

IMPROVEMENT OF PHARMACEUTICAL PROPERTIES OF OLMESARTAN BY RECRYSTALLIZATION TECHNIQUE

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ABSTRACT

In the present research work an attempt has been made to improve the aqueous solubility and dissolution properties of Olmesartan medoxomil (OLM) a poorly soluble anti hypertensive drug by the recrystallization technique. The recrystallized OLM products were evaluated for solubility and *in vitro* dissolution properties. The water solubility of methanol (MET), ethanol (ETH), acetone (ACE) and acetonitrile (ACN) recrystallized products of OLM is significantly higher when compared to untreated OLM. Similarly, the dissolution rate constant (k^{-min}) values for recrystallized OLM products were superior when compared to untreated OLM and are in the order of Acetonitrile > Methanol > Ethanol \geq Acetone > OLM.

KEYWORDS: Olmesartan medoxomil, recrystallization, solubility, dissolution studies

INTRODUCTION

The enhancement of oral bioavailability of sparingly water soluble drugs remains one of the most challenging aspects of drug development. Together with the permeability, the solubility characteristics of a drug are a key determinant of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Crystallization is the natural/artificial process for the formation of solid crystals from a uniform solution. It is the formation of solid crystals from a homogeneous solution. Since the structural properties of a solid material (e.g. polymorphism) can dramatically affect the physicochemical properties and solubility characteristics (i.e. dissolution rate, for example), monitoring and controlling the isolation of solids for the various applications through crystallization is of paramount interest. Crystals can be modified by recrystallizing the drug under different conditions, which will affect physical and physicochemical properties such as melting point, solubility, true density, dissolution profile, flowability, and tableability (Hlaeblian, 1969)

Olmesartan medoxomil (OLM) is a potent, highly selective and orally active antihypertensive drug. In order to afford therapeutic efficacy, OLM needs to have a quick onset of action. However, OLM is sparingly soluble in aqueous fluids and its absorption is thus dissolution rate limited. The poor aqueous solubility and hence the undesirable dissolution properties of a drug like OLM often results in variable oral bioavailability (29%). Several reports have been published that have focused on improving the dissolution properties of OLM. Most or all of these studies have involved cyclodextrin inclusion complexation and solid dispersion and other solubilization technologies for improving the solubility and dissolution properties of OLM. So far, no reports have been published on the application of recrystallization technique in order to improve the pharmaceutical properties of OLM, such as aqueous solubility and *in-vitro* dissolution characteristics. Hence, in the present investigation an attempt has been made to improve the aqueous solubility of OLM by investigating the recrystallization of OLM from different organic solvents, and evaluating the recrystallized drug for its physicochemical characteristics and *in vitro* dissolution properties.

MATERIALS AND METHODS

OLM was provided by Mylon Laboratories Ltd (Hyderabad, AP, India). Hydrochloric acid, sodium hydroxide, sodium acetate, potassium dihydrogen phosphate, boric acid, potassium chloride, glacial acetic acid, methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, ethyl acetate, dichloromethane, tetra butyl methyl ether, N,N-dimethyl formamide, tetra hydro furan were purchased from Loba Chemie Pvt, Ltd., (Mumbai, MS, INDIA).

Preparation of OLM recrystallization products: 2 g of OLM was added to 5mL of a specific pure organic solvent in a 15 mL beaker and heated slowly to 45°C to afford a supersaturated solution. The resulting mixture was then cooled down to room temperature. The resulting recrystallized drug was then collected, dried at 40°C for 15min, and passed through a #80 sieve to afford a product of uniform particle size. The powdered drug was packed in glass bottles and stored in a dessicator until experimentation.

Analytical procedures: UV-VIS spectrophotometric analytical method was utilized in the present investigation. UV-VIS spectrophotometric analysis (UV-Double Beam Spectrophotometer, UV-1800, Shimadzu, Japan) utilized absorbance at 258nm in a methanol stock solution of OLM.

Solubility studies: Excess of OLM and its recrystallized products (50mg) were added to 5mL of distilled water in 10mL stoppered conical flasks and the mixtures were shaken for 24 hours at room temperature on a rotary flask shaker. After 24 hours of shaking, 0.5mL aliquots were withdrawn at different time intervals and filtered immediately using a 0.45 μ nylon disc filter. The filtered samples were diluted if necessary and assayed for OLM content utilizing the UV- spectrophotometric method. Shaking was continued until three consecutive estimations afforded consistent results. All solubility experiments were run in triplicate.

In-vitro dissolution studies: *In vitro* dissolution studies of OLM and its recrystallized products were carried out in 900mL of pH 6.8 phosphate buffer using USP XXI type 2 (paddle method) Dissolution Rate Test Apparatus (DISSO 2000, Lab India). The powder samples were dispersed in dissolution medium. Samples equivalent to 20mg of OLM, a paddle speed of 50 rpm and a temperature of $37 \pm 1^{\circ}$ C were used in each test. A 5mL aliquot was withdrawn at different time intervals, filtered using a 0.45 micron nylon disc filter, and replaced with 5mL of fresh dissolution medium. The filtered samples were suitably diluted if necessary and assayed for OLM content by measuring the absorbance at 258nm. Each dissolution experiment was conducted in triplicate.

RESULTS AND DISCUSSION

Preparation of OLM recrystallized products: OLM was recrystallized from a variety of organic solvents that were selected based upon their boiling points. Solvents with relatively low boiling points were selected, since the lower the boiling point of the solvent; the faster will be the drying process. The process of recrystallization of OLM in different solvents took different duration of time to produce a dry product, though all the samples were dried under similar temperature and moisture conditions. Among the entire solvents used acetonitrile, methanol and ethanol and acetone gave dry product quickly in few minutes even at room temperature.

Solubility studies: Solubility studies of OLM and its recrystallized products were carried out in water and the data was shown in Fig.1. The solubility of untreated OLM in water is 0.010 ± 0.003 mg/mL. A 17, 15, 14 and 13 fold increase in the solubility of OLM in water when compared to the untreated OLM was observed with acetonitrile (ACN), methanol (MET), ethanol (ETH) and acetone (ACE) recrystallized products, respectively. The increase in the solubility may be due the increase in the wettability and decrease in crystallinity of OLM with the recrystallized products. Based on the results obtained with the water solubility studies, acetonitrile (ACN), acetone (ACE) Methanol (MTH), Ethanol (ETH) recrystallized OLM products were selected for further physicochemical characterization and *in vitro* dissolution studies.

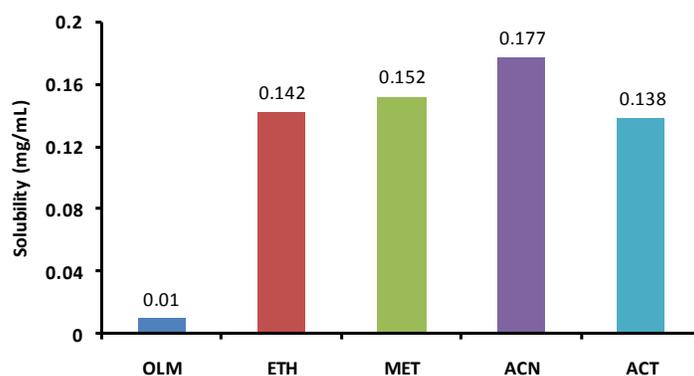


Figure.1.OLM and its recrystallized products solubility data

In-vitro dissolution studies: The dissolution studies were performed to analyze the solubility characteristics of the recrystallized OLM products and to compare the results obtained with that of untreated OLM. The *in vitro* dissolution studies were performed for all the samples using 6.8 pH buffer as the dissolution medium to assess various dissolution properties such as drug percent released at 10 min (DP10) and 120min (DP120), time to

release 50% of OLM, and first order rate constants. The release profiles are shown in the Fig 2 and data are given in Table.1.

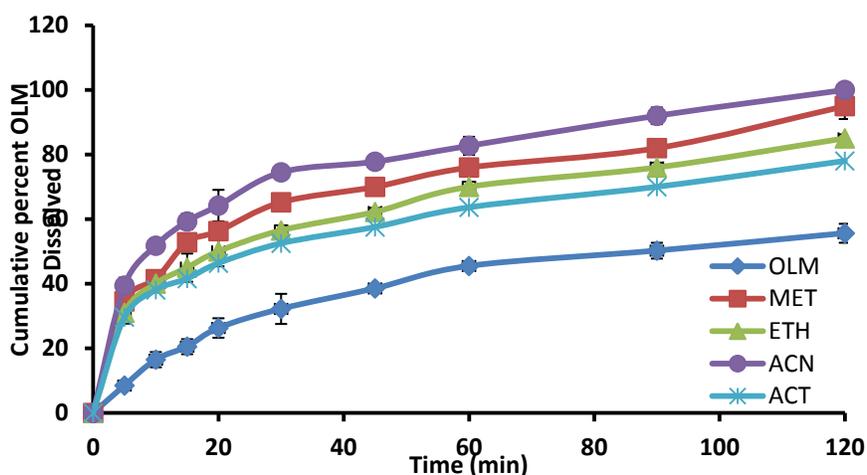


Figure.2. In-vitro dissolution profiles of OLM and its recrystallized products

The $t_{50\%}$ values for OLM and its recrystallized products ACN, MET, ETH and ACE were 90, 9, 14, 20 and 25 min respectively. The $t_{50\%}$ values for ACN, MET, ETH and ACE were significantly lower ($P < 0.05$) when compared to the untreated OLM and are in the order of OLM > ACE > ETH > MET > ACN (Table I). The DP10 values for OLM and its recrystallized products ACN, MET, ETH and ACE were 16.52, 51.78, 41.43, 40.05 and 38.07 respectively, whereas, DP120 values were 55.64, 100, 95, 85 and 78 respectively. The DP10 and DP120 values for are significantly higher ($P < 0.05$) when compared to pure OLM. The DP10 and DP120 values are in the order ACN > MET > ETH > ACE > OLM. The first order rate constant ($k^{-\text{min}}$, 0-60 min) values for ACN, MET, ETH and ACE were significantly higher ($P < 0.05$) when compared to pure OLM and are in the order ACN > MET > ETH > ACE > OLM. A 2.52, 2.25, 1.75 and 1.50 fold increase in 'k' values respectively was observed for ACN, MET, ETH and ACE when compared to pure OLM.

Overall, it can be concluded that the increased dissolution properties of the recrystallized OLM products is a result of various factors: (i) an increase in solubility, (ii) improved wettability, and (iii) a decrease in crystallinity. For BCS class II and IV compounds drug absorption can often be improved by rendering the drug amorphous when low solubility presents a significant barrier for oral absorption (Amidon, 1995). Thus, the utilization of metastable solid forms, such as amorphous phases, and amorphous solid dispersions, can be a powerful tool in combating the poor ADME profiles of many modern drug candidates (Hancock, 2001). Selecting the appropriate solid forms for development is thus critical to the facile development of high quality products.

CONCLUSION

Hence, utilizing recrystallization technique, the solubility and dissolution rate of OLM was increased. Among the solvents used for recrystallization technique, acetonitrile, acetone, methanol and ethanol showed improved aqueous solubility and dissolution properties and potentially therapeutic efficacy.

ACKNOWLEDGEMENTS

The authors are thankful to the Siddhartha Academy of General and technical Education, Vijayawada, AP. INDIA for providing the necessary facilities to carry out this research work.

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