

SOLUBILITY AND DISSOLUTION RATE ENHANCEMENT OF OLMESARTANMEDOXOMIL BY CHITOSAN BASE CO-CRYSTAL APPROACH

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ABSTRACT

Co-crystal of Olmesartan Medoxomil were prepared by solvent change technique. chitosan solution was prepared by soaking chitosan and chitosan chlorhydrate in glacial acetic acid. A weighed amount of drug was dispersed in chitosan solution by stirring. The dispersion was added to sodium citrate solution to precipitate chitosan on drug crystals. The precipitate obtained was filtered through whatman no.1 filter paper using vaccum filtration unit and dried at 45°C for 24 h. the prepared co-crystals were characterized in the terms of saturation solubility, drug content, infrared spectroscopy (FTIR), diffrential scanning calorimetry (DSC). Powder X-ray diffraction (PXRd), in-vitro dissolution studies. The considerable improvement in the dissolution rate of drug from optimized batch co-crystal formulation was attributed to the decreased drug crystallinity. Altered surface morphology and reduction in particle size.

KEY WORDS

Solvent change technique, Chitosan Solution, FT-IR, DSC.

INTRODUCTION

The rate of absorption and bioavailability of poorly waters oluble drugs is often controlled by the rate of dissolution of the drug in the gastrointestinal tract. Many technological methods of enhancing the dissolution characteristics of slightly water-soluble drugs have been reported in various literatures.¹ These include reducing particle size to increase surface area ², solubilization in surfactant systems, formation of water-soluble complexes, use of pro-drug, drug derivatization and manipulation of solid staten of drug substance to improve drug dissolution, i.e. by decreas-ingcrystallinity of drug substance.³ Recently, natural polymers such as polysaccharides and proteins have received much attention in the pharmaceutical field owing to their good biocompatibility and biodegradability.⁴ Among polysaccharides, chitosan has been

considered to be one of the mostpromising biopolymer for drug delivery purposes. Chitosan(_(1-4)-2-amino-2-deoxy-d-glucose) is a linear hydrophilicpolysaccharide polymer of d-glucosamine. It is a non-toxic naturalpoly cationic polymer that is degraded by the microflora inthe colon. It is abundant in nature and is present in the exoskeletonof crustaceans such as crabs and shrimp.⁵ Chitosan, being a cationic polysaccharide in neutral orbasic pH conditions, contains free amino groups and hence, itis insoluble in water. In acidic pH, amino groups can undergo protonation thus, making it soluble in water. It breaks downslowly to harmless products (amino sugars), which are completelyabsorbed by the human body.⁶ Chitosan has been demonstrated to be a good vehicle for enhancingthe dissolution properties and bioavailability of a number of poorly water-

soluble drugs.⁷ Low molecular weight chitosan can function as drug release enhancers for poorly water-soluble drugs due to an improvement in wettability resulting from the solubility of low molecular weight chitosan in water.⁵

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%. Olmesartanmedoxomil exhibits very slight solubility in water and as a consequence it exhibits low bioavailability after oral administration.⁸

Therefore, the improvement of olmesartanmedoxomil dissolution from its oral solid dosage forms is an important issue for enhancing its bioavailability and therapeutic efficacy.⁹

MATERIALS AND METHODS

Olmesartanmedoxomil was obtained as a gift sample Glenmark Pharmaceutical, Nashik, India. Chitosan (80% deacetylated, chitosan chlorhydrate

obtained from methanex chitosan, India. Hydrochloric acid (35-38%), glacial acetic acid (99.5%) sodium citrate (99.5%) was purchased from Modern science pvt ltd, Nashik, India. All other chemicals were of analytical grade.

Preparation of co-crystal

The composition of different crystal formulations is given in Table 1. Chitosan solution was prepared by soaking chitosan in 1% glacial acetic acid for 3 h. A weighed amount of the drug was dispersed in chitosan solution by using high dispersion homogenizer (Polytron, PT-MR 3100, Kinematica AG, Switzerland) at 15,000 rpm for 5 min. This dispersion was then added to distilled water or sodium citrate solution to precipitate chitosan on drug crystals. The precipitate obtained was filtered through Whatmann No. 1 filter paper using vacuum filtration unit and dried at 45 °C for 24 h. The dried product was then passed through sieve No. 60 to obtain a uniform size distribution. A control crystal formulation without chitosan was also prepared. The practical yield of the prepared crystals was calculated.

Table 1: composition of olmesartanmedoxomil-chitosan, chitosan chlorhydrate co-crystal formulation

Batch code	Olmesartanmedoxomil (mg)	Chitosan (%)	Chitosan chlorhydrate (%)	Glacial acetic acid (ml)	Sodium citrate (2%)
C1	500	0.2		20	100
C2	500	0.4		20	100
C3	500	0.6		20	100
C4	500	0.8		20	100
C5	500	1.0		20	100
C6	500	-	0.2	20	100
C7	500	-	0.4	20	100
C8	500	-	0.6	20	100
C9	500	-	0.8	20	100
C10	500	-	1.0	20	100

Saturation solubility:

An excess amount of olmesartan and prepared cocrystals was placed in vials containing 10 ml of

different solvents (water and 0.1N HCL) the vials were agitated in an incubator shaker (100 rpm/min) for 24 hours at room

temperature. The solution was filtered and the amount of drug solubilized was analyzed spectrophotometrically (Shimadzu 2401pc, Japan) at 248 nm. This study was carried out to determine the saturation solubility of olmesartan medoxomil in water and 0.1N HCL.

Drug Content

For determination of drug content, prepared cocrystals (10mg) were triturated in 0.1N HCL and finally volume was made up to 10 ml with the same. The solution was filtered, the amount of drug solubilized was analyzed spectrophotometrically (SHIMADZU UV-2401pc, Japan) at 248nm.

Infrared (IR) spectroscopy

IR spectroscopy was conducted using Shimadzu FT-IR 8400s Spectrophotometer (Shimadzu 8400s, Japan) and the spectrum was recorded in the wavelength region 4000-400 cm⁻¹. The procedure consisted of dispersing a sample (drug or prepared cocrystal) in KBr and compressing into disc by applying pressure. The pellet was placed in light path and the spectrum was recorded.

X-ray diffraction (XRD)

For characterization of crystalline state, the powder x-ray diffraction (XRD) pattern of optimized batch 1 and optimized batch 2 was determined. Powder X-ray diffraction (XRD) was carried out using a Bruker AXS Advance D-8 scanner with filter Ni, Cu-K α radiation, voltage 40kV and a current 20mA. The scanning rate employed was 10/min over the 5 to 50 diffraction angle (2 θ) range.

Differential scanning Calorimetry

DSC was performed using SHIMADZU, DSC60, Japan calorimeter to study the thermal behavior of drug alone and prepared cocrystals. The sample were heated hermetically sealed

aluminium pans under nitrogen flow (50ml/min) at a scanning rate 10C/min from 50C to 300C. empty aluminium pan was used as reference.

In-Vitro Dissolution study

The dissolution rate of olmesartan alone and prepared co-crystal were measured in a dissolution apparatus (Electrolab, EDT-08Lx, India) using apparatus USP Type II. Dissolution studies were carried out using 900ml 0.1 N HCL at 37 $\pm$ 0.5C at 50 rpm. Using 40 mg of olmesartan medoxomil and its equivalent cocrystals were added to 900 ml 0.1N HCL. 5ml samples were withdrawn after 15, 30, 45, and 60 and replaced each time with 5ml fresh 0.1N HCL. The solutions were immediately filtered, diluted and concentration of olmesartan medoxomil was determined spectrophotometrically.

Stability study of co-crystals:

After determining the drug content, the optimized batch crystals were charged for accelerated stability studies as per ICH guidelines. The samples were kept for stability studies at 40 $\pm$ 2°C and 75 $\pm$ 5% RH for a period of 6 months in environmental test chamber. The sample were kept in glass vials sealed with rubber plugs. 10mg of stored crystals were taken out at 15, 30, 60, 90 and 180 days and analyzed for drug content and physical changes.

RESULT AND DISCUSSION

Practical yield, drug content and solubility

The solubility, dissolution behavior and permeability of a drug are key determinations of its oral bioavailability. The solubility data of olmesartan medoxomil reveals that it is poorly soluble in water. Therefore, the improvement of olmesartan medoxomil dissolution from its oral solid dosage forms is of great concern. The practical yield was found to be decreased with

increase in polymer concentration due to the formation of thick viscous chitosan solution from which separation of the drug crystal was difficult.

The drug content was found to be good and uniform among the different batches of crystals prepared and ranged from 96.24-99.22%.

Table2: practical yield, drug content, solubility data in water and 0.1 N hcl for the pure drug and prepared co-crystal

Formulation code	% yield	Drug content	Water (mg/ml)	0.1NHCL
Olmesartan Medoxomil	-	-	0.12±0.008	0.016±0.001
C1	86.62	96.23±0.52	0.21±0.005	0.25±0.004
C2	81.23	98.23±0.23	0.34±0.004	0.39±0.008
C3	76.20	97.20±0.65	0.75±0.007	0.99±0.005
C4	65.20	98.23±0.23	0.55±0.005	0.39±0.016
C5	60.23	98.19±0.42	0.49±0.007	0.31±0.008
C6	87.65	97.23±0.45	0.23±0.008	0.27±0.008
C7	83.23	96.23±0.33	0.39±0.005	0.40±0.008
C8	74.25	98.23±0.25	0.95±0.005	1.05±0.008
C9	70.45	99.23±0.69	0.42±0.004	0.48±0.008
C10	68.23	99.23±0.92	0.44±0.005	0.50±0.008

In the solubility studies of the prepared crystals from chitosan formulation batch C3 batch showed highest solubility of drug in both water (0.75±0.007mg/ml) and 0.1 N HCL(0.99±0.005mg/ml) in comparison with pure drug(water 0.12±0.008 mg/ ml) and (0.016±0.001mg/ml). if we compare the solubility data of chitosan and chitosan chlorhydrate formulation code C8 showed better aqueous solubility(0.95±0.005). The difference in aqueous solubility of chitosan and chitosan chlorhydrate may be due to better wetting property and low molecular weight of chitosan chlorhydrate. In addition, as concentration of chitosan or chitosan chlorhydrate increased in the formulation, the solubility gradually increased up to certain concentration followed by decrease in solubility.

Infrared (IR) spectroscopy

FTIR studies have been performed for the pure drug, co-former and prepared co-crystals. From the FTIR results as shown in figure 1 and 2 it can be confirmed that there is an interaction between the pure drug and excipients. In the FTIR spectrum of the optimized batch 1(C3) the peak attributed to the C-H stretch at 2973.37 has been shifted to 2974.33, whereas the peak attributed to C-H stretch at 3050.10 and peak attributed to C=O at 1706.09 has been shifted to 3231.63 and 1739.85 respectively. The peaks at 1505, 1000-1300 due to presence of N-H stretch, O-H stretch consistent with the aromatic compound and C-OH stretch respectively. It was observed that all important peaks due to functional group of drug are present in cocrystal along with some new intense peaks indicating the presence of hydrogen bonding. , it can be confirmed that there is an interaction between the pure drug and excipients. In the FTIR spectrum of the

optimized batch 2(C8) as shown in figure 3 the peak attributed to the C-H stretch at 2973.37 has been shifted to 2974.33, whereas the peak attributed to C-H stretch at 3050.10 and peak attributed to C=O at 1706.09 has been shifted to 3291.63 and 1832 respectively. The peaks at 1505, 1000-1300 due to presence of N-H stretch, O-H stretch consistent with the aromatic compound and C-

OH stretch respectively. It was observed that all important peaks due to functional group of drug are present in cocrystal along with some new intense peaks indicating the presence of hydrogen bonding. Also there are peaks observed in the range of 400-800 in co-crystal prepared from chitosan chlorhydrate indicative of halogen hydrogen interaction.

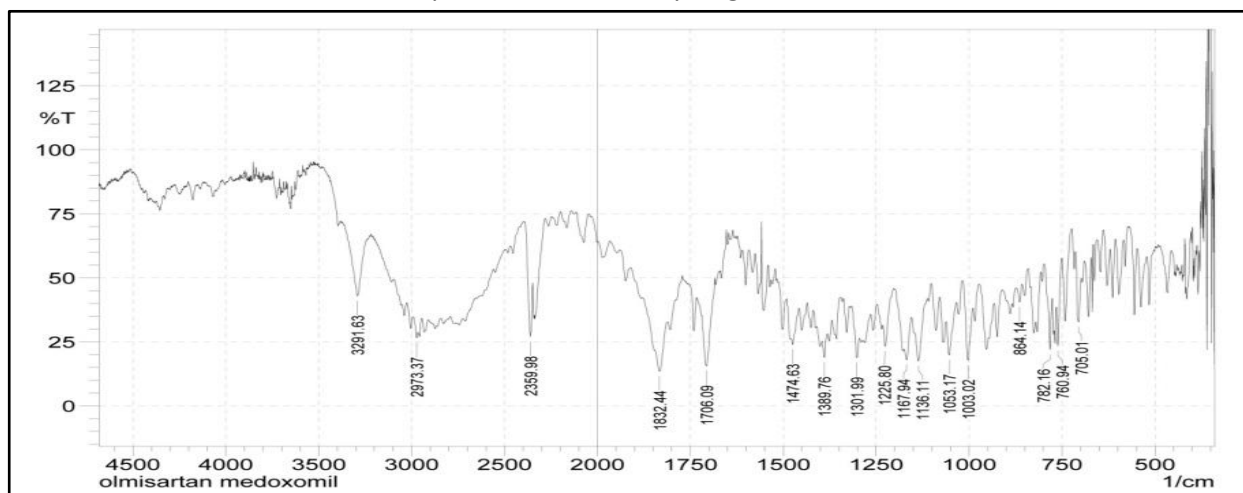


Figure 1: FT-IR Spectrum of Olmesartan Medoxomil

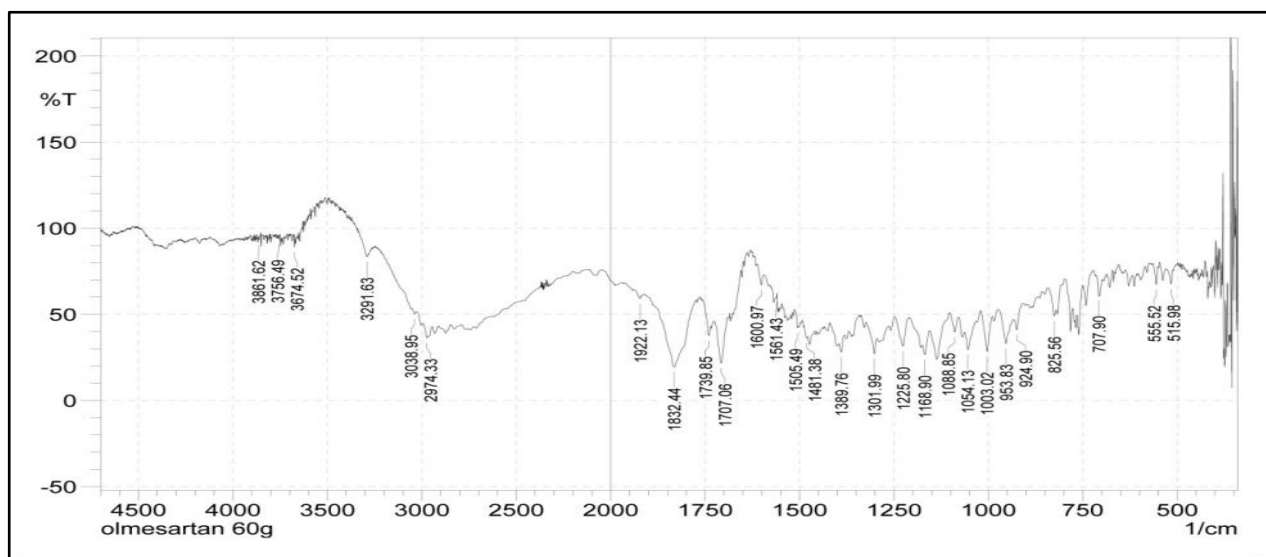


Figure 2: FT-IR Spectrum of Cocrystal Optimized batch 1 (Formulation code 3)

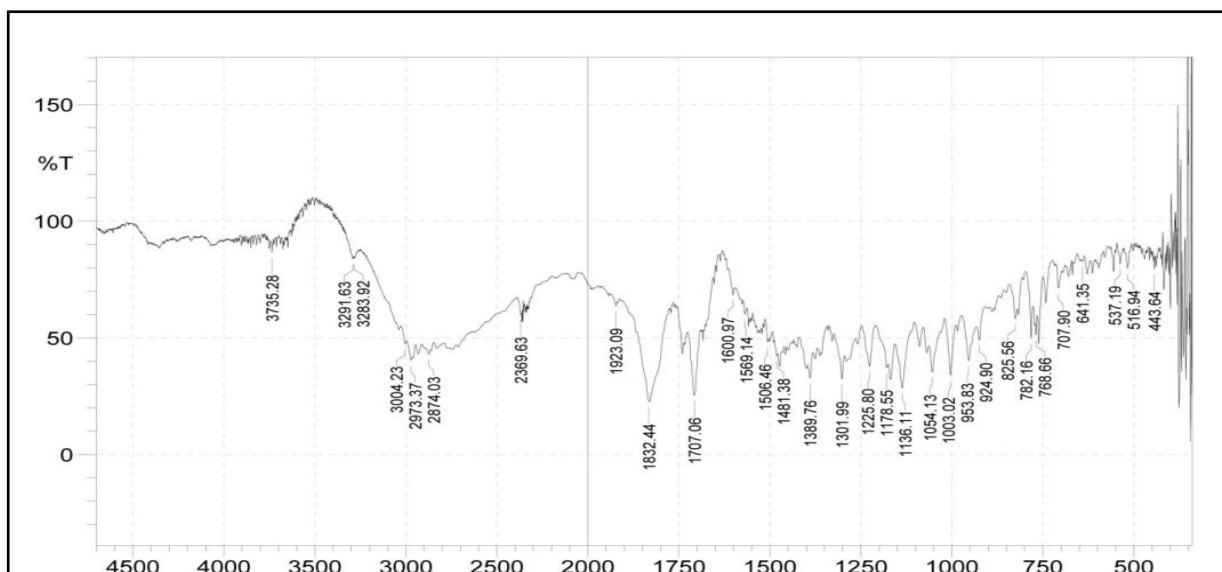


Figure 3: FTIR Spectrum of Cocystal Optimized batch 1 (Formulation code 3)

X-ray diffraction (XRD)

Powder X-ray diffraction studies of OlmesartanMedoxomil shown in Figure 4, 5 and 6. The pure OlmesartanMedoxomil and co-crystal exhibited intense crystalline peak between 50 to 500. Characteristic diffraction peaks at 6.20, 16.60, 17.70, 20.20, 22.40, 25.10, 27.70 and 28.60 were observed with intense peak at 20.20

indicating crystalline nature of OlmesartanMedoxomil. While co-crystals of shows characteristic at 6.30, 8.30, 16.70, 17.30, 20.30, 22.40, 23.90, 25.90 and 27.80 and intense peak was observed at 16.70 indicating crystalline nature of optimized batch. The shift in intense peak indicate formation of new crystalline form.

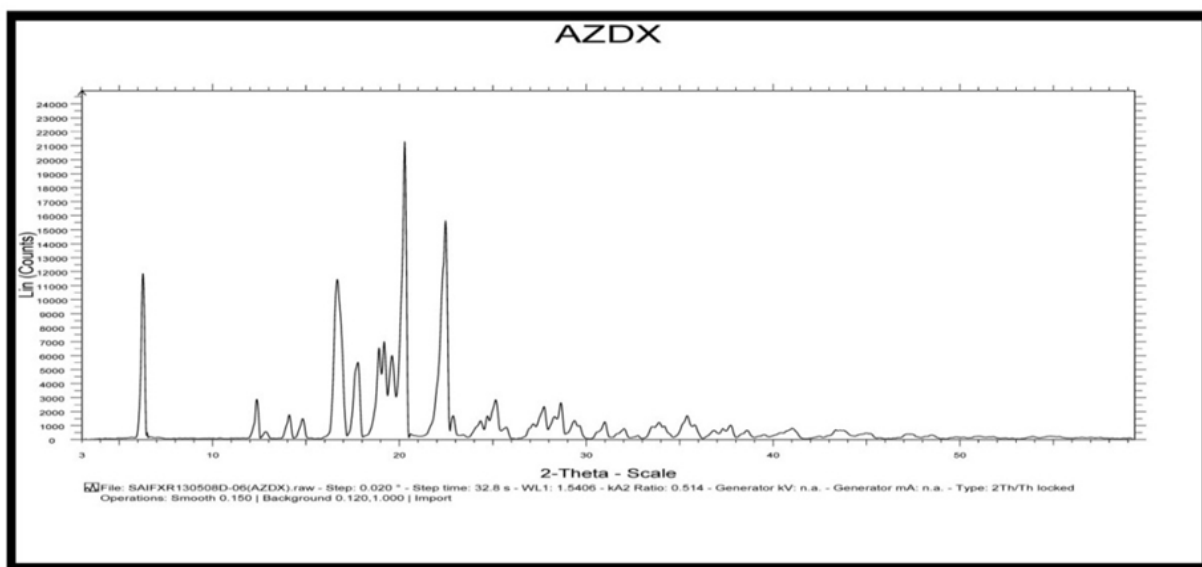


Figure 4: XRD patterns of OlmesartanMedoxomil

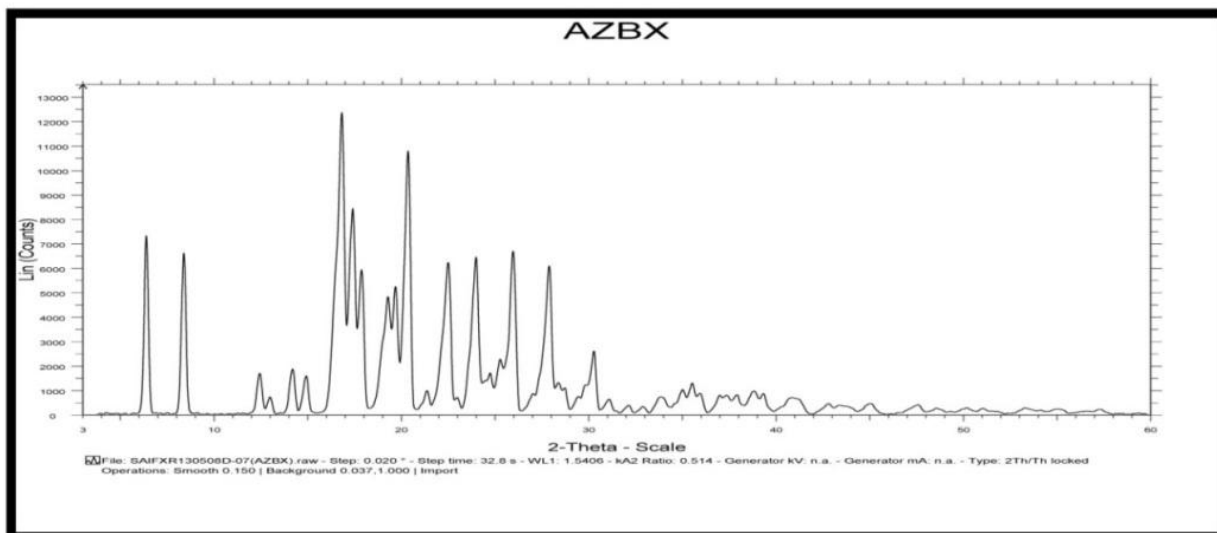


Figure 5: XRD pattern of formulation code 3

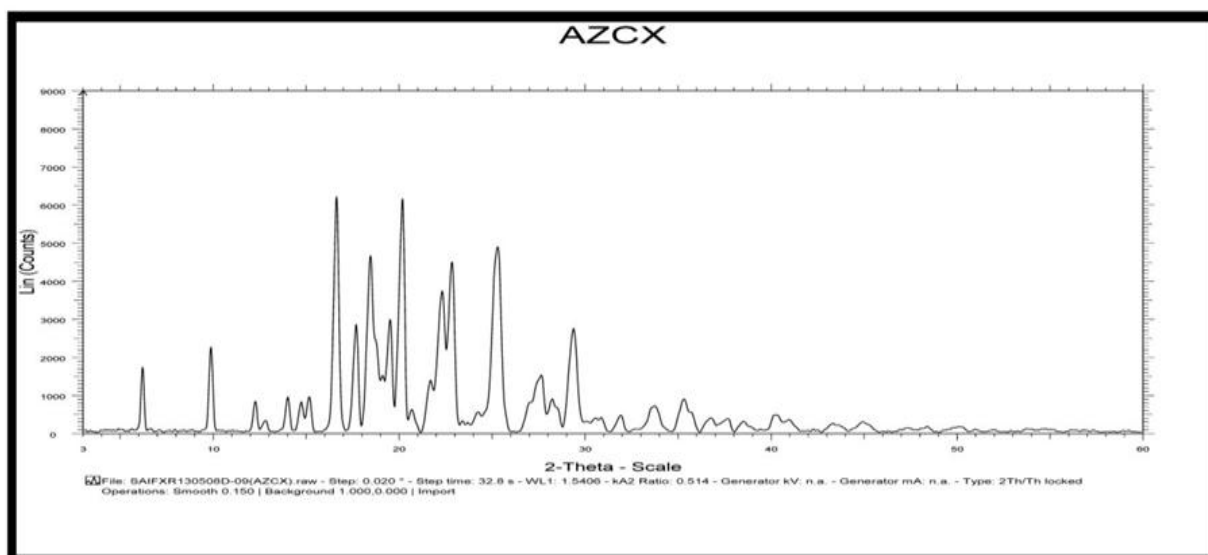


Figure 6: XRD pattern of formulation code 8

Differential scanning calorimetry:

The thermogram of Olmesartan Medoxomil were recorded by using a differential scanning calorimeter equipped with a computerized data station. The thermogram of Olmesartan Medoxomil had shown a single endothermic peak maxima at 178 °C due to melting of drug as shown in figure 7.

DSC experiment was carried out to study the thermal behaviour of the optimized batch cocrystals shown in figure 8 and 9 had shown a single endothermic peak maxima at 110°C due to

melting of cocrystals. The endotherm started at around 97 °C. The T_{max} values for Formulation code C3 cocrystals and the individual components agreed with the measured melting range in the melting point determination. DSC thermogram of formulation code 8 cocrystals was recorded by using a differential scanning calorimeter with a computerized data station. DSC experiment was carried out to study the thermal behaviour of the optimized batch cocrystal had shown a single endothermic peak maxima at 106°C due to melting of cocrystals. The

endotherm started at around 103 °C. The thermal behaviour was distinct, with a different melting transition from that seen with either of the individual component; this suggest formation of new phase: optimized formulation code C3 cocrystals. The melting point of cocrystal was

found to be below the melting point of both the drug and cocrystal former. A single endothermic transition for the optimized batch cocrystals indicates the absence of any unbound or absorbed solvent or water and also demonstrates the stability of the phase until the melting point.

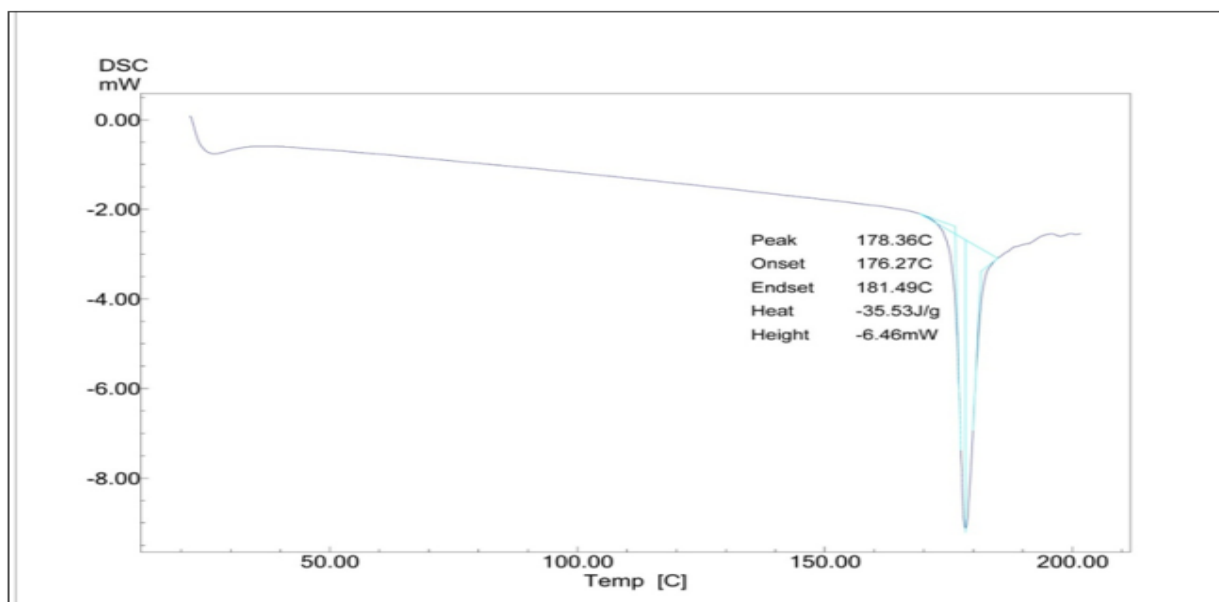


Figure 7: DSC themogram of OlmesartanMedoxomil

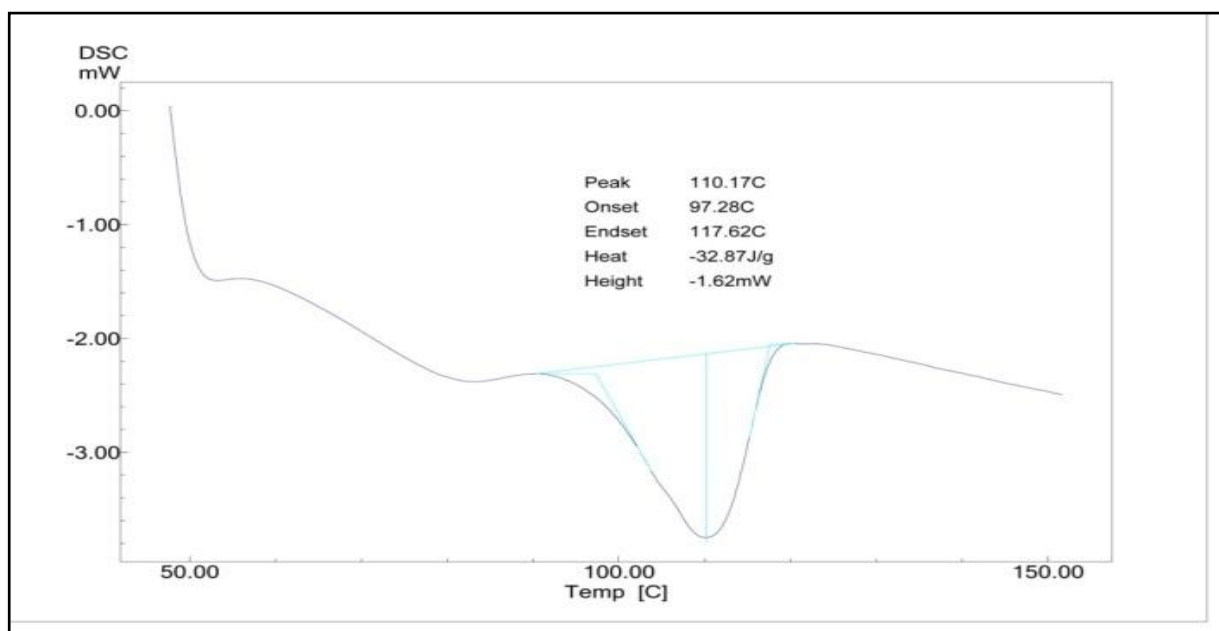


Figure 8: DSC thermogram of formulation code 3

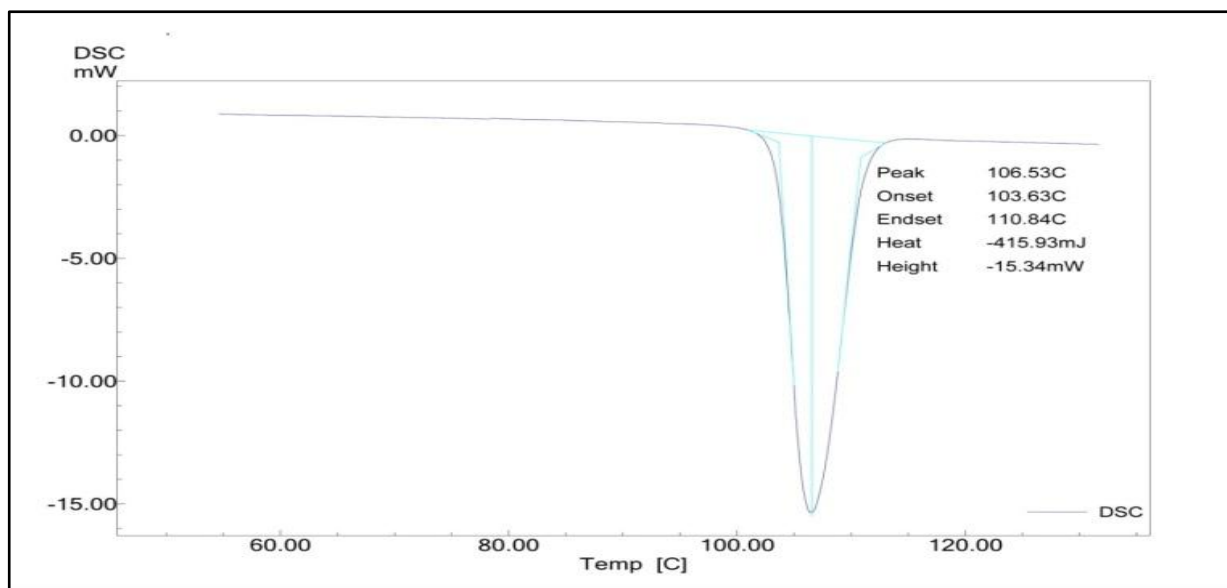


Figure 9: DSC thermogram of formulation code 8

***In-vitro* dissolution study**

The results of *in-vitro* drug release studies in 0.1 N HCL for 1hr. are depicted in figure .various crystals (C1 to C5) were prepared using increasing concentration of chitosan using sodium citrate (2%) as a dispersion medium. The chitosan salted out with the sodium salt of citric, tartaric, malic acids was in general more soluble in dilute aqueous acetic acid^{10,11} The C1 crystal containing 0.2% chitosan showed a drug release of 35% in 1 hr. crystal C2 to C5 was again prepared by increasing the chitosan concentration. The highest drug release was observed with C3 crystals with 0.6% (48% in 1 hr.) further increase in concentration of C4,C5 decrease in drug release was observed compare to C3. It was interesting to note that chitosan was able to increase the dissolution rate at lower concentration when associated with sodium citrate. It has been reported that polymers with positively or negatively charged groups interact with molecules of opposite charge to form three dimensional network. The reaction of chitosan with multivalent anion like sodium citrate allows the formation of bridges between the polymeric chains and results in a crosslinking between the

chitosan molecules, which might have eventually resulted in efficient absorption of chitosan on drug particles.¹⁰

Cocrystals prepared by using chitosan chlorhydrate showed better drug release than chitosan this might be due to water soluble nature of chitosan chlorhydrate. (figure 10,11)(C3 48% and C7 50% in 1 hr)

The increase in olmesartanmedoxomil solubility, although little, and significant increase in dissolution rate from prepared crystals can be explained as following: Chitosan has been proposed as a very useful excipient for enhancing the bioavailability of poorly water soluble compounds. Chitosan and its derivative has been reported as good vehicle for enhancing the solubility and dissolution of poorly water soluble.^{12,13} Chitosan dissolves readily in most of acid solutions and upon dissolution, amine group of polymer become protonated, resulting in positively charged polysaccharides (RNH_3^+) and chitosan salt (chloride, glutamate etc) that are water soluble.¹⁴ The earlier literature reveals that dissolution rate not only depend on surface area and particle size of the processed powder, but is greatly affected by crystal morphology and

wettability.¹⁵ So increased wettability of drug by adsorption of chitosan and chitosan chlorhydrate on to the hydrophobic surface of the drug is the first reason. In the previous study also chitosan showed increased solubility and dissolution rate of naproxen due to the adsorption of its surface.¹⁶ The difference in dissolution rate enhancement by chitosan and chitosan chlorhydrate can be explained as the bond found was that for two types of chitosan (base and salt) the lower the molecular weight, the faster was the drug dissolution. The behavior was predictable taking into account the relationship between molecular weight and viscosity of

polymer solution.¹⁷ Upon contact with acidic medium, chitosan swells and form a gel into the release medium would be retarded by increasing the viscosity of the polymer and hence of the ge.¹⁸ on the other hand the chitosan chlorhydrate led to faster dissolution than chitosan. The explanation to this behavior was found the differences in the wetting rate, solubilities and swelling capacity of the chitosan and chitosan salts, chitosan chlorhydrate rapidly wet and dissolves upon its incorporation into the dissolution medium whereas the chitosan base being less water soluble, would take more time to dissolve.

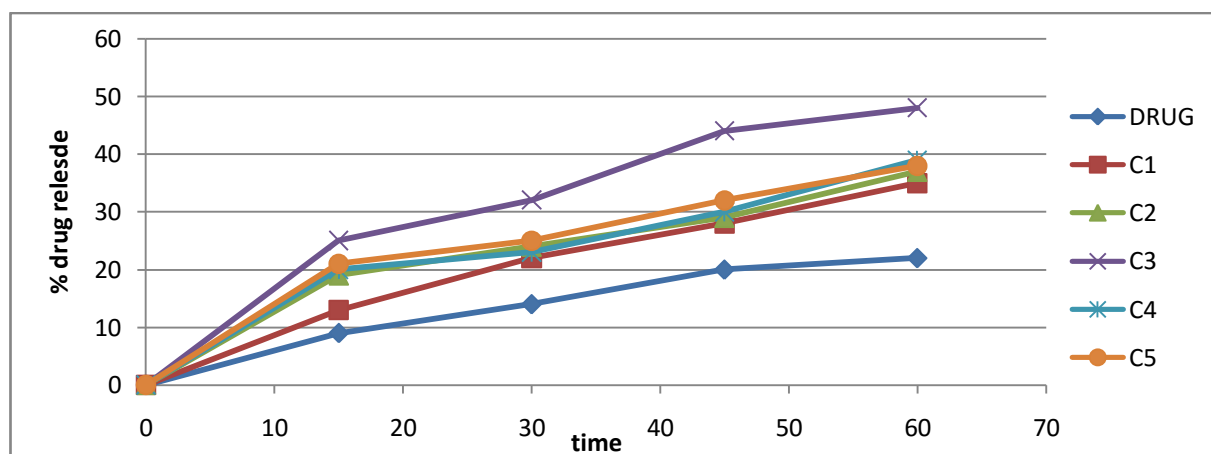


Figure10 :In-vitro drug release of olmesartanmedoxomil from the prepared co-crystal formulations in 0.1 N HCL(C1-C5)

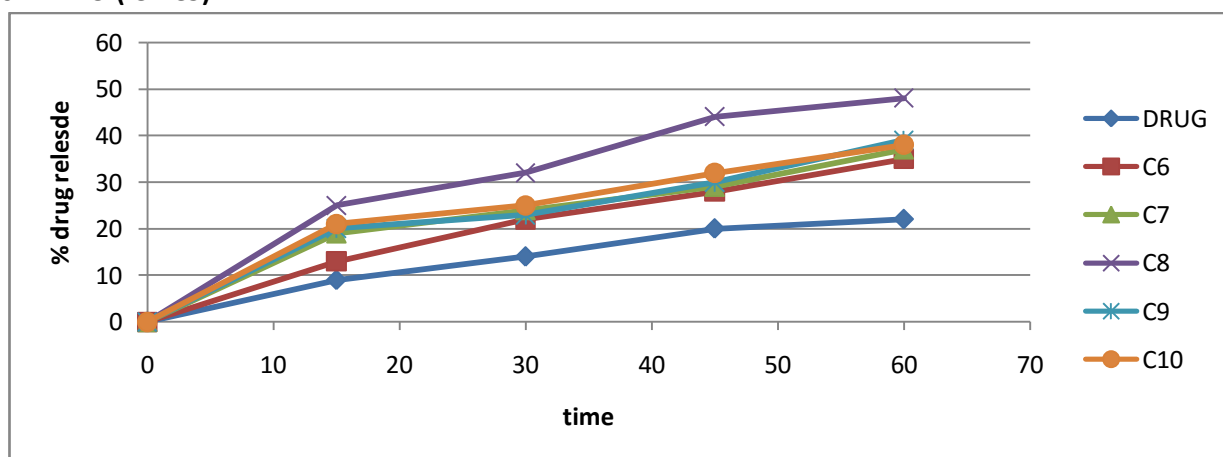


Figure11 :In-vitro drug release of olmesartanmedoxomil from the prepared co-crystal formulations in 0.1 N HCL(C6-C10)

Stability studies

The physical stability of co-crystal was compared with drug. The co-crystals was found to be stable during the study periods as no any change in

colour was found. The drug content in both the co-crystals was found to be within the limit. The drug content within the formulation is shown in the table.

Table : drug content of formulation after stability studies.

Storage conditons 30±2°C/65±5% RH	Drug content (%) of formulation		
	Olmesartan medoxomil	0.6% Chitosan	0.6% Chitosan chlorhydrate
Time 0 days	99.56±1.14	98.77±1.21	98.2.12±2.12
Time 90 days	99.42±1.35	98.±1.12	98.09±2.23
Time 180 days	99.21± 1.14	98.42±1.22	97.62±2.03

CONCLUSION

The present stability of co-crystals was compared with the drug. The co-crystals were found to be stable during the study period as no any change in color was found. The drug content in all the co-crystals was found to be within the limit. The drug content within the formulation is shown in table

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