermic peak due to decomposition were also shifted to high T_m.

The DSC thermograms of olmesartan crystals which was prepared by surface solid dispersion in presence of higher ratio of PVP (F4) produced thermal behavior in which the melting transition of the drug was absent with the degradation exotherm of the drug being noticed at 233.33°C in agreement with Abdelquader et al., 2019.[13]

In DSC, the recorded changes in the main endothermic peak was due to possible partial transformation to the amorphous state or possible polymeric stabilization by surrounding each drug particle.[23, 24]

Fourier–transform infrared spectroscopy (FTIR)

The spectrum of unprocessed Olmesartan Medoxomil and that prepared by precipitation are shown in figure 2,

which reveales a peak at 3430 cm^{-1} for OH stretching vibration, at 3040 and at 3004 cm^{-1} for aromatic C-H stretching and at 2972 and 2930 cm^{-1} for aliphatic C-H stretching. The peaks corresponding to the carbonyl group depended on its nature with lactone C=O dominating at 1832 cm^{-1} and ester C=O appearing at 1708 cm^{-1}. The C=N stretching was noticed at 1602 cm^{-1} with N=N stretching being revealed at 1533 cm^{-1}. The C-O stretching was shown at 1169 and 1136 cm^{-1} for the lactone and ester groups, respectively. The peaks corresponding to the N-H wagging were shown as intense and small peaks which were recorded at 761 and 742 cm^{-1}, respectively in agreement with Abdelquader et al., 2019.[13]

The FTIR spectra of aerosil showed a very broad absorption band in the range of 3700 and 3100 cm^{-1}. This peak corresponds to its hydrogen bonding of the adsorbed water or water of crystallization and the silica oxygen. It was also attributed to chelation. The presence of water of crystallization has also revealed a peak due to H-O-H bending vibrations at 1631 cm^{-1}. The Si-O was manifested by its symmetric stretching at 1110 cm^{-1} with its asymmetric vibrations being evident at 808 and 473 cm^{-1} in agreement with Essa et al., 2017; Rus et al., 2012.[8,25]

The FTIR spectrum of pure PVP (Figure 2) was characterized by its carbonyl group which was detected at a lower frequency (1657 cm^{-1}) due to hydrogen bonding with the adsorbed water. The hygroscopic property of PVP was evidenced as broad band for the hydrogen-bonded -OH group at 3445 cm^{-1} in agreement with Essa et al., 2017; El Maghraby et al., 2014.[8,22]

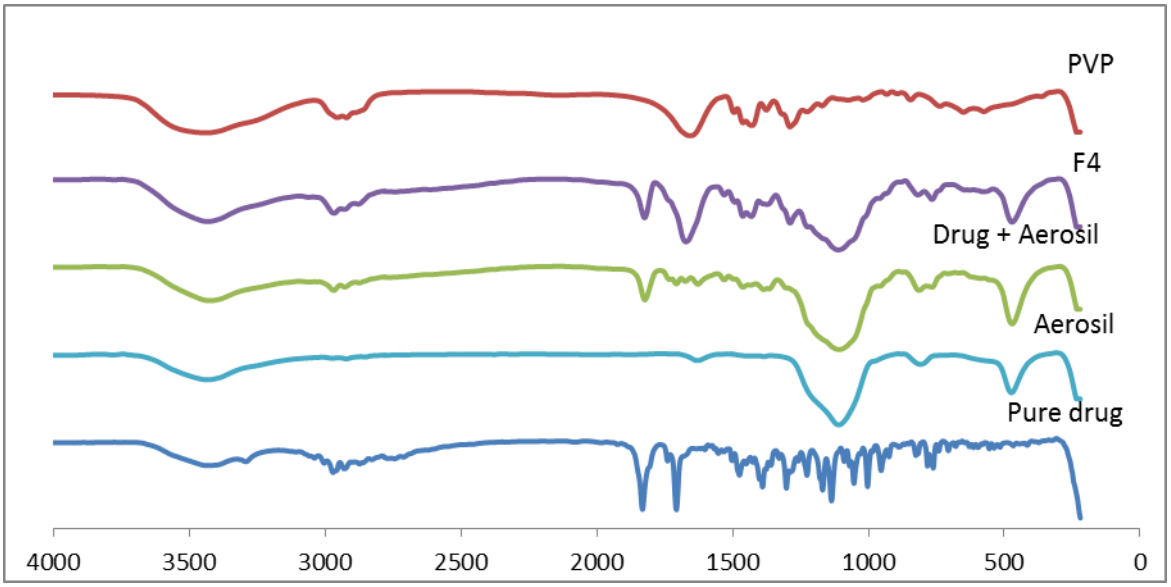

Figure 2: FTIR spectra of unprocessed Olmesartan Medoxomil, Aerosil, drug + aerosil, F4 and PVP.

FTIR spectra of all tested formulations revealed the main absorption bands of Olmesartan Medoxomil and showed no significant changes compared with the spectrum of pure drug. This suggests the absence of any interaction between PVP, Aerosil, and drug.

Drug content

The drug content were in the range of 98.5 – 101.4 % w/w, for the prepared formulations which is acceptable from USP and indicates good recovery of the drug after precipitation.

In vitro drug release from prepared formulations

The dissolution parameters represented as percentage drug released after 5 minutes (Q5), % dissolution efficiency after 10 minutes (DE_{10}) and % dissolution efficiency after 60 minutes (DE_{60}) are revealed in a table (1).

Table (1) and figure (3, A) shows the dissolution of a pure unprocessed drug (negative control), drug crystals prepared with no additives (positive control), and drug crystals in presence of Aerosil in different ratios with their corresponding physical mixtures in 0.1 N phosphate buffer solution. Data of unprocessed drug showed slow drug dissolution with a Q_5 and DE_{60} of about 5.5% and 22.5%, respectively. This poor dissolution may be due to the hydrophobic nature of the drug.[26]

For positive control, precipitated drug alone in absence of any additives, there was a noticeable increase in drug dissolution as evidenced by higher Q5 and %DE60 of 16.5% and 41.9 %, respectively, which is considered a significant increase in dissolution efficiencies ($P<0.05$). This may result from increased surface area by reducing particle size and/or possible formation of amorphous structure. Preparation of Olmesartan Medoxomil by surface solid dispersion using Aerosil 200 in different ratios (F1, F2) produced drug crystals significantly higher dissolution rate compared with the unprocessed drug ($P <0.05$). This was indicated from the initial drug released (Q5) of about 22.24% and 55.97% of the total

dose from F1 and F2, respectively. This may due to increased drug wettability and possible adsorption of drug particles to carrier during the mixing process.[26] Thus increasing surface area Such moderately rapid release pattern is advantageous for poorly soluble drug especially those suffering from first-pass metabolism.[27]

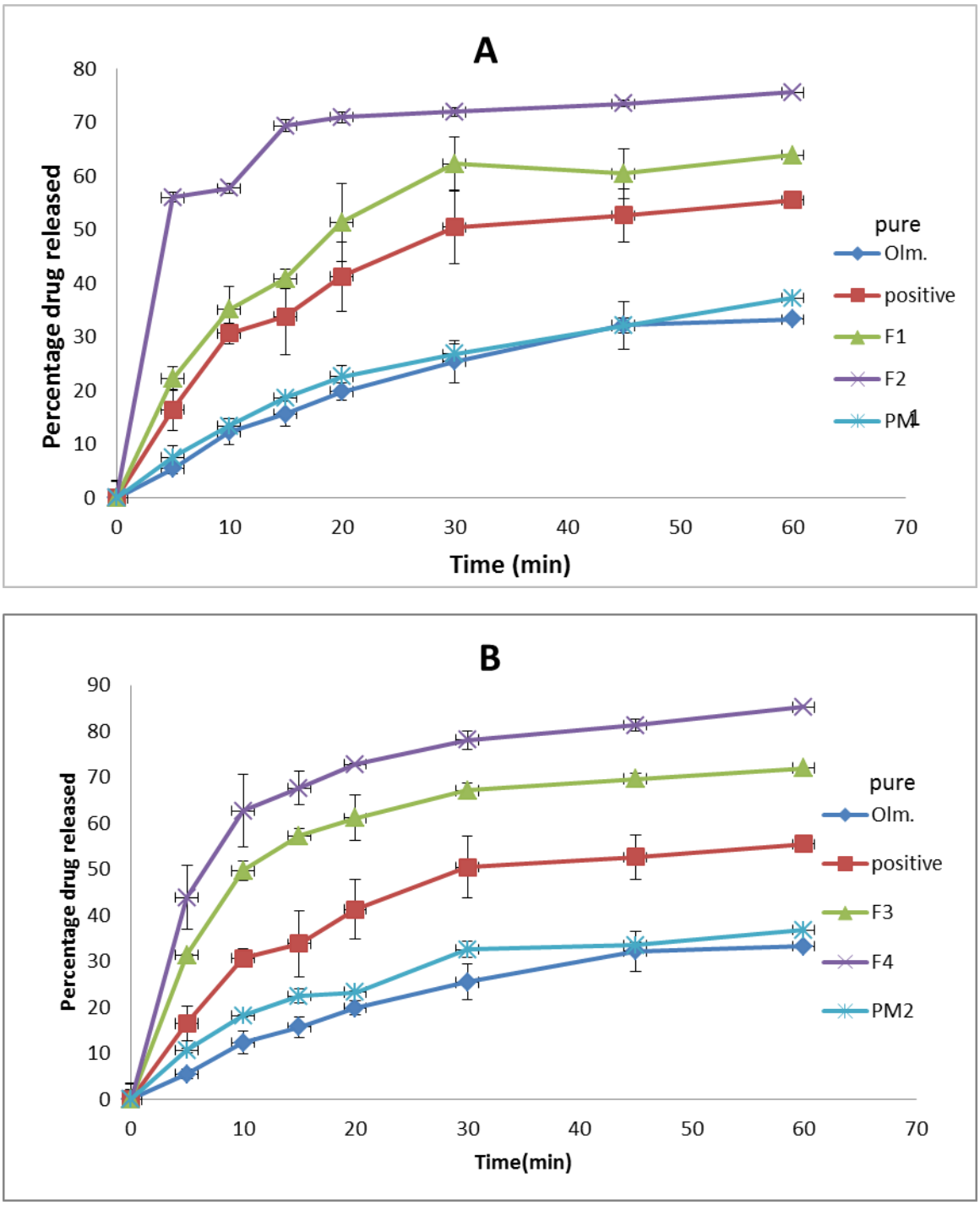

Figure 3: In vitro dissolution profiles of Olmesartan Medoxomil from different crystals prepared in presence of Aerosil (A), PVP (B) and their corresponding physical mixtures in 0.1 N phosphate buffer solution.

Table (1) and figure (3, B) show the dissolution of the pure drug, positive control, and drug crystals in the presence of PVP in different ratios with their corresponding physical mixtures in 0.1 N phosphate buffer solution. The formulation F3 and F4 showed a significant increase in drug dissolution in 0.1 N phosphate buffer solution ($P<0.05$) with a Q_5 of about 31.4% and 43.9%, DE60 of about 58.59, and 69.67, respectively. This higher dissolution was due to the possible formation of an amorphous structure with subsequent enhancement in the dissolution rate as suggested by Differential Scanning Calorimetry. The corresponding physical mixtures showed a significant increase of drug dissolution ($P<0.05$) with a Q_5 of about

10.7% and DE60 of about 26.6 , This may due to increase in surface area exposed to dissolution medium.

CONCLUSION

Surface solid dispersion technique in presence of hydrophilic polymer has improved the dissolution rate of Olmesartan Medoxomil. Adsorption of polymer chains and amorphous drug micro particles on the large surface area of the carrier explains such enhancement. This is expected to increase drug bioavailability by increase solubility which encourage completion of further studies on this drug.

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