Original Article

Studies on inclusion complex as potential systems for enhancement of oral bioavailability of olmesartan medoxomil

Abstract

Background: Olmesartan medoxomil (OLM), an anti-hypertensive agent administered orally, has absolute bioavailability of only 26% due to the poor aqueous solubility (7.75 μg/ml). Inclusion complexation with cyclodextrins (CD) has been reported to increase the aqueous solubility of various compounds. **Aim:** The present investigation aimed to enhancing the oral bioavailability of OLM by inclusion complexation with 2-hydroxypropyl-β-cyclodextrin (HP-β-CD). **Materials and Methods:** The inclusion complexes with HP-β-CD were prepared using two different methods, viz., physical mixture and kneading. The prepared complexes were characterized for various parameters such as drug content, aqueous solubility, dissolution study, *in vitro* diffusion, intestinal permeability and stability study. The formation of the inclusion complex was confirmed by differential scanning calorimetry, X-ray diffraction, and Fourier transform infrared spectroscopy. **Results:** The solubility, dissolution, diffusion rate, and intestinal permeability of the prepared complexes were found to be significantly higher than that of the plain drug. Among the two methods used for formation of inclusion complex, KN method gave higher solubility rates and hence is a better method when compared with PM. **Conclusion:** The approach seems to be promising in improving the oral bioavailability of OLM.

Key words:
Bioavailability enhancement, differential scanning calorimetry study, fourier transform infrared study, 2-hydroxypropyl-β-cyclodextrin, inclusion complex, olmesartan medoxomil, X-ray diffraction study

Introduction

Oral administration is the most preferred route of drug delivery. It shows certain advantages such as convenient route of administration, possibility of self-administration, and comparatively simple and inexpensive manufacturing. Oral route thus offers an attractive way of drug administration. However, oral delivery of 50% of drugs is hampered because of the high lipophilicity of the drug itself. Every 4 of 10 new candidate drugs have poor water solubility, and the oral delivery of such drugs is frequently associated with implications of low bioavailability, high intra- and intersubject variability, and lack of dose proportionality.[1] Poor aqueous solubility of a drug is in most cases associated with poor bioavailability. The contents of gastrointestinal tract are aqueous and hence a drug having poor aqueous solubility has a low saturation solubility, which is typically correlated with a low dissolution velocity, resulting in poor oral bioavailability as only the dissolved drug can be absorbed through the gastrointestinal mucosa.[2]

A limiting factor for *in vivo* performance of poorly water-soluble drugs, following oral administration, is their resistance to being wetted by and dissolved into the fluid in the gastrointestinal tract. About 10% of the present drugs are poorly soluble, about 40% of the drugs in the pipeline possess a poor solubility, and even 60% of drugs

Access this article online	
Website: http://www.cysonline.org	Quick Response Code
DOI: 10.4103/2229-5186.98685	

Hetal Paresh Thakkar, Bindesh Vishnubhai Patel, Mayur Prakashbhai Parmar, Nirav Pravinkumar Chauhan, Arpita Ashokbhai Patel

Department of Pharmacy, Centre of Relevance and Excellence in New Drug Delivery System, Shri G.H Patel Building, Donor's Plaza, Opposite University Main Office, The Maharaja Sayajirao University of Baroda, Fatehgunj, Vadodara, Gujarat, India

Address for correspondence:
Dr. Hetal P. Thakkar,
Department of Pharmacy, Centre of Relevance and Excellence in New Drug Delivery System, Shri G. H. Patel Building, Donor's Plaza, Opposite University Main Office, The Maharaja Sayajirao University of Baroda, Fatehgunj, Vadodara - 390 002, Gujarat, India.
E-mail: hetal_thakkar11@yahoo.com

coming directly from synthesis have a solubility below 0.1 mg/ml.[3] Low bioavailability is the most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs. Increasing the solubility and dissolution rate of poorly water-soluble drugs is thus important for enhancing bioavailability.

The approaches used for improving the solubility and dissolution velocity of the drugs include physical modifications such as particle size reduction, modification of the crystal habit, drug dispersion in carriers, and inclusion complexation and chemical modifications such as change in pH of system and salt formation. The formulation-based approaches include the use of solvent mixtures, co-solvents and solubilizer, and hydrotrophy. Most of the techniques used for solubility and dissolution rate enhancement except particle size reduction require large number of additives and hence are not feasible as evidenced by very less number of marketed products based on these approaches.[4,5]

Out of various available approaches, inclusion complexation is one of the interesting approach for increasing solubility and dissolution rate of poorly bioavailable drugs. Cyclodextrins (CD) and their derivatives have been used as host for inclusion complex to increase water solubility, dissolution rate, and bioavailability of lipophilic drugs for oral delivery. CD has a hydrophilic exterior and a hydrophobic internal cavity. This cavity enables CD to complex guest drug molecules and hence alters the properties of the drugs. This is a so-called "specific approach," that means the solubility of a molecule can be increased if it "matches" to the requirements of the delivery system (e.g., a molecule needs to fit into the cavity of a CD ring).[6,7] The chemical structure, shape, and properties of different type of CD complexes are shown in [Figure 1 and Table 1], respectively.

In addition, CD have been used to reduce or prevent gastrointestinal or ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent drug–drug or drug–additive interactions, or even to convert oils and liquid drugs into microcrystalline or amorphous powders. Among the CDs available, hydroxypropyl-β-cyclodextrin (HP-β-CD) has shown superior results when compared with β-CD, as reported by several researchers.[8]

OLM is a selective AT1 subtype angiotensin II receptor antagonist that is approved for the treatment of hypertension.[9] OLM dose dependently reduces blood pressure through arterial vasodilatation and reduced sodium retention, as do other angiotensin receptor blockers.[9]

It is a prodrug that is rapidly de-esterified during absorption from the gastrointestinal tract to produce an active metabolite, olmesartan. Clinical trials in hypertensive patients revealed excellent pharmacological actions and a good tolerance without serious adverse effects.[9] Aqueous solubility of OLM is 7.75e-03 g/l.[9] Its marketed product Benicar is available in the form of tablet. Oral bioavailability of this tablet formulation is only 26% in healthy humans due to low aqueous solubility.[9,10] The unabsorbed drug leads to gastrointestinal side effects such as abdominal pain, dyspepsia, gastroenteritis, and nausea. Thus, in the present investigation, an attempt was made to increase the aqueous solubility of OLM by preparing its inclusion complex, which in turn is expected to increase its oral bioavailability.

Table 1: Properties of different type of cyclodextrins

Type of CD	Cavity diameter A°	Molecular weight	Solubility (g/100ml)
α-CD	4.7-5.3	972	14.5
β-CD	6.0-6.5	1135	1.85
Gamma-CD	7.5-8.3	1297	23.2
δ-CD	10.3-11.2	1459	8.19

CD – Cyclodextrins

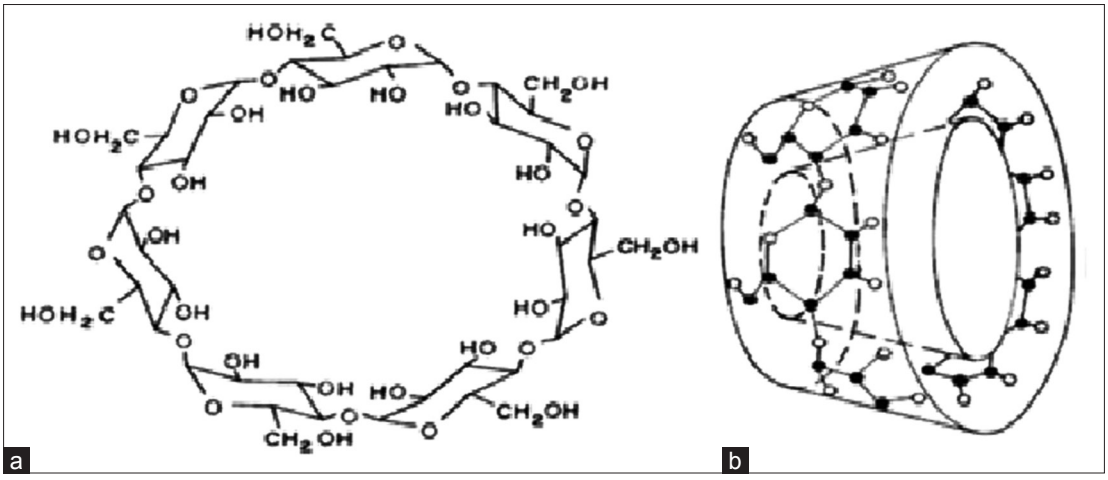

Figure 1: The chemical structure (a) and the toroidal shape of the cyclodextrin molecule

Materials and Methods

OLM was obtained as a gift sample from Cipla Ltd., India; poloxamer 407 from BASF, Germany; HP-β-CD from Himedia, India; methanol from S.D. fine chemicals, India; sodium lauryl sulfate (SLS) from S.D. fine chemicals, India; mannitol from Loba Chemie Pvt. Ltd., India; and polytetrafluoroethylene (PTFE) syringe filter from Whatman Inc., Clifton, NJ. Phosphate buffer pH 6.8 and 7.4 were freshly prepared in laboratory as per I.P. 2007, with the reagents all of analytical reagent grade.

Phase-solubility study

Phase-solubility studies were performed by the method of Higuchi and Connors.[9] OLM, in constant amounts (10 mg) that exceeded its solubility, was transferred to a centrifuge tube containing 10 ml of aqueous solution of HP-β-CD at various molar concentrations (0, 2.0, 4.0, 6.0, 8.0, and 10.0, 12.0, 14.0 mM). The contents were stirred on mechanical stirrer for 48 hours at 50 rpm. The time duration was fixed based on pilot experiment and found to be sufficient to achieve equilibrium of mixture. After reaching equilibrium, samples were centrifuged and supernatant was filtered through a 0.22-μm membrane filter, suitably diluted and analyzed spectrophotometrically for drug content at 256 nm with UV/Visible spectrophotometer (Model:1700, Shimadzu, Japan).[9] Solubility studies were performed in triplicate. The apparent 1:1 stability constant K_s was calculated from the phase-solubility graph using the following equation:

$$Ks = \frac{\text{Slope}}{\text{So}\,(1 - \text{slope})}$$

where S_o is the solubility of OLM in the absence of HP-β-CD.

Preparation of CD inclusion complex[9]

- OLM and HP-β-CD were sieved through 100 # before their use. A complex of HP-β-CD with OLM was prepared in the molar ratio of 1:1 by different methods mentioned below. Physical mixture (PM): PM of HP-β-CD and OLM were prepared by simply mixing powders with a spatula for 15 min and then sieved through 100 #.
- Kneading (KN) method: for preparation of complex by KN method, the HP-β-CD and OLM were taken in 1:1 molar ratio. The HP-β-CD was triturated in a mortar with small quantity of water to obtain a homogeneous paste. OLM was then added slowly while grinding; the mixtures were then ground for 1 hour. During this process, an appropriate quantity of water was added to the mixture to maintain a desired consistency. The pastes were dried in an oven at 45–50°C for 24 hours. The dried complexes were pulverized and then passed through 100 # sieve.

Determination of drug content in complexes

The samples of complex prepared by PM and KN were assayed for OLM content by dissolving a fixed amount of the complex in methanol and analyzing for the OLM content spectrophotometrically at 256 nm.[10]

Aqueous solubility study

The aqueous solubility of compounds, i.e., pure drug powder and OLM and HP-β-CD inclusion complex, were determined in distilled water. Solubility was measured by shaking a well-powdered or well-dispersed solute in excess (10 mg) with water (100 ml) until equilibrium was attained. Solute and solvent were placed in stoppered centrifuge tube and agitated continuously for 24 hours. After 24 hours, the solution was filtered through a 0.22-μm membrane filter, suitably diluted, and analyzed spectrophotometrically for drug content at 256 nm (UV/visible spectrophotometer). By using the calibration curve, aqueous solubility was determined.

Infrared spectroscopy study

The infrared (IR) spectra of bulk OLM powder and HP-β-CD inclusion complexes prepared by PM and KN were obtained using a Shimadzu FTIR-8400S spectrophotometer with IR solution software (Shimadzu). The samples were prepared by grinding a small amount of the dried sample and the corresponding amount of potassium bromide (2/98 w/w) in an agate mortar. Data were collected over a spectral region from 4000 to 650 cm^{-1} with resolution of 4 cm^{-1} and 100 scans.

X-ray diffraction pattern

The X-ray diffraction (XRD) studies of bulk OLM powder and HP-β-CD inclusion complexes prepared by PM and KN were carried out using X-ray diffractometer (Brucker AXS, D8 advanced, Germany) at ERDA (Electrical Research and Development Association, Baroda, Gujarat).

Differential scanning calorimetry

The differential scanning calorimetry (DSC) thermograms of bulk OLM powder and HP-β-CD:HP-β-CD inclusion complexes prepared by PM and KN were taken on a Shimadzu DSC-60 Differential Scanning Calorimeter between 40 and 300°C at a heating rate of 10°C/min with nitrogen supplied at 40 ml/min.

In vitro release study

Dissolution study

Dissolution experiments were performed using USP 24 paddle instrument (ELECTROLAB TDT-06P). 0.05 M phosphate buffer saline (pH 6.8) containing 1% SLS (1 g in 100 ml) (PBSS, pH 6.8) was used as dissolution medium. To minimize foaming of the medium during the experiment, medium was gently transferred into the dissolution vessel. Dissolution was performed at 37°C, using a paddle speed of 100 rpm. Samples of plain drug and HP-β-CD inclusion complexes prepared by PM and KN equivalent to 15 mg were added to dissolution vessels. Samples of 5 ml were taken after suitable time interval for 60 min. Samples were filtered immediately through 0.1 μm PTFE syringe filter (Whatman Inc.). Subsequently, 5 ml of fresh medium was added to the

dissolution vessel. Quantification of the samples was done by UV method at 256 nm. The experiments were performed three times and the mean value was determined.

In vitro diffusion study

A 4- to 5-cm-long portion of the dialysis tubing was made into a dialysis sac by folding and tying up one end of the tubing with thread, taking care to ensure that there is no leakage of the contents from inside the sac. The sac was kept for hydration in (PBS) (pH 7.4) containing 1% SLS (PBSS, pH 7.4) for 24 hours before permeation studies. The dialysis bags were prepared as follows: the wet sac was gently opened and washed copiously with PBSS (pH 7.4). Then it was filled up with PBSS (pH 7.4) and examined for the leaks. The sac was then emptied and 1 ml of the plain OLM suspension and HP-β-CD inclusion complexes prepared by PM and KN to be investigated was accurately transferred into the separate sac which becomes the donor compartment. The sac once again examined for leak and then suspended in the glass beaker containing 50 ml PBSS (pH 7.4) which become the receptor compartment. Receptor compartment containing 50 ml of PBSS (pH 7.4) was kept at constant stirring at 50 rpm speed. The temperature of the beaker was maintained at 37°C±0.5°C using the thermostatically controlled heater of the magnetic stirrer. At predetermined intervals of time, 3-ml aliquots were withdrawn from the receptor compartment and subjected to analysis. Fresh buffer was used to replenish the receptor compartment. Analysis was carried out immediately after withdrawal. Samples were withdrawn after 15 min, 30 min, 45 min, 60 min, 1, 2, 3, 4, 5, 6, 7, and 8 hours.

The study was also carried out by taking 4 mg of plain OLM suspension and HP-β-CD inclusion complexes prepared by PM and KN containing drug equivalent to 4 mg and results obtained were compared. The diffusion studies and sample analysis were carried out three times each.

In vitro intestinal permeability study

All experiments and protocols described in this study were approved by the Institutional Animal Ethics Committee of the M S University of Baroda and are in accordance with the Committee for Purpose of Control and Supervision of Experiments on Animals, Ministry of Social Justice and Empowerment, Government of India. Male Wistar rats (250–300 g) were killed by cervical dislocation. Stomach and a part of intestine were isolated and placed in 0.1 N HCl with 1% SLS and PBSS (pH 7.4), respectively. The isolated organs were washed with their respective solutions. 1 ml of the PM and inclusion complexes of HP-β-CD sample (4 mg/ml) was filled into the stomach, which was tied at both the ends.

The tissue was placed in an organ bath with continuous aeration at 37°C. The receiver compartment (organ tube) was filled with 30 ml of 0.1 N HCl with 1% SLS. At predetermined intervals (15, 30, 60, 90, and 120 min) of time and 3 ml of aliquots were withdrawn from the receptor compartment. Fresh buffer was used to replenish the receptor compartment. The HP-β-CD inclusion complexes prepared by PM and KN sample (1.0 ml of 4 mg/ml) were injected into the lumen of the intestine using a syringe, and the two sides of the intestine were tightly closed. The tissue was placed in an organ bath with continuous aeration and a constant temperature of 37°C. The receptor compartment was filled with 30 ml of phosphate-buffered saline (pH 7.4 PBSS).[8,9] At predetermined intervals (15 min, 30 min, 45 min, 1, 1.5, 2, 3, 4, 5, and 6 hours) of time, 2 ml aliquots were withdrawn from the receptor compartment and subjected to analysis. Fresh buffer was used to replenish the receptor compartment. Analysis was carried out immediately after withdrawal.

Stability study

Stability studies for HP-β-CD inclusion complex were conducted at the following storage condition for 2 months: 40°C/75% RH (accelerated stability condition). Three batches of HP-β-CD inclusion complex were used for study at this condition. Assay was carried out periodically to determine the stability of drug in the formulation at storage conditions.

Results and Discussion

Phase-solubility analysis is among the preliminary requirements for optimization of the parameters for inclusion complexation. This study is used for evaluation of the affinity between HP-β-CD and drug molecule in water. HP-β-CD are known to generate aggregates (self-associates) in aqueous solvents. The method is widely used for the determination of the molar ratios in drug HP-β-CD complexes. The phase-solubility graph for the complex formation between OLM and HP-β-CD is shown in [Figure 2].

The plot showed that the drug solubility increased with increase in the concentration of HP-β-CD. According to

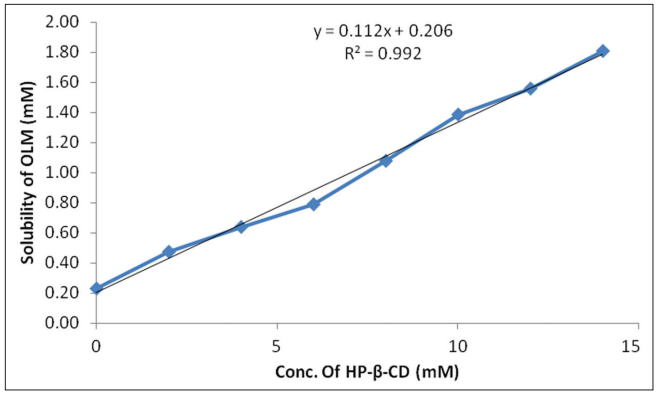

Figure 2: The phase-solubility graph for the complex formation between the drug and HP and#946; cyclodextrin

Higuchi and Connors, the phase-solubility profile can be considered as AL (linear) type. The slope calculated was 0.112, which is less than 1, thus 1:1 stoichiometry was suggested. Solubility of OLM was increased by 7.78 fold at 37°C at 14 mM concentrations of HP-β-CD. The stability constants (Ks) for the complexes at 37°C, assuming a 1:1 stoichiometry, calculated from the slope of the phase solubility curve 612.26 M^{-1} for HP-β-CD: OLM, which indicated stable complex formation. As Ks of HP-β-CD: OLM is in the range of 200–5000 M^{-1}, there is a possibility of an increase in the dissolution profile, which would result in increased bioavailability of OLM.

Actual drug contents in PM and KN product were 90.14%±2.56 and 92.73%±1.10, respectively. This shows good agreement between the theoretical and actual drug content. The aqueous solubility of the optimized inclusion complexes, i.e., OLM: HP-β-CD, was significantly higher than that of the pure drug, i.e., OLM in distilled water, as shown in [Table 2].

Table 2: Aqueous solubility study

Compound	Aqueous solubility (mg/mL) n=3 (Mean±S.D)
	Distilled water
Pure olmesartan medoxomil	0.12±0.004
OLM/HP-β-CD physical mixture (PM) complex(1:1)	0.65±0.013
OLM/HP-β-CD kneaded product (KN) complex(1:1)	1.01±0.023

Thus, the increase in the solubility due to complexation of OLM with HP-β-CD was 5.26 fold (0.65±0.013) for PM and 8.11 fold (1.01±0.023) for KN.

The Fourier transform infrared (FTIR) spectra of PM and KN were compared with spectra of HP-β-CD and OLM [Figure 3]. The spectrum of pure OLM depicts the characteristic peaks at 1832, 1740, 1707cm^{-1}, respectively. The FTIR spectrum of HP-β-CD is characterized by intense bands at 3300–3500 cm^{-1} due to O–H stretching vibrations. The vibration of the –CH and –CH2 groups appears in the 2800–3000 cm^{-1} region. The presence or absence of characteristic peaks associated with specific structural groups of the drug molecule was noted. The chemical interaction has been reflected by changes in the characteristic peaks of OLM, depending on the degree of interaction. The FTIR spectra of PM and KN showed a slight shift of peak with decrease in peak intensities than those of OLM indicating chemical interaction between HP-β-CD and OLM during KN, and PM. The FTIR spectra showed the diminished characteristic peak of olmesartan at 1832, 1740, and 1707 cm^{-1} in complexes, indicating inclusion of olmesartan in HP-β-CD cavity. Hence, it could be presumed the formation of inclusion of tetrazole ring and 1, 4-disubstituted benzene ring of OLM in the CD complexes.[11-14]

DSC analysis has largely been used to detect all processes in which energy is required or produced. The thermograms of all samples are presented in [Figure 4]. OLM showed a melting peak at 180°C, which is indicative of its melting temperature. In the thermogram of the HP-β-CD, peak

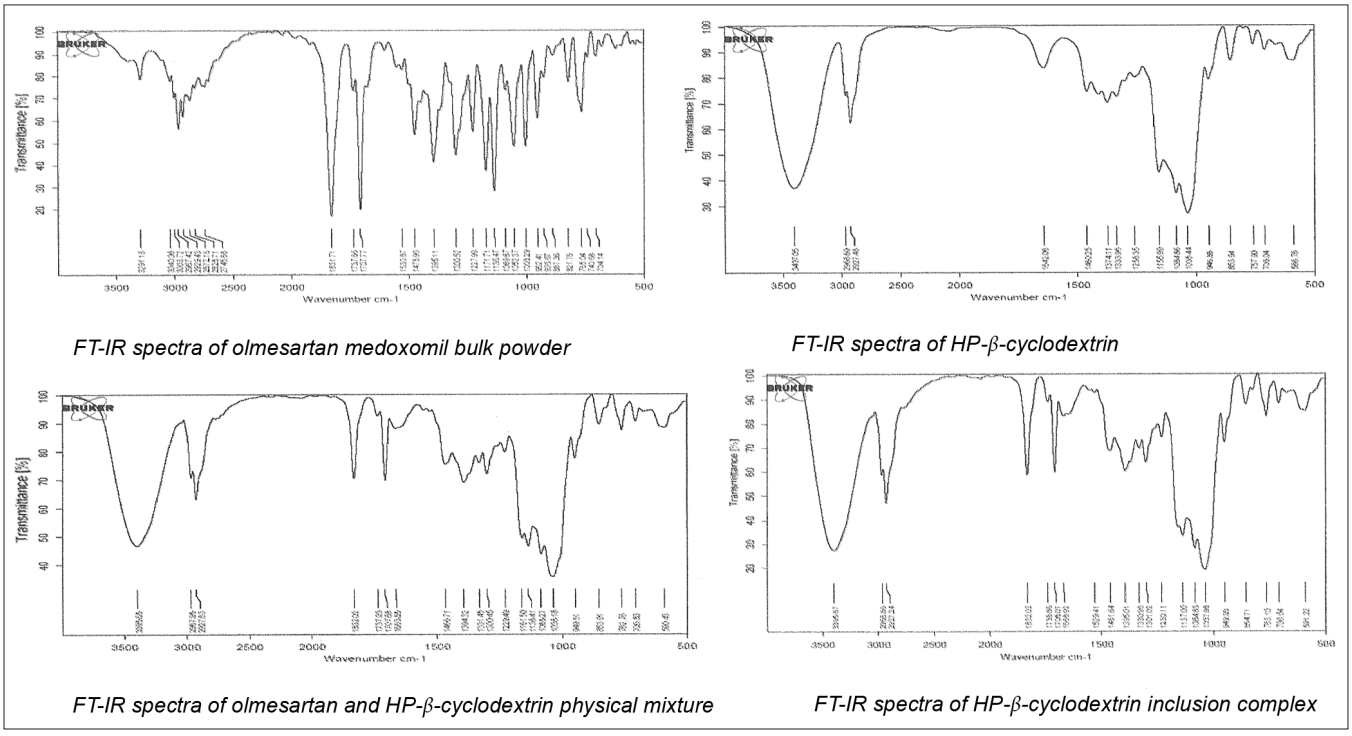

Figure 3: FTIR study

between 75°C and 125°C was due to loss of water from CD molecules. In the thermogram of all samples, peaks due to HP-ß- CD were observed at the same position, i.e., between 75°C and 125°C. The peak of OLM at 180°C was present at the same position, i.e., near to 180°C in PM. In contrast, the DSC curve of inclusion complexes (KN) showed a weak endothermic peak corresponding to the drug melting peak in the case of a 1:1 HP-β-CD complex and thus it confirmed the complex formation. This further confirms that KN is a better method for the preparation of inclusion complexes.

Powder XRD spectroscopy has been used to assess the degree of crystallinity of the given sample. The peak position (angle of diffraction) is an identification tool of a crystal structure, whereas the number of peaks is a measure of sample crystallinity in a diffractogram. The formation of an amorphous state proves that the drug was dispersed in a molecular state with CD. When complexes of drug and CD are formed, there was an increase in amorphousness and consequently solubility of drug. The XRD spectra of all the samples are shown in [Figure 5]. The powder XRD pattern of pure OLM exhibited a series of intense peaks at 2θ values of 12.68, 14.52, 15.75, 18.48, 20.60, and 21.88, which were intense and sharp, indicating its crystalline nature. Due to amorphous nature of HP-β-CD, no major peaks were detected in its spectrum. In PM, the crystalline peaks are somewhat decreased, while in inclusion complexes the peaks decreased in intensity, indicating the decreased crystallinity of the drug. The degree of crystallinity was decreased to maximum extent in case of complexes prepared using HP-β-CD. Hence, from present structural data of complexes, it can be confirmed that inclusion of OLM in HP-β-CD cavity has occurred.

In PM and KN inclusion complex, more than 50% and 60% drug dissolved within 5 min, respectively, and about 100% within 15 min, while plain drug showed only 12% dissolved at the end of 5 min and 92% dissolved in 60 min [Figure 6]. The KN systems among all showed the higher

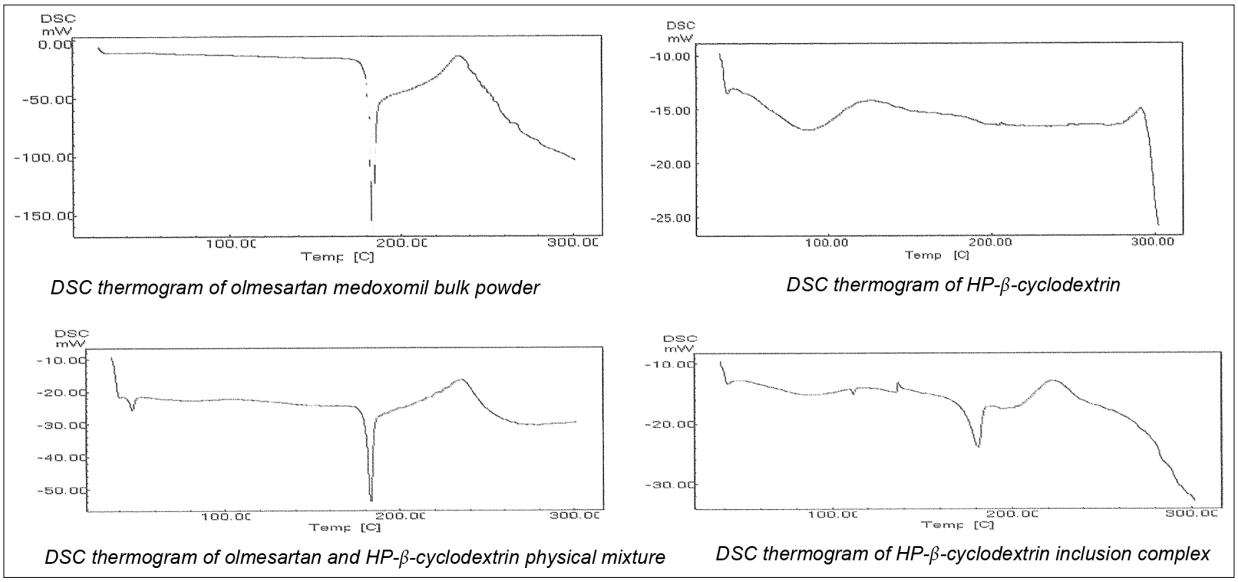

Figure 4: DSC study

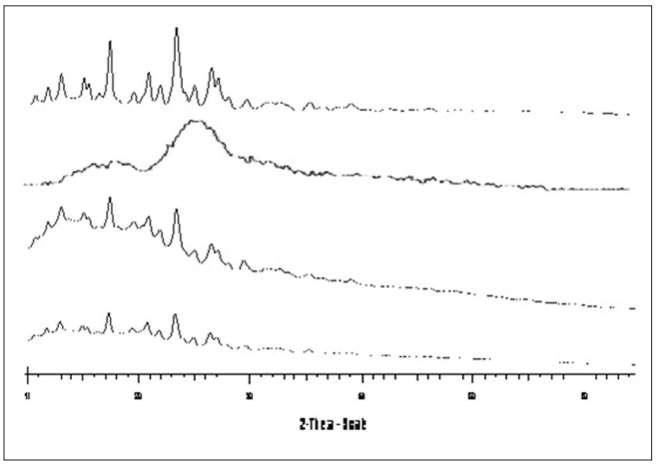

Figure 5: X-ray diffraction patterns

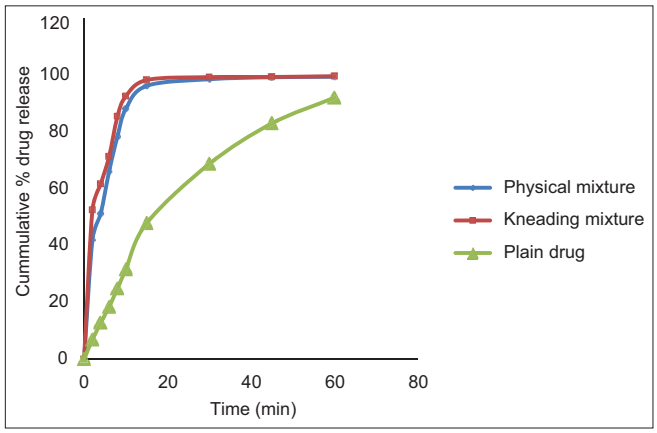

Figure 6: *In vitro* dissolution study of plain drug, physical mixture and kneading mixture

amount of OLM dissolved. This could be due to increase in the hydrophilicity of drug by HP-β-CD, which may contribute to the enhancement in dissolution of PMs. The improvement in the dissolution rate of the drug/CD systems may be attributed to the degree of crystallinity of the active material, together with the increase in both the wettability and the solubility of the drug. A very high increase of the drug dissolution rate in case of KN system may be probably due to several reasons such as the formation of inclusion complex along with change of crystalline form of drug to amorphous resulting into better wettability and increased solubility.

Comparative diffusion studies were carried out for plain OLM suspension and PM and inclusion complexes of HP-β-CD using dialysis sac technique for a period of 8 hours [Figure 7].

The total percentage diffusion was much higher for the PM and inclusion complexes of HP-β-CD system, than for the OLM suspension. After 8 hours of diffusion, 65.11% and 71.25% of the drug were diffused from the PM and inclusion complexes of HP-β-CD system, respectively, when compared with 43.2% diffusion from the OLM suspension. Drug release profiles of OLM, PM, and inclusion complexes of HP-β-CD formulations were markedly different from that of the plain drug suspension mainly due to inclusion of drug in CD moiety, which enhances drug solubilization. Paired T test was applied (using Graphpad Instat Software, at 95% confidence interval; *P* value less than 0.05 was taken as significant) between various drug release profiles. The two-tailed *P* value obtained was less than 0.0001 and the result was found to be statistically significant. CD inclusion complex gives better release compared with PM. So, KN is the best method for the preparation of inclusion complexes. The $R^{[2]}$ (square of correlation co-efficient) value for PM and the inclusion complex by KN was 0.9583 and 0.9625, respectively, for KorsmeyerPeppas model, confirming that the release pattern of both methods follows this model.

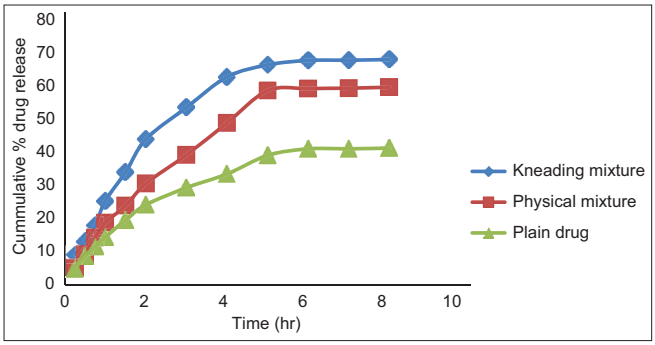

Figure 7: *In vitro* diffusion study of the plain drug, physical mixture and the kneading mixture

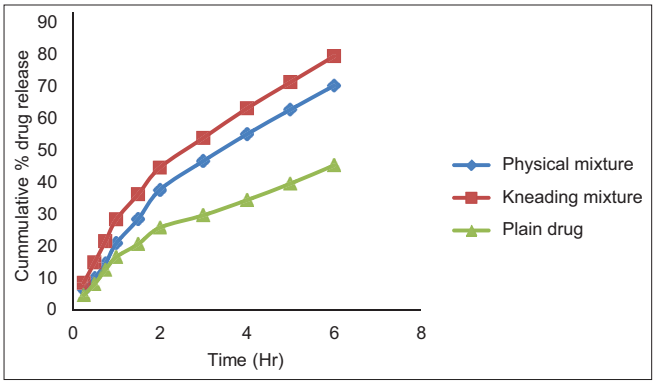

Figure 8: *In vitro* intestinal permeability study of the plain drug, physical mixture and the kneading mixture

Ex vivo diffusion study was carried out from stomach, but the amount of drug released after 2 hours was negligible. So, *ex vivo* intestinal permeability study was carried out. The total percentage diffusion was much higher for the PM and inclusion complexes of HP-β CD system, than for the OLM suspension. After 6 hours, 70.4% (for PM) and 79.9% (for inclusion complexes of HP-β-CD with the drug) were diffused through the intestinal tissue, while for plain drug suspension only 45.44% was diffused [Figure 8]. The increase in the diffusion is due to the increase in the solubility and dissolution rate of the drug when present in the complex form. Another important phenomenon is the permeation enhancement due to the presence of HP β-CD.[15,16]

To access the stability of the OLM, complexes were stored at 40°C/75%RH for 2 months [Table 3]. At the end of the study, the formulation was observed for changes in drug content. There was no change in the drug content, which supported that the complexes were stable in these conditions.

Conclusion

In the present investigation, inclusion complexation as a method of enhancement of solubility and thus bioavailability of OLM was studied. The inclusion complex was found to have significantly higher saturation solubility, dissolution rate, and intestinal permeation compared with

Table 3: Assay of optimized batch of HP-β-cyclodextrin inclusion complex at 40 °C/75% RH conditions

Stability conditions	Formulation	% Assay (%±SD)					
		Initial	10 days	20 days	30 days	45 days	60 days
40 °C/75% RH	HP-β-cyclodextrin inclusion complex	92.64±0.14	92.49±0.26	92.34±0.17	92.20±0.34	92.05±0.25	91.76±0.18

the plain drug. Among the two methods used for formation of inclusion complex, KN method gave higher solubility rates and hence is a better method when compared with PM. The accelerated stability studies indicated that the prepared complexes were stable. An increase in the solubility and the dissolution velocity suggests the possibility of the formulations to increase the bioavailability of OLM, which is poorly bioavailable due to low solubility.

References

1. Robinson JR. Introduction: Semi-solid formulations for oral drug delivery. Bull Tech Gattefossé 1997;89:11-3.
2. Lipinski CA, Lombardo F, Dominy B, Feeney P. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 1997;23:3-25.
3. Merisko-Liversidge E. Nanocrystals: resolving pharmaceutical formulation issues associated with poorly water-soluble compounds In: Marty JJ (Editor), Particles, Orlando: Marcel Dekker; 2002.
4. Yalkowsky SH. Techniques of Solubilization of Drugs 1–14 . New York: Marcel Dekker; 1981.
5. Müller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy Rationale for development and what we can expect for the future. Adv Drug Deliv Rev 2001;47:3-19.
6. Challa R, Ahuja A, Ali J, Khar R. Cyclodextrin in drug delivery: An updated review. AAPS PharmSciTech 2005;6:E329-57.
7. Loftsson T, Brewester M. Pharmaceutical applications of cyclodextrins. Drug solubilization and stabilization. J Pharm Sci 2005;85:1017-25.
8. Nagarsenker MS, Meshram RN, Ramprakash G. Solid dispersion of hydroxypropyl beta-cyclodextrin and ketorolac: Enhancement of *in-vitro* dissolution rates, improvement in anti-inflammatory activity and reduction in ulcerogenicity in rats. J Pharm Pharmacol 2000;52:949-56.
9. Ahlin P, Kristl J, Kristl A, Vrecer F. Investigation of polymeric nanoparticles as carriers of enalaprilat for oral administration. Int J Pharm 2002;239:113-20.
10. Rawat S, Jain SK. Enhancement of intestinal absorption of few cox-2 inhibitors through interaction with β-cyclodextrin. Indian J Pharm Sci 2007;69:529-34.
11. Maski NK, Girhepunje, Ghode P, Randive S, Pal R. Studies on the preparation, characterization and solubility of B-Cyclodextrin –Diacerein inclusion complexes. Int J Pharm Pharm Sci 2009;1:129-35
12. Reddy MN, Rehana T, Ramakrishna S, Chowdary KP, Diwan PV. β-Cyclodextrin Complexes of celecoxib: Molecular-modeling, characterization, and dissolution studies. AAPS PharmSci 2004;6:1-9.
13. Patel AR, Vavia PR. Preparation and evaluation of taste masked famotidine formulation using drug/β-cyclodextrin/polymer ternary complexation approach. AAPS PharmSciTech 2008;9:544-50.
14. Babboota S, Dhaliwal M, Kohli K. Physicochemical characterization, *In Vitro* dissolution behavior, and pharmacodynamic studies of rofecoxib-cyclodextrin inclusion compounds. Preparation and properties of rofecoxib hydroxypropyl β-cyclodextrin inclusion complex: A technical note. AAPS PharmSciTech 2005;6:E83-90.
15. Cui CY, Lu WL, Xiao L, Zhang SQ, Huang YB, Li SL, et al. Sublingual delivery of insulin: effects of enhancers on the mucosal lipid fluidity and protein conformation, transport, and in vivo hypoglycemic activity. Biol Pharm Bull 2005;12:2279-88.
16. Shanker G, Kumar CK, Gonugunta CS, Kumar VB, Veerareddy PR. Formulation and evaluation of bioadhesive buccal drug delivery of tizanidine hydrochloride tablets. AAPS PharmSciTech 2009; 10:530-9.

How to cite this article: Thakkar HP, Patel BV, Parmar MP, Chauhan NP, Patel AA. Studies on inclusion complex as potential systems for enhancement of oral bioavailability of olmesartan medoxomil. Chron Young Sci 2012;3:129-36.

Source of Support: Nil, **Conflict of Interest:** None declared