Original Article

Formulation and Evaluation of Mucoadhesive Buccal Tablets of Candesartan

Ramakrishna Raparla[*1]. Ankamma Chowdary Y[2], Srikanth Thatipamula[3] and S.Pragna[1]

[1]Department of Pharmaceutics, Vaageswari Institute of Pharmaceutical Science,Beside LMD police station, Ramakrishna Colony, Karimnagar, Andhra Pradesh – 505481
[2]Department of Pharmaceutics, NRI college of Pharmacy,pothavarappadu(V), Agirapally(M), Krishna District, Andhra Pradesh- 521 212.
[3]Department of Pharmaceutics, Vaageswari College of Pharmacy,Beside LMD police station, Ramakrishna Colony, Karimnagar, Andhra Pradesh - 505481.

Address for Correspondence
Department of Pharmaceutics, Vaageswari Institute of Pharmaceutical Sciences, Beside LMD police station, Ramakrishna Colony, Karimnagar, Andhra Pradesh - 505481.
Tel. +91-9502588615
E-mail:
ramakrishna.raparla @gmail.com

ABSTRACT

The purpose of this research work was to develop and evaluate the buccal tablets of Candesartan using various mucoadhesive polymers viz. Hydroxy Propyl Methyl Cellulose K4M, Sodium Corboxy Methyl Cellulose, Sodium alginate individually and in combination. Candesartan is an angiotensin II receptor blocker used in the treatment of hypertension. It shows the oral bioavailability 15% due to first pass metabolism and has a biological half-life of approximately 9hrs. It is poorly absorbed after oral administration and having poor solubility and wettability leads to poor dissolution. The solubility and dissolution rate were improved by preparing solid dispersions with melt agglomeration and inclusion complexes techniques using Poloxamer188 and kneading method by β-Cyclodextrin. The solid dispersion complex prepared with Poloxamer 188 and β- Cyclodextrin were compressed into a tablet by direct compression method using mucoadhesive polymers. The compressed mucoadhesive buccal tablets prepared were subjected to various evaluation processes such as pre compressional parameter and post compression parameters. Later the optimized formulations from each enhancer with Poloxamer 188 and β- Cyclodextrin complexes were selected for further process.

Keywords: Candesartan, Phase solubility, Inclusion complex, Buccal tablets.

INTRODUCTION

The delivery of drugs through the buccal mucosa has attracted much research interest over the past two decades and has been developed in an attempt to deliver a variety of pharmaceutical compounds via the buccal route[1]. Since the early 1980s there has been renewed interest in the use of bioadhesive polymer to prolong contact time in the various mucosal routes of drug administration. Per oral drug delivery has been most widely utilized route of administration for the systemic delivery of drug. The lack of efficacy of certain drugs due to decreased bioavailability, GI intolerance, unpredictable, erratic absorption and pre-systemic elimination of other potential route for administration. The recent development in the drug delivery has intensified investigation of mucosal delivery of drug such route includes oral, buccal, ocular, nasal and pulmonary routes etc[2]. Buccal mucosa is a potential site for the delivery of drugs to the systemic circulation. A drug administered through the buccal mucosa enters directly the systemic circulation, thereby minimizing the first-pass hepatic metabolism and adverse gastro-intestinal effect[3]. However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability.

Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption[4]. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. These poorly water soluble drugs with slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist5

MATERIALS AND METHODS

Material

Candesartan (CAN) was purchased from Allied Fabrichem Pvt Ltd. Hyderabad. Poloxamer188 was obtained as a gift sample from Dr. Reddy's Laboratories (Hyderabad). β-Cyclodextrin(CD) was purchased from Signet Chemical Corporation Pvt Ltd (Mumbai, India). HPMC K4M, Sodium CMC and Sodium alginate polymers were obtained from Dr. Reddy's Laboratories (Hyderabad), SD Fine Chemicals (Mumbai, India) and SD Fine Chemicals (Mumbai, India) respectively.

Phase solubility studies

Phase solubility studies were performed by Higuchi and Connors method[6]. Briefly, excess amounts of drug were added to buffer solutions containing various concentrations of β-CD (1-10mM). The suspensions were vigorously shaken in a mechanical shaker and the samples were filtered through a 0.45μm membrane filter. The Candesartan concentration was determined UV spectrophotometer at λ_{max} 212 nm. The apparent stability constant (K_{st}) can

be calculated from the phase solubility diagrams using the equation:

Apparent stability constant $(K_{st}) = \dfrac{Slope}{So\ (1-Slope)}$

Where, Slope is obtained from the graph, S_o = Intercept (Candesartan solubility in the absence of β-Cyclodextrin).

Preparation of binary systems

Binary systems of the Candesartan and carriers were prepared by two methods i.e., Melt agglomeration and Kneading method, using Poloxamer188 and β-Cyclodextrin respectively with different ratios.

Preparation of Solid Dispersions

Solid dispersions of Candesartan were prepared by melting agglomeration (MA) method. In this method, required quantity of the drug with Poloxamer 188 in different ratios (1:0.5, 1:1 and 1:2) were taken in a china dish, melted up to a temperature just beyond the melting points of the carrier and mixed well. The mixture was cooled to room temperature and pulverized and passed through the sieve no. 40[7].

Preparation of Inclusion complexes

Different molar ratios of Candesartan and β-Cyclodextrin (1:0.5, 1:0.75 and 1:1) were mixed together in a mortar and then water was added in proportions to obtain a homogenous paste. The mixture was then ground for 30min. During this process, an appropriate quantity of water was added to the mixture in order to maintain a suitable consistency. The paste was dried in oven at 40°C. The dried complex was pulverized into a fine powder[8].

Differential scanning calorimetry (DSC)

Differential scanning calorimetry thermograms of the samples (3-6mg) were recorded using a thermal analysis system

(SETARAM.DSC 131, France). After calibration with indium and lead standards, the samples were heated at 10°C/min in an aluminum pan under nitrogen atmosphere. A similar empty pan was used as the reference. The samples were scanned from 25°C to 300°C.

X-ray diffractometry (XRD)

X-ray powder diffraction patterns were recorded using a powder diffractometer at 40mV, 45 kV and with monochromatized Cu K_α radiation (λ=1.54056Å). The samples were scanned at room temperature in the continuous scan mode over the 3°-40° range, with 0.01671 2θ step size and with counting time of 19.95s.

FTIR spectroscopic studies

The spectra of pure candesartan, cyclodextrin and their mixtures were collected on IR spectroscopy (IR spectroscopy Bruker Vecctor 22, Germany) at 4000 cm^{-1} resolution for scans. Samples (1% w/w) were mixed with KBr powder and compressed to a 12 mm disc by a hydraulic press at 10tonnes compression force for 30sec. The disc was placed in the sample holder and scanned from 400 to 4000 cm^{-1}.

Bioadhesive tablets preparation

The buccal tablets were prepared by using selected mucoadhesive polymers loaded with drug, free (or) in the form of solid dispersion and inclusion complexes by direct compression method. All the ingredients including drug, polymers and excipients were weighed accurately according to the batch formula as shown in Table 1. Then all the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant and glidant were added and again mixed for 2 min. The prepared blend of each formulation

was compressed by using rotary tablet punching machine with 8mm punch[9].

In vitro evaluation of candesartan buccal tablets

Weight variation

Thirteen tablets from each formulation (F1 to F13) were weighed using an electronic balance and the average weight was calculated.

Hardness

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated and the results are shown in Table 2.

Friability

Friability is the measure of tablet strength. Roche type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss was determined by the following equation.

$$\% \, Friability = \frac{Initial \, weight - Final \, weight}{Initial \, weight} \times 100$$

Thickness

The thickness of three randomly selected tablets from each formulation was determined in mm using a vernier caliper (Pico India). The average values were calculated.

Determination of tablet swelling index

Tablets weighed (w1) were placed separately in petri dishes containing 20 ml of distilled water and the dishes were stored at room temperature. At predetermined time intervals, the discs were removed and the excess water on their surface was carefully removed using filter paper[10]. The swollen discs were reweighed (w2) and the index of swelling was calculated by the following formula:

$$Swelling \, index \, (SI) = \frac{w_2 - w_1}{w_1} \times 100$$

Where W_1 was initial weight of tablet and W_2 was final weight of tablet after swelling.

Surface pH measurement

A combined glass electrode was used for this purpose. The microenvironment pH (surface pH) of the buccal tablets was determined to investigate the possibility of any side effects in *in-vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, the surface pH was kept as close to neutral as possible. The tablet was allowed to swell by placing it in contact with 5 mL of distilled water (pH 6.5 ± 0.05) for 2hrs at room temperature. The pH was measured by placing the electrode in contact with the surface of the tablets and it was allowed to equilibrate for 1 min[11].

Measurement of mucoadhesion time

The *ex-vivo* mucoadhesion time was examined by application of the buccal patch on freshly cut porcine buccal mucosa. The fresh porcine buccal mucosa was tied on the glass slide and a mucoadhesive core side of each patch was wetted with 1 drop of phosphate buffer (pH 6.8) and the tablet prepared was placed on to the porcine buccal mucosa by applying little force with fingertip for 30 seconds. The glass slide was placed in the beaker, which contains 800 ml of the phosphate buffer and kept at $37 \pm 0.5°C$. The

time taken for the tablet to detach from the buccal mucosa was recorded as the mucoadhesion time[12].

Measurement of mucoadhesive strength

Bioadhesive strength was measured in terms of weight in grams required to detach the tablet from the porcine buccal mucosa. The weights were added until tablet gets detached from porcine buccal mucosa. The weight required to detach the tablet from buccal mucosa was noted as *exvivo* mucoadhesive strength. Mucoadhesive strength was performed in triplicate at 37±1°C and average Mucoadhesive strength was determined[10].

Drug content

An equivalent weight of 30 mg of candesartan was obtained by powdering 20 prepared tablets. This was dissolved in 20 ml of methanol and filtered. The filtrate was diluted in a 100ml volumetric flask with phosphate buffer pH 6.8. The amount of the drug present in the prepared tablets was calculated by taking the absorbance at 212nm.

In vitro dissolution studies

The United States of Pharmacopoeia (USP) XXIV rotating paddle method was used to study the drug release from the buccal tablets. 500mL of phosphate buffer (pH 6.8) was used as dissolution medium, with rotation of speed of 50rpm at 37± 0.5°C. 5mL samples were withdrawn at predetermined time intervals and the same volume of fresh medium was replaced. The samples were filtered through Wattman filter paper No.40 and analyzed for Candesartan by UV spectrophotometer at λ_{max} 212nm. The % drug release was calculated.

Ex vivo permeation studies

Ex vivo permeation studies were carried out in the standard Franz diffusion cell, with a diffusion area of 4.09 cm^2 and the receptor compartment volume of 25ml. A fresh porcine buccal mucosa was obtained from slaughter house and it was clamped between the donor and acceptor compartments. The receptor compartment was filled with 6.8pH phosphate buffer and was continuously stirred at 600 rpm using a magnetic stirrer. The tablet was placed into the donor compartment, and was wetted with 1 ml of phosphate buffer. The amount of drug permeated through the membrane was determined by removing aliquots from the receptor compartment, and by replacing the same volume of buffer. The samples were analyzed by UV spectrophotometer at λ_{max} 212nm. The flux of Candesartan through the membrane was calculated using the following equation:

$$J = \frac{dQ}{A\,dt}$$

Where J is the steady-state flux and A is the diffusion area.

Statistical analysis

To understand the drug release kinetics and mechanism of drug release from prepared tablets in vitro drug release data was analyzed by different model depend kinetics like zero order, First order, Higuchi, krosmeyer-peppas models. Regression coefficient (R2) values obtained by kinetic models were illustrated in Table 3. From the kinetic data of krosemeyer-peppas model, we can confirm the mechanism of drug release. If 'n' values is <0.45, that follows Fickian diffusion, 'n' value is in between 0.45-0.89 it follows non Fickian transport mechanism and if 'n' is more than 0.89 it follows case II transport.

RESULTS AND DISCUSSION

Candesartan binary systems

From the phase solubility diagram obtained for CAN- β-CD complex, the shape of the solubility diagram followed an A_L type system. The apparent stability constant, K_s,

was calculated to be 1.128 x 10^3 M^{-1}. The phase solubility study suggested the formation of a CAN- β-CD inclusion complex with 1:1 stoichiometry, so the equimolecular CAN- β-CD solid system was prepared. Freeze drying of solubilized CAN in cyclodextrin solution yielded a solid amorphous product. As the concentration of β-CD increases, the Candesartan concentration increases linearly. Thus, Candesartan- β-CD Inclusion complexes show the A_L type of Phase solubility graphs and forms complexes in m:1 stoichiometric ratio.

Based on the Phase solubility diagram and solubility studies the 1:2 ratio of Candesartan- Poloxamer 188 and 1:1 ratio of Candesartan- β-CD showed the better solubility. These ratios were used to prepare the buccal tablets. Further evidence of the complex formation was obtained by differential scanning calorimetry, X-ray diffractometry.

Differential scanning calorimetry (DSC)

The DSC curve of CAN showed an endothermic event as a melting peak with the onset temperature of 170°C, indicating a cubic crystal polymorph form. The thermal behavior of β-CD exhibited no phenomena in any temperature intervals. The disappearance of the endothermic peak in the thermogram of the complex could be attributed to the inclusion of CAN in the β-CD cavity. On the other hand, the absence of DSC signal can also be expected for complexes because of their amorphous character. In the thermogram of the mixture of amorphous components, the peak was still present as free amorphous candesartan recrystallized before melting during the scanning time. This indicated that, in the complex, candesartan was dispersed in the amorphous host clathrate and its crystallization was hampered. The recorded thermograms were shown in Fig.2.

X-ray diffractometry

The X-ray diffractometry studies revealed the crystalline nature of CAN, as well as the amorphous state of β-CD. The X-ray diffraction pattern of the physical mixture can be interpreted as a superposition of CAN and amorphous β-CD. The peaks obtained were of less intense than those of the drug. The diffractogram of the drug: β-CD complex showed less intense crystal signals, demonstrating the amorphous nature of the product. The X-ray diffraction graphs were shown in Fig. 3.

FTIR spectra

Drug excipients interactions were effectively analyzed by Fourier transform infrared (FTIR) spectroscopy (Shimadzu). FTIR spectra of Candesartan pure drug, solid dispersions, inclusion complexes and the physical mixture of Candesartan, HPMC and sodium alginate were performed and the characteristic wave numbers were showed in Fig.4. The presence of all the characteristic bands due to functional groups in physical mixtures indicated chemical stability and also indicated that the drug is not involved in any chemical reactions. However, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers.

Evaluation of buccoadhesive tablets

Weight variation

Weight variation for all the formulations found within limits i.e. 148.4-149.9mg. The percentage deviation from average tablet weight for all the formulations ranged from 0.01 to 1.88 as shown in table 2.

Thickness and Diameter

The diameter of the tablets of all formulations were found to be 8.0 mm and thickness ranged between 2.9±0.04 to 2.9±0.15mm.

Hardness

Hardness of all the formulations shows between the range of 3.3±0.1 to 5.4±0.5 kg/cm^2 with standard deviation of <0.6. This indicates good tablet strength. The values were in table 2.

Friability

Friability of the formulations is ranged from 0.14±0.31 to 0.40±0.04 %. So, the percentage Friability of all the formulations was found to be less than 1% and it was noted that all the formulated tablets are mechanically stable.

Content Uniformity

In the evaluation of tablets, drug content of all the formulations found to be ranged from 96.8±0.55 to 98.8±0.64. The results in table 2 showed that the all formulations having uniform percentage drug content as per limits.

Surface pH Study

The results showed that the surface pH of all the tablets were within the range of 6.34 to 6.83. These results indicated that there is no risk of mucosal damage or irritation while administering these formulations on buccal mucosal region as the pH of the buccal mucosa is similar to the surface pH of the tablets prepared the results of the pH study were shown in Table 3.

Ex vivo Mucoadhesion time

The *ex vivo* mucoadhesion time for all the formulated tablets were approximately in the range of 08 to 12 hours. Due to the low mucoadhesive properties of Sodium CMC, the F5 and F11 formulations showed the lower mucoadhesion time. Thus formulations having Sodium CMC shows the lowest mucoadhesion time compared to other formulations. In the formulations prepared with Drug: Poloxamer188 along with HPMC: Sodium alginate combinations, F6

formulation showed the highest mucoadhesion time compared to other formulations. The formulations prepared with Drug: β-CD along with HPMC: Sodium alginate combinations F12 showed the highest mucoadhesion time compared to other formulations. The sodium alginate had the better mucoadhesion, due its flexibility, so it easily diffused and interpenetrated into the mucin and got entangled. Thus Sodium alginate gave the highest mucoadhesion effect on mucin as compared to HPMC and Sodium CMC. The results of the mucoadhesion time were shown in the Table 3.

Mucoadhsive strength

The bioadhesive forces of buccal tablets were affected by the nature of the polymer. Swelling of the polymer contributed to the interpenetration of mucus and polymer which made bioadhesion possible. In the formulation prepared with drug: Poloxamer 188, the highest adhesion strength was observed with the formulation F6 containing Sodium alginate: HPMC K4M combination, followed by F7 and the least bioadhesion was observed in F3 formulation containing Sodium CMC itself. The polymer combinations showed the higher mucoadhesion strength compared to the single polymer itself. In the formulation prepared with drug: β-CD, the highest adhesion strength was observed with the formulation F12 containing Sodium alginate: HPMC K4M combination, followed by F13 formulations. The least bioadhesion was observed in F9 formulations containing Sodium CMC itself.

Swelling Studies of Buccal tablets

The bioadhesion and drug release profile were dependent upon swelling behavior of the tablets. Swelling index was calculated with respect to time. Swelling index increased as the weight gain by the tablets increased proportionally with the rate

of hydration. The formulation F3 containing combination of Sodium CMC and poloxamer 188 showed higher swelling index 97.19±0.76, while the formulation F9 containing combination of Sodium CMC and β-CD showed higher swelling index up to 99.69±1.65. The formulation F6 containing combination of poloxamer 188 with Sodium alginate and HPMC K4M showed lesser swelling index 42.64±1.03, while the formulation F12 containing combination of β-CD with HPMC K4M and Sodium alginate showed lower swelling index 45.07±0.50. The results of the swelling index were reported in Table 3.

In vitro Drug release studies

The prepared buccal tablets of the candesartan prepared with the combination of poloxamer 188 and β-CD with different combinations and as such with different polymers were subjected for the dissolution studies for the drug release. The drug release profiles were compared with the tablets prepared with only candesartan as such and with the tablets prepared with combination of polymers. The formulation F1 prepared with the free of polymer has shown its release up to 55.25% for a period of 12 hrs. The tablets prepared with the poloxamer 188 and the different combination of the polymers has shown its release up to 95% and the formulations prepared with the combination of β-CD has released up to 99% for a period of 12 hrs. The release profiles were shown in the fig:5

Dissolution of Candesartan in Poloxamer 188 based tablets were slower compared to the tablets containing the cyclodextrin complex. The Candesartan: β-CD complex dissolves easily in a hydrated polymeric environment, resulting in a higher diffusional driving force and faster drug release. Due to the Candesartan low aqueous solubility, only a limited amount of drug can dissolve inside the hydrated polymeric

matrices. Incorporation of β-CD in the matrix improved the drug solubility and dissolution rate. The dissolved β-CD in the gel matrix formed a complex with Candesartan, and improved its solubility. The solubilization due to the in situ complex formation was the main reason for enhanced Candesartan release from β-CD containing polymeric matrices.

Relationship between the Swelling Index and drug release of buccal tablets containing the drug loaded with Poloxamer 188

As the swelling index of formulations increases, drug releases was decreased in most of the formulations. The formulations F3 and F5 containing Sodium CMC show the 80.47% and 82.97±0.14 drug release respectively. These formulations show the higher swelling index up 97.19 and 79.55±0.62 respectively. Thus prolonged drug release was observed due to more viscous solution around the tablet. Formulations F6 shows the erosion before complete swelling could take place, and low swelling up to 42.64 resulting in faster release of drug 95.33%. The ability of more viscous polymers to capture water is greater, results in a rapid swelling, and strong, homogeneous structures were obtained. Thus, crossing the gel layer will be more difficult for drugs in formulations with polymers of high viscosity. Another reason that could explain the faster drug release of tablets is a higher elastic modulus caused by the less water uptake and higher erosion. This resulted in a shorter path length for drug diffusion into release medium. Therefore, the swelling capacity of the matrix was low and provided a faster drug release.

Relationship between the Swelling Index and Drug release of buccal tablets containing the drug loaded with β-Cyclodextrin

As the swelling index of formulations increases, drug releases was decreased in most of the formulations. The formulations F9 and F11 containing Sodium CMC shows

the 80.91% and 83.30±1.94 drug release respectively. These formulations show the higher swelling up 99.69 and 82.42±0.44 respectively. Thus prolonged drug release was observed due to more viscous solution around the tablet. Formulations F12 shows the erosion before complete swelling could take place, and low swelling up to 45.07 resulting in faster release of drug 96.07%. Swelling studies were carried out for all formulations revealed that, as the percentage of swelling increases as the viscosity of polymer increases. The ability of more viscous polymers to capture water is greater, results in a rapid swelling, and strong, homogeneous structures are obtained. Thus, crossing the gel layer will be more difficult for drugs in formulations with polymers of high viscosity. Another reason that could explain the faster drug release of tablets is a higher elastic modulus caused by the less water uptake and higher erosion. This resulted in a shorter path length for drug diffusion into release medium. Therefore, the swelling capacity of the matrix was low and provided a faster drug release.

In vitro Drug Release Kinetics of Buccal tablets

Further to characterize the release mechanism of Candesartan from buccoadhesive tablets, the dissolution data was subjected to the different model such as zero- order, first order, Korsmeyer- peppas and Higuchi diffusion models. For all formulations the R^2 values for the zero order release is more, and all the formulations shows the zero order drug release kinetics. R^2 values are in the range of 0.978 to 0.996. From the kinetic data of krosemeyer-peppas model, we can confirm the mechanism of drug release. In this model release exponent 'n' explains the mechanism of drug release from prepared tablets. If n values is <0.45, that follows Fickian diffusion. Similarly, n value is in between 0.45 -0.89 which follows non-Fickian transport mechanism. If 'n' is

more than 0.89 which follows case II transport. As for this present work concerns, all formulations shows the n value below 0.89 and drug release profile of all formulations follows non Fickian transport to release the drug from prepared tablets.

Ex vivo permeation study

The F1 formulation with pure candesartan shows the least permeation up to 7.85 mg. The F6 formulation containing the Sodium alginate: HPMC polymer combination shows the higher cumulative amount permeated (Q) up to 13.12mg in 12hr. The F1 formulation with pure candesartan shows the least permeation up to 7.85mg. The F12 formulation containing the Sodium alginate: HPMC polymer combination shows the higher cumulative amount permeated (Q) up to 13.29mg in 12hr.

CONCLUSION

XRD, DSC and FTIR studies results indicated that no interaction of the drug with the carriers and conversion of crystalline form to amorphous form of drug results in improvement of solubility. Results conclude that the formulations containing the solid binary system and the drug complexed with β-cyclodextrin showed a great potential as a buccal drug delivery formulation, in which a good compromise among mucoadhesion, dissolution and permeation properties was achieved. Based on the saturation solubility data, two drug-carrier combinations, Poloxamer (MA 1:2) and β-Cyclodextrin (1:1 M) were selected as optimized formulations to load the drug into the mucoadhesive formulations. Formulations F6 and F12 has shown the better mucoadhesion time (12±0.34, 12±0.37 hrs.), *ex vivo* mucoadhesion strength (26.15±1.23 26.6±0.52 g), and low swelling, higher *in vitro* drug release 95.33% and 96.07%, higher cumulative amount permeated (Q) up to

13.12mg and 13.29 mg respectively. Hence Formulation F6 and F12 considered being optimized formulas. According to these results, the formulations containing the solid binary system and the drug complexed with β-cyclodextrin showed a great potential as a buccal drug delivery formulation, in which a good compromise among mucoadhesion, dissolution and permeation properties was achieved.

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Table 1. The composition of Candesartan buccal tablets containing various polymers with the combination of different carriers like Poloxamer 188 and with β-cyclodextrin

Ingredients (mg)	Formulation Code												
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Candesartan	16	16	16	16	16	16	16	16	16	16	16	16	16
Poloxamer188	-	32	32	32	32	32	32	-	-	-	-	-	-
β-CD	-	-	-	-	-	-	-	41.23	41.23	41.23	41.23	41.23	41.23
HPMC K4M	-	50	-	-	25	25	-	50	-	-	25	25	-
Sodium CMC	-	-	50	-	25	-	25	-	50	-	25	-	25
Sod. Alginate	-	-	-	50	-	25	25	-	-	50	-	25	25
MCC	91.5	41.5	41.5	41.5	41.5	41.5	41.5	32.27	32.27	32.27	32.27	32.27	32.27
PVP K30	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Mg stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Total weight of tablet = 150mg

Table 2. Evaluation of physico-chemical properties of Buccal tablets containing the drug loaded with Poloxamer 188 with β-cyclodextrin

Formulation Code	Average weight (mg)*	Thickness (mm)**	Hardness (Kg/cm^2)**	Friability**	% Drug content**
F1	149.9±0.02	2.9±0.1	3.3±0.1	0.20±0.01	98.68±0.21
F2	148.6±0.1	2.9±0.04	5.0±0.6	0.20±0.05	98.3±0.87
F3	148.8±0.3	2.9±0.06	5.2±0.5	0.40±0.04	98.5±0.40
F4	149.3±0.01	2.9±0.07	4.9±0.4	0.27±0.44	98.8±0.84
F5	149.1±0.08	2.9±0.1	4.9±0.1	0.20±0.24	98.5±1.02
F6	149.5±0.2	2.9±0.04	5.1±0.4	0.27±0.55	99.1±0.23
F7	148.9±0.5	2.9±0.08	5.3±0.1	0.27±0.56	96.8±0.55
F8	149.8±0.09	2.9±0.06	5.1±0.6	0.20±0.25	97.5±0.22
F9	149.9±0.19	2.9±0.08	5.4±0.2	0.27±0.14	98.6±0.15
F10	149.4±0.11	2.9±0.09	5.1±0.5	0.14±0.31	98.1±0.24
F11	148.6±0.25	2.9±0.1	4.9±0.4	0.20±0.45	98.4±0.27
F12	149.8±0.64	2.9±0.11	5.2±0.2	0.27±0.08	98.2±0.41
F13	148.4±1.88	2.9±0.15	5.1±0.1	0.34±0.19	98.4±0.37

All values are expressed as mean± SD. (*n = 10, **n = 5)

Table 3. Evaluation of physico-chemical properties of Candesartan buccal tablets prepared with various polymers

| Formulation Code	Surface pH measurement	Swelling Index	Mucoadhesion time (hr)	Mucoadhesive strength (gm)	% Drug content
F1	6.7±0.23	10.34±0.89	0.16±0.48	2.68±0.14	98.68±0.21
F2	6.5±0.02	67.43±0.39	10.50±0.24	19.26±0.61	98.3±0.87
F3	6.63±0.15	97.19±0.76	08.30±0.54	15.24±0.25	98.5±0.40
F4	6.80±0.06	44.82±0.87	10.2±0.66	21.54±0.88	98.8±0.84
F5	6.83±0.14	79.55±0.62	09.2±0.28	19.42±0.45	98.5±1.02
F6	6.74±0.11	42.64±1.03	11.55±0.34	26.15±1.23	98.2±0.45
F7	6.69±0.21	54.80±0.73	10.05±0.22	20.67±0.89	97.6±0.39
F8	6.6±0.16	69.53±1.39	11.00±0.16	20.21±1.86	97.5±0.22
F9	6.75±0.14	99.69±1.65	09.02±0.26	16.21±0.56	98.6±0.15
F10	6.49±0.24	46.99±2.06	10.45±0.48	22.55±0.24	98.1±0.24
F11	6.68±0.16	82.42±0.44	10.20±0.34	20.02±0.35	98.4±0.27
F12	6.81±0.31	45.07±0.50	11.55±0.37	26.6±0.52	97.8±0.33
F13	6.34±0.52	58.84±2.75	11.05±0.24	20.14±0.81	98.3±0.24

All values are expressed as mean± SD. (n=3)

Table 4. *In vitro* Drug Release Kinetics of Candesartan buccal tablets prepared with various polymers

| Formulation Code	Zero		HIGUCHI		PEPPAS			FIRST		Hixson Crowell	
	R^2	K	R^2	k	R^2	k	n	R^2	K	R^2	K
F1	0.978	6.616	0.854	21.385	0.962	15.286	1.184	0.948	0.015	0.961	0.133
F6	0.984	8.903	0.957	30.378	0.957	3.656	0.563	0.934	0.025	0.975	0.251
F12	0.984	8.909	0.962	30.469	0.969	3.540	0.549	0.928	0.025	0.973	0.256
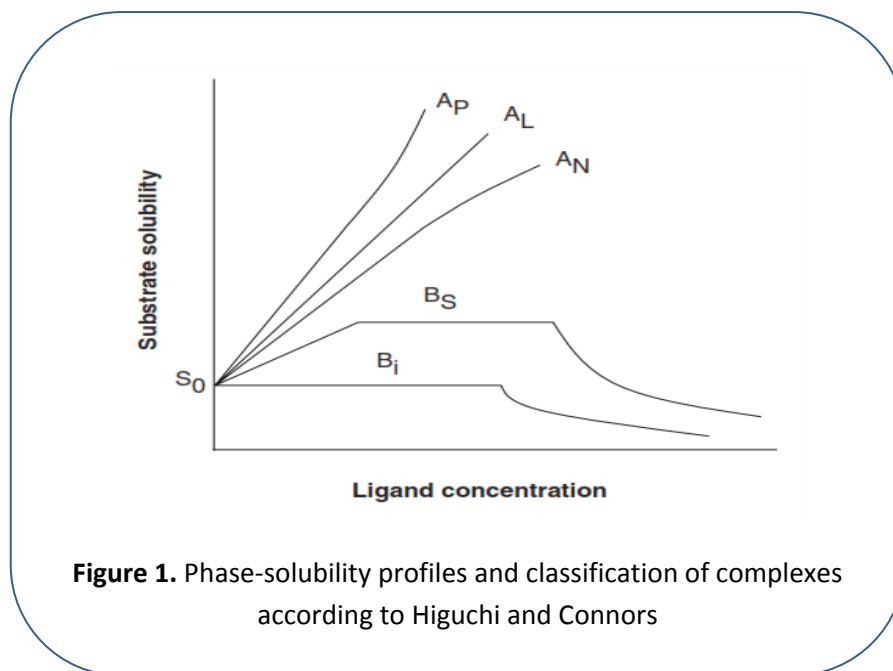
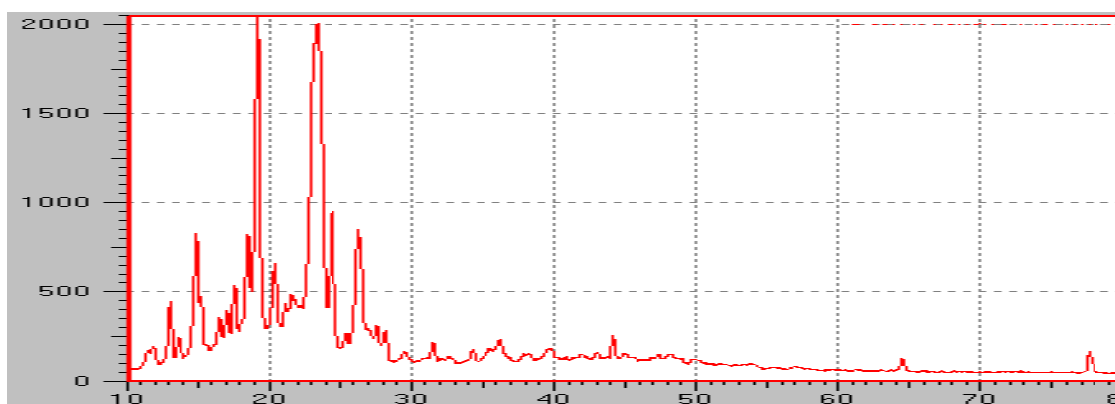**Figure 1.** Phase-solubility profiles and classification of complexes according to Higuchi and Connors
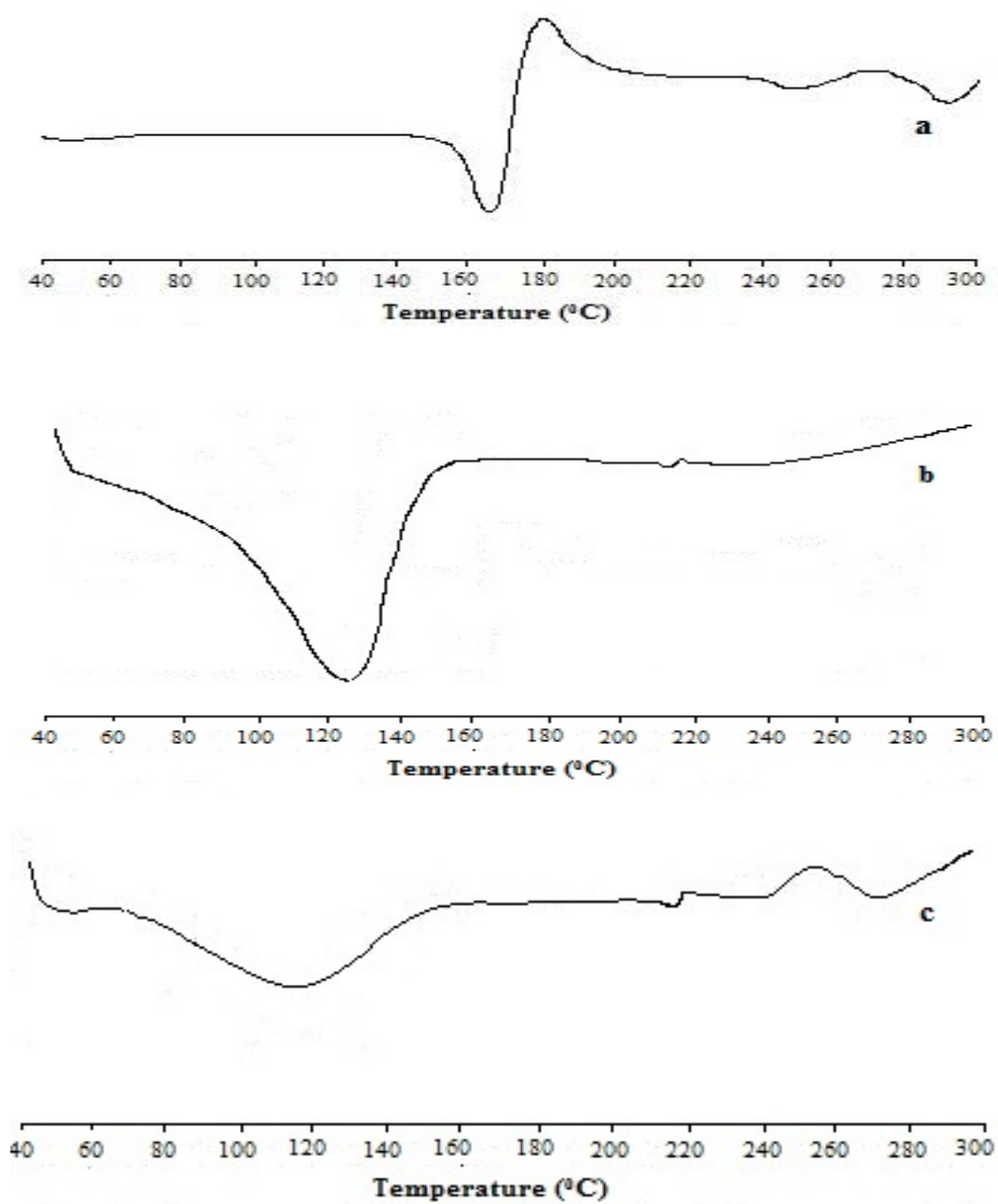
Figure 2. DSC thermograms of Candesartan/β-CD systems: (a) Candesartan, (b) β-CD, (c) 1:1 CAN/β-CD complex
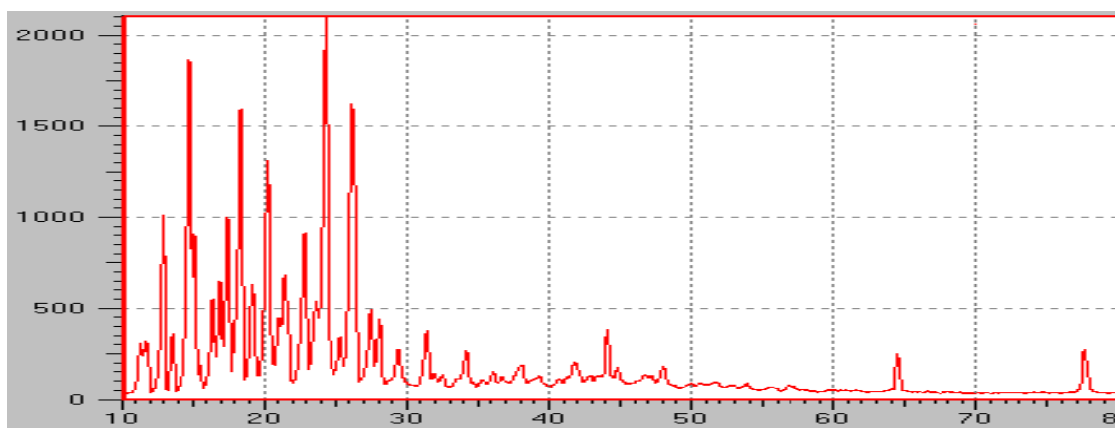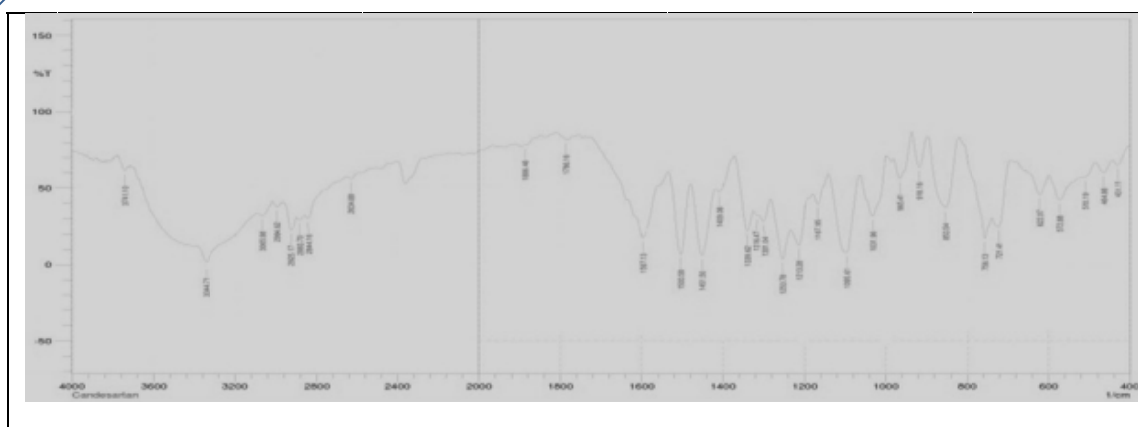
3a: X-ray diffraction patterns of Candesartan

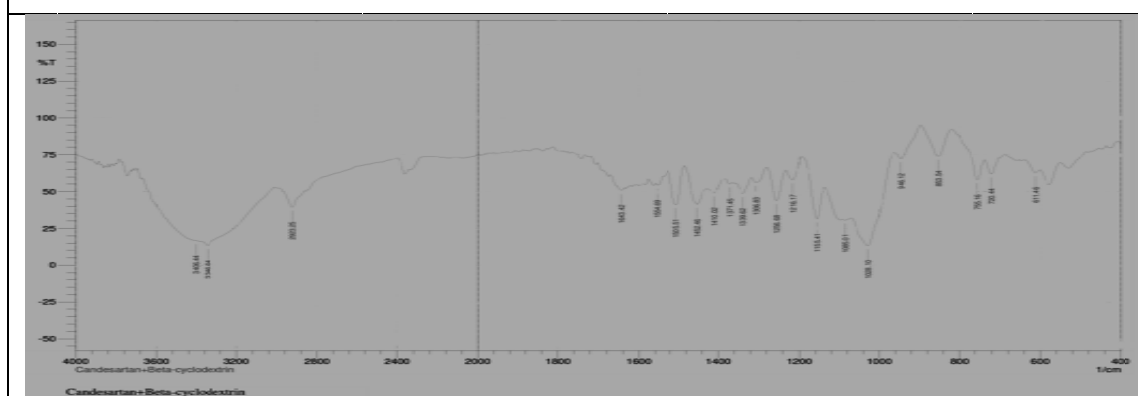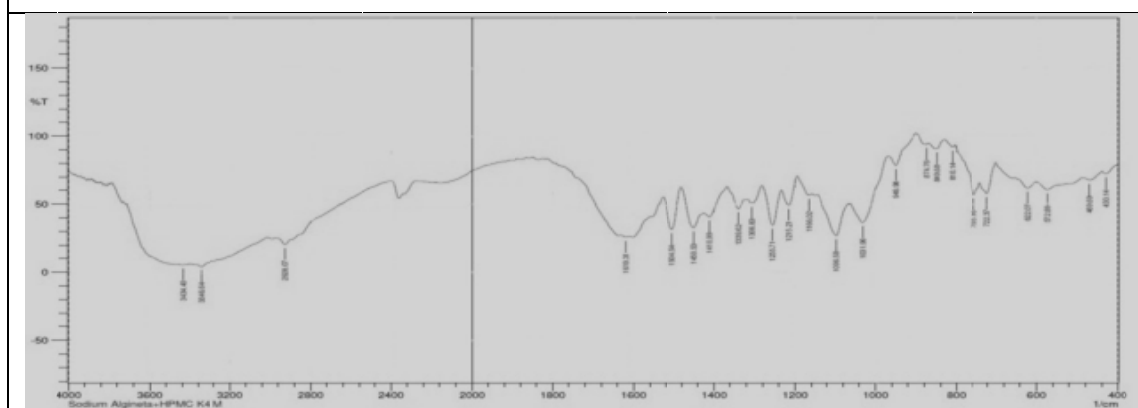3b: X-ray diffraction patterns of Candesartan: Poloxamer 188 (1:2)

3c:X-ray diffraction patterns of Candesartan β-CD (1:1)
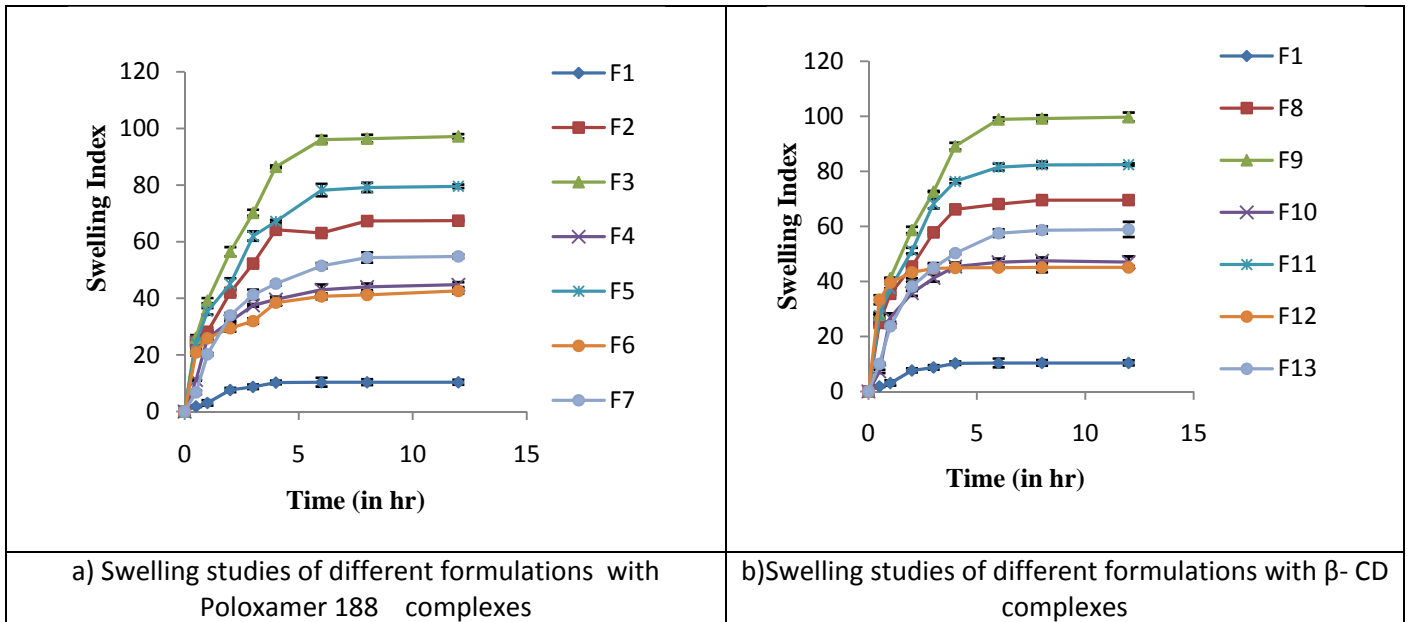
**Figure 3.** X-ray diffraction   patterns

a): FTIR spectrum of Candesartan

b): FTIR spectrum of CAN: β-Cyclodextrin

c) FTIR spectrum of Candesartan: HPMC: Sodium alginate mixture

Figure 4. Characterization of Binary systems and of Candesartan buccal tablets prepared with various polymers by FTIR studies

| a) Swelling studies of different formulations with Poloxamer 188 complexes | b)Swelling studies of different formulations with β- CD complexes |

Figure 5. Swelling studies profiles of Candesartan buccal tablets prepared with various polymers of different formulations

| a).Formulations with Poloxamer 188 complexes | b)Formulations with β-CD complexes |
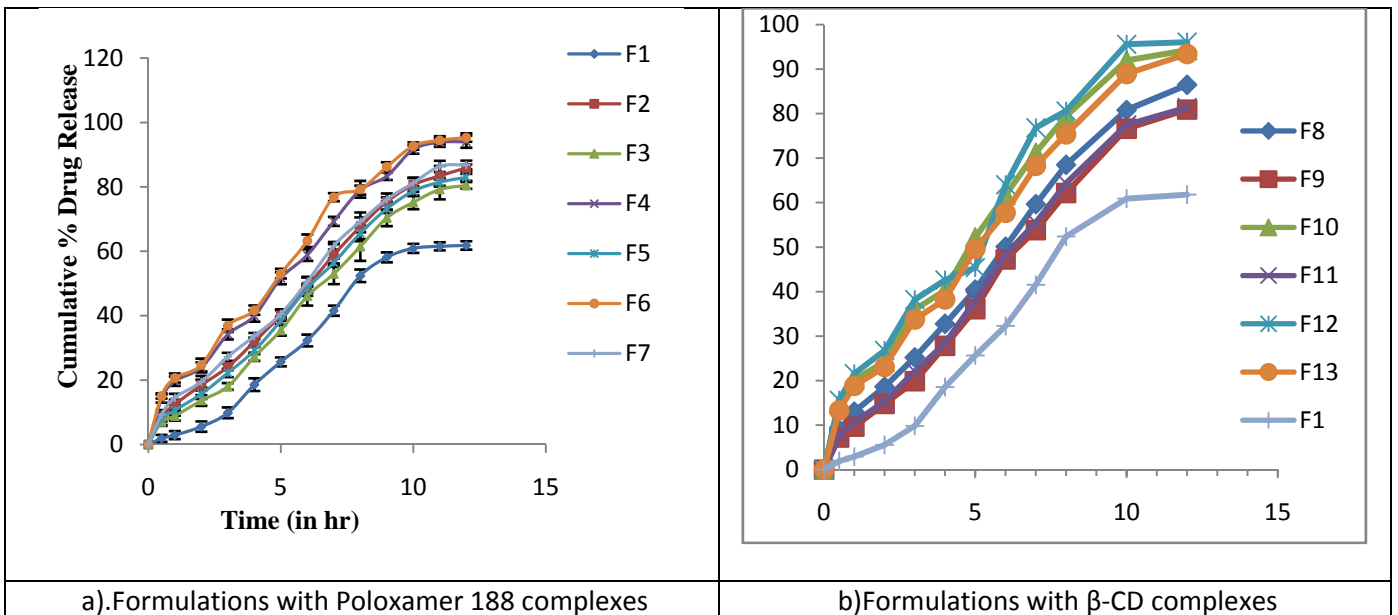
Figure 6. Drug release profile of different formulations of Candesartan formulated with Poloxamer188 and β-CD complexes with different types of polymers
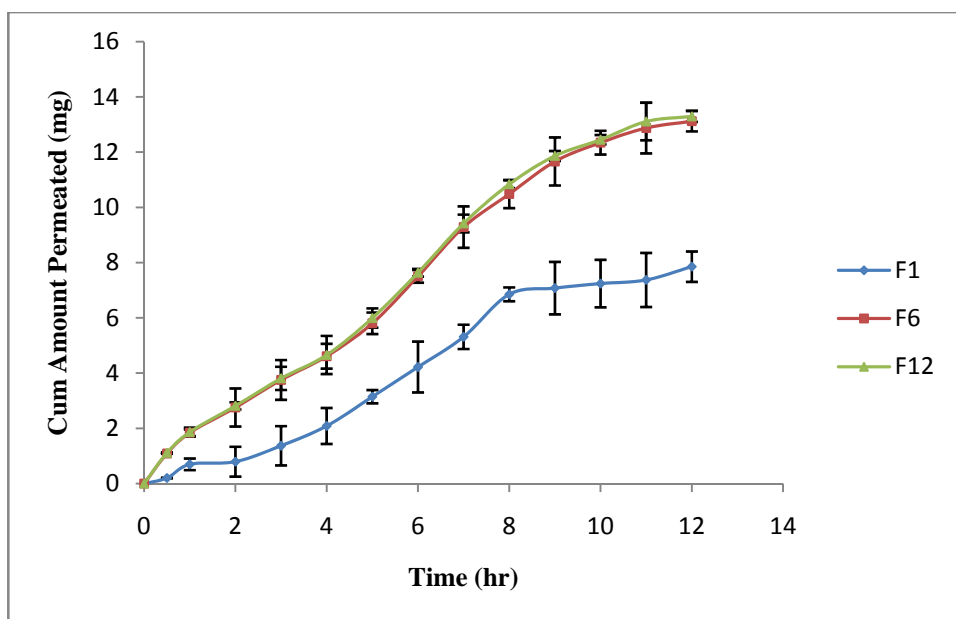
Figure 7. *Ex vivo* permeation studies of Candesartan for F1, F6 and F12 formulation