

Design and Evaluation of Enteric Compression-coated Tablet for Chronotherapeutic Drug Delivery

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Abstract

Aim: The aim of the present study was to design and evaluate compression-coated pulsatile drug delivery system intended for the treatment of early morning rise in blood pressure. Candesartan cilexetil which is a non-peptide angiotensin II Type 1 receptor antagonist was selected for pulsatile drug delivery. **Materials and Methods:** Candesartan cilexetil is potent drug and used in the treatment of hypertension and congestive heart failure. Compression-coated tablets were prepared to achieve the predetermined lag time. This coated tablet contains inner core containing active drug, excipients, and outer barrier layers of different compositions of enteric polymers such as Eudragit L 100, S 100, and L100-55 with ethyl cellulose. Both core and coated tablets were evaluated for its flow properties, hardness, friability, weight variations, and dissolution studies. The drug-excipients interactions were carried out by Fourier transform infrared. *In vitro* drug release was performed using simulated gastric fluids with 0.1 N HCl (pH 1.2) followed by phosphate buffer (pH 6.5). **Results and Discussions:** Core tablets give drug release of 98.27-99.59% within 30 min. Hardness of core tablets was in the range of 5-5.2 kg/cm². Friability values found to be 0.37-0.44%. Drug contents were found for coated tablets in the range of 97.59 ± 0.24-99.56 ± 0.23%. The optimized formulation was selected as F2 which gives 99.79% release within 12 h. **Conclusion:** Pulsatile tablet of Candesartan cilexetil was successfully evaluated, which provided a desired drug release in early morning rise in blood pressure.

Key words: Candesartan cilexetil, compression coated, eudragit as enteric polymers, ethyl cellulose, pulsatile

INTRODUCTION

Extended release dosage form was developed, which releases the drug continuously over a longer period of time. These dosage forms offer many advantages, such as nearly constant drug levels at the site of action and therefore minimization of peak-trough fluctuations, reduced frequency of administration, and an improved patient compliance. In the recent years, pulsatile released systems have gained increasing interest. Ideally, with a pulsatile system, drug is released rapidly and completely after a defined lag time of no drug release.^[1]

Pulsatile drug delivery aims to release drugs on a programmed pattern, i.e., at appropriate time and site of action.^[2] The concept of the chronopharmacokinetics and chronotherapy of drugs has been extensively utilized in clinical therapy for improving the drug efficacy

and preventing the side effects and tolerance of drugs.^[3] Chronotherapeutics is a relatively new practice in clinical medicine that varies according to physical need at different times during the dosing period. A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to circadian onset of disease or syndrome. These systems are mainly appropriate for the drugs that are metabolized to pharmacologically active compounds, drugs which have long *in vivo* half-lives showing an inherently prolonged duration of action, drugs with very short *in vivo* half-life which require a prohibitively large amount of active

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ingredients in dosage form, drugs which are required in large doses for therapeutic effect, and drugs which are require in very low doses.

In addition, a delayed burst release can also be utilized for enhancing absorption, reducing side effects, site specific delivery, improving the stability of drug, and reduction of dosage forms without affecting the therapeutic effect.^[4,5]

MATERIALS AND METHODS

Materials

Candesartan cilexetil was obtained as gift sample from Mylan Pharmaceuticals, Hyderabad. Dibasic calcium phosphate, magnesium stearate was provided as gift sample from Nitika Pharmaceuticals, Nagpur. Eudragit L 100, S 100, and L 100-55 grades were received as gift samples from Evonik, Mumbai. Ethyl cellulose was supplied as gift sample from Colorcon Asia Pvt. Ltd., Goa. All other chemicals were of analytical grade.

Methods

Preformulation study: Calibration of Candesartan cilexetil

A stock solution of Candesartan cilexetil was prepared by dissolving 100 mg of accurately weighed drug into 100 ml volumetric flask containing 50 ml of 0.2 M NaOH and phosphate buffer pH 6.5. The solution was sonicated and final volume was adjusted to 100 ml to give the stock solution of 100 µg/ml. From this stock solution, suitable dilutions were prepared using the same solvent in the range of 2-12 µg/ml. The λ max of the drug was determined by scanning one of the dilutions between 400 and 200 nm using a ultraviolet (UV)-visible spectrophotometer (Shimadzu-1800), and it was found to be 251 nm. The absorbance of all other solutions measured in 0.2 M NaOH and phosphate buffer pH 6.5.^[6]

Drug-excipients compatibility study by Fourier transform infrared (FTIR)

FTIR spectroscopy was carried out to check the possible interactions between drug, excipients, and polymers. In this method, pellets were prepared by mixing with KBr disk method by compressing it. The prepared pellets were scanned in the range of 4000-400 cm^{-1} .^[7]

Enhancement of solubility

Candesartan cilexetil having very low aqueous solubility as it comes in BCS Class II drug. Solubility was enhanced by liquisolid technique using various non-volatile solvents.^[8]

Formulation of core tablets

The inner core tablets were prepared using direct compression method. Powder of Candesartan cilexetil was dissolved in tween 80, followed by addition of dibasic calcium phosphate and sodium starch glycolate. All ingredients were dry blended for 20 min, followed by addition of magnesium stearate and talc. The powder blends were compressed using Rimek mini press II machine (Karnavati Engineering, Ahmedabad, India) with 7 mm punch to give the core tablet. The formulation was shown in Table 1.

Formulation of mixed blends for barrier layer

To achieve lag time, different compositions of Eudragit S 100, Eudragit L 100, Eudragit 100-55, and ethyl cellulose of 10 cps were weighed and blended about 20 min and used as press coating material for pulsatile tablet.

Formulation of press coating tablet

The core tablet was press coated with different ratios of barrier material of 200 mg as 100:0, 25:75, 50:50, 75:25, and 0:100. The core tablet was placed at the center, and above mixture was added into the die and compressed using Rimek Mini Press II machine.

Evaluations

Flow properties of power blends

The flow properties of powder blends were characterized in terms of bulk density, tapped density, Carr's index, angle of repose, and Hausner ratio.^[9,10]

Weight variation test

All the prepared tablets were evaluated for its weight variation as per I.P. All the test passes the weight variations test as average percentage weight variation was found within the pharmacopoeia limits of $\pm 7.5\%$.^[11]

Table 1: Formulation of core tablet

Ingredients (mg)	C1	C2	C3
Candesartan cilexetil	8	8	8
Tween 20	q.s	q.s.	q.s.
Starch Rx 1500	155	-	-
Microcrystalline cellulose	-	155	-
Dibasic calcium phosphate	-	-	155
Sodium starch glycollate	5.25	5.25	5.25
Magnesium stearate	1.75	1.75	1.75
Talc	1.75	1.75	1.75
Total weight	175	175	175

Hardness and friability

For each formulation, the hardness of three tablets was determined using Monsanto hardness tester, and average is calculated and presented with deviation. Friability represents mechanical strength of tablets. Roche friabilator was used to determine the friability by rotated at 25 rpm for 100 rotations. After the test, tablets were reweighed; loss in the weight is calculated by following expression.

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

Dissolution of core tablets

An in vitro dissolution study was performed using Type II apparatus (paddle method) at a speed of 50 rpm using phosphate buffer of pH 6.5. Sample was withdrawn at regular intervals and analyzed spectrophotometrically at 251 nm using UV visible spectrophotometer (Shimadzu 1800, Japan).^[12]

Determination of lag time for coated tablets

The intention of developing the pulsatile tablets was to release the drug rapidly in the intestine to protect from gastric environment. Hence, enteric polymers were used for this purpose which shows variations in lag time with different compositions.

Content uniformity

For the determination of drug content, ten tablets were selected randomly, crushed, and powdered quantity which is equivalent to one tablet was diluted with 100 ml of phosphate buffer of pH 6.5. Then, aliquots of the filter were diluted and analyzed spectrophotometrically at 251 nm. The drug concentration was calculated from the calibration curve.^[13,14]

Stability studies

The purpose of stability testing is to provide evidence on how the quality of drug product varies with time under the influence of environmental factors such as temperature, humidity, light, and shelf life to be established. The accelerated stability study was carried out as per the ICH guidelines for 3 months for optimized formulation. The samples were packed in an aluminum foil placed in a tightly closed high-density polyethylene bottle and kept at $40 \pm 2^\circ\text{C}$ and relative humidity $75 \pm 5\%$. Samples were taken at regular time interval of 1 month for 3 months and analyzed. Any changes in evaluation parameters, if observed, were noted. Test was carried out in triplicate, and mean value was noted with standard deviation. These studies were given good

results which mean optimized formulation had good stability up to 3 months. The data shown in Table 2.^[14,15]

RESULTS AND DISSOLUTION

Preformulation study: Calibration of Candesartan cilexetil

Calibration of Candesartan cilexetil was carried out in 0.2 M NaOH and phosphate buffer of pH 6.5 solvent. The drug was shown more linearity in phosphate buffer of pH 6.5 which is indicated in Figures 1 and 2.

Identification of drug

The FTIR spectrum obtained of pure drug shows characteristic absorption peaks and found that there are no interactions of drug with excipients and polymers. It shows that there was no significant change in the chemical integrity of the drug. The FTIR spectrum was given in Figures 3-8.

Solubility enhancement

Candesartan cilexetil is a BCS Class II drug hence it having very low solubility. Hence, attempt has been made to enhance the solubility and dissolution of this drug with non-volatile solvents. Drug was allowed to dissolve in various solvents such as glycerin, span 80, PEG 400, propylene glycol, and tween 80. Solubility of Candesartan cilexetil was significantly increased with tween 80. Hence, in all formulations, tween 80 was used to dissolve the drug.

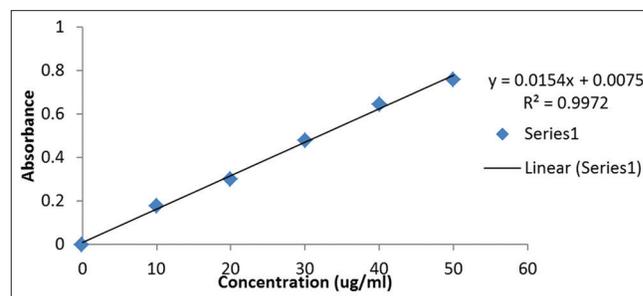


Figure 1: Calibration curve of Candesartan cilexetil in 0.2 M NaOH

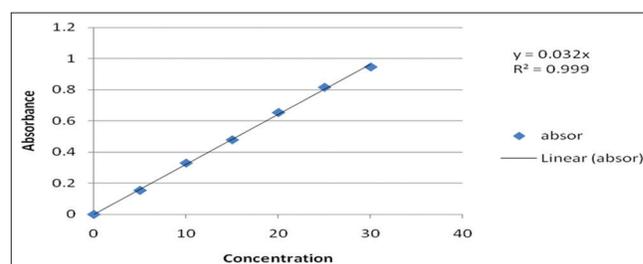


Figure 2: Calibration of Candesartan cilexetil in pH 6.5 phosphate buffer

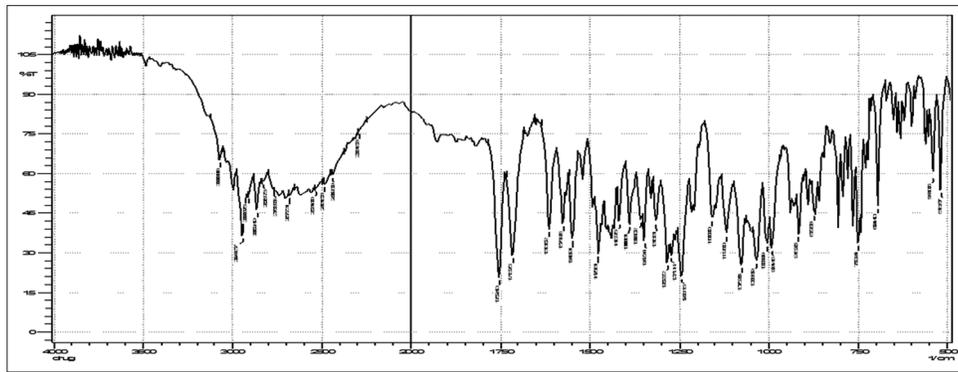


Figure 3: Infrared spectrum of Candesartan cilexetil (pure drug)

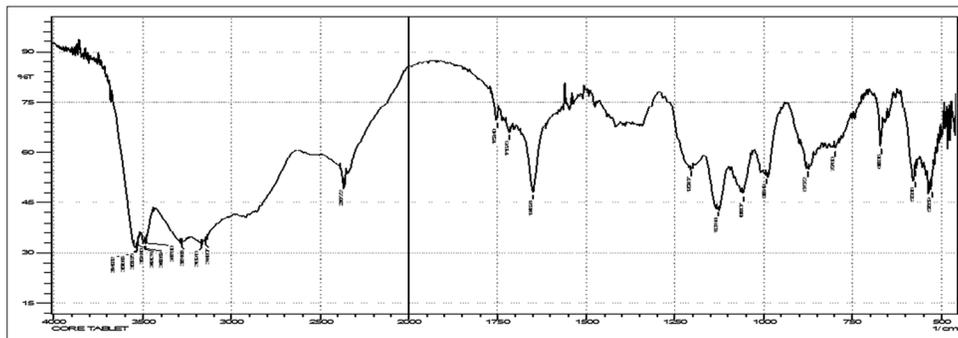


Figure 4: Infrared spectrum of core tablet of Candesartan cilexetil

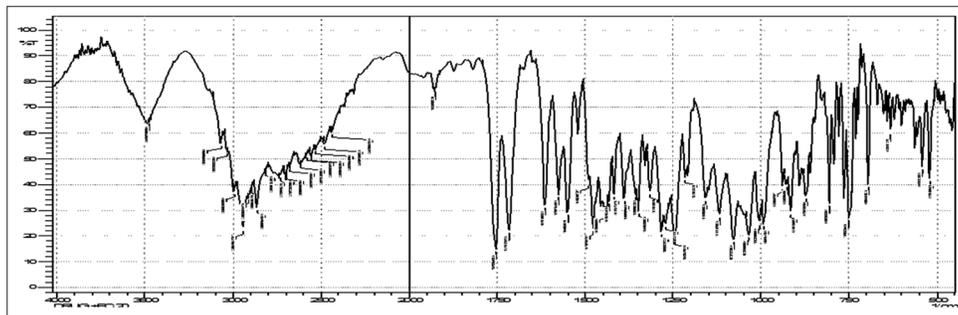


Figure 5: Infrared spectrum of Candesartan cilexetil with EC

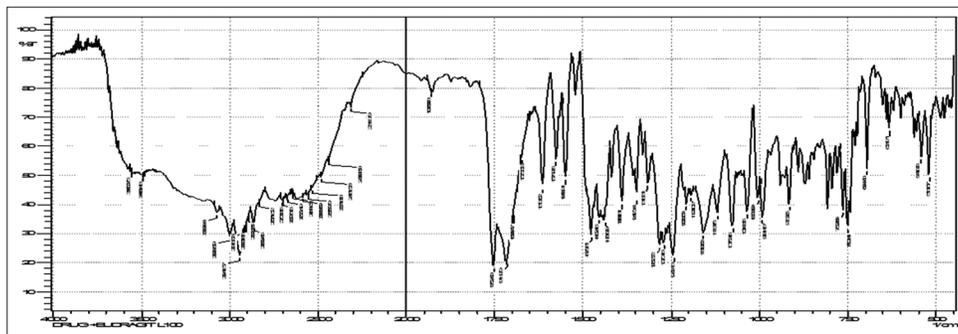


Figure 6: Infrared spectrum of Candesartan cilexetil with Eudragit L 100

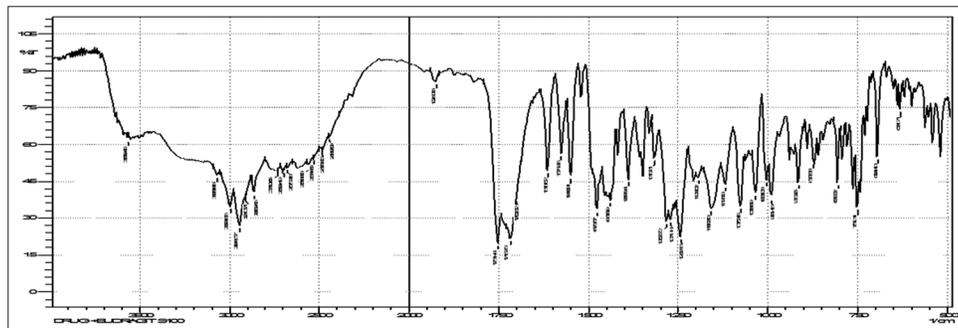
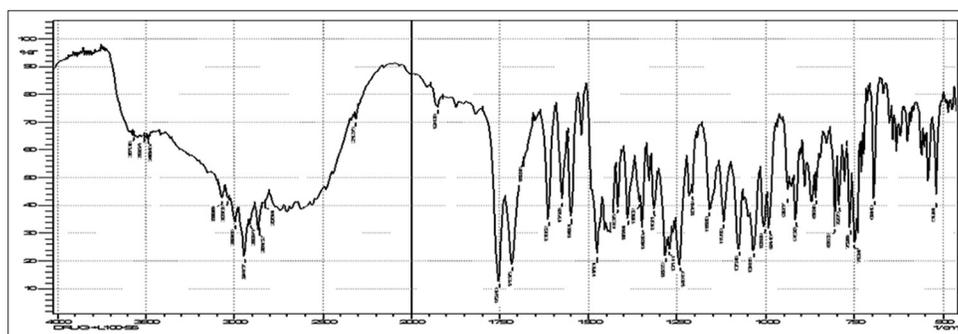
Pre-compression formulation of powder blend

Blends of formulation were subjected for pre-compression evaluations such as bulk and tapped density, compressibility

index, angle of repose, and Hausner's ratio. The values of pre-compression parameters were within prescribed limit as per USP XXVII and indicate good flow properties. The results were shown in Table 3.

Table 2: Accelerated stability studies for optimized batch F2

Property	Initial	After 1 month	After 2 months	After 3 months
Physical appearance	white to off-white color	no change	no change	no change
Hardness	9.3	9.2	9.0	8.9
Drug content (%)	98.57	98.16	97.75	97.48

**Figure 7:** Infrared spectrum of Candesartan cilexetil with Eudragit S 100**Figure 8:** Infrared spectrum of Candesartan cilexetil with Eudragit 100-55

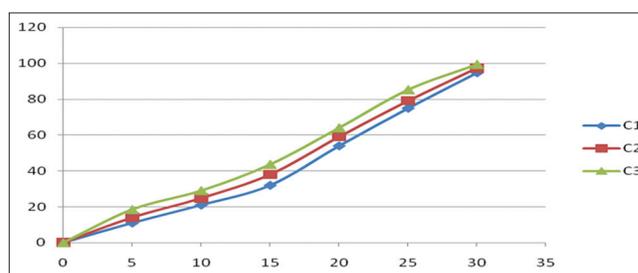
Post-compression parameters for tablets

Tablet quality control tests such as weight variation, hardness and friability, thickness, dissolution, and content uniformity were performed.

The weight variations of all core and coated formulations passed the test indicating that average percentage weight variation was found within the pharmacopoeial limits. Hardness of all core tablets was found in between the range of 5.0-5.2 kg/cm². Similarly, for coated tablets, values found in the range of 9.3-9.7 kg/cm². Friability values for core and coated tablets were found in the range of 0.37-0.44% and 0.30-0.41%, respectively. The formulated tablets were assayed for its content. The tablets of all batches showed drug content in the percentage range of 97.59 ± 0.24-99.56 ± 0.23. The results were shown in Table 4 and 5 respectively

In vitro drug release studies

An *in vitro* dissolution studies were carried out using USP Type II (paddle method) apparatus using phosphate buffer of pH 6.5 as dissolution media. Release pattern was studied by

**Figure 9:** *In vitro* drug release from core tablet

withdrawing the sample of 5 ml at a specified time intervals. Sample was diluted with buffer and measured the absorbance at 251 nm. The release pattern of core tablets was shown in Figures 9-12.

CONCLUSION

Blood pressure rises sharply in the morning in response to the activation of the sympathetic nervous system when one arises. The early morning BP surge is associated with an stroke and myocardial infarction. Hence, there is a need of

Table 3: Flow properties of core tablets

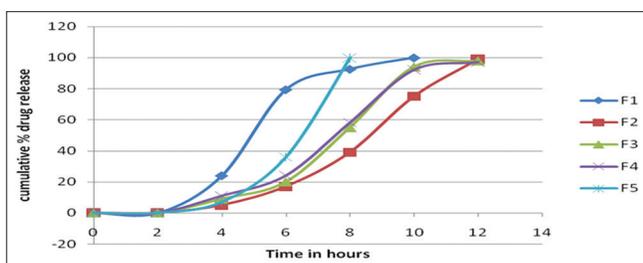
Batch code	Bulk density	Tapped density	Carr's index (%)	Angle of repose (°)	Hausner's ratio
C1	0.474	0.605	21.65	34.56	1.27
C2	0.479	0.598	19.89	32.76	1.24
C3	0.480	0.587	18.22	29.42	1.22

Table 4: Evaluation of core tablets

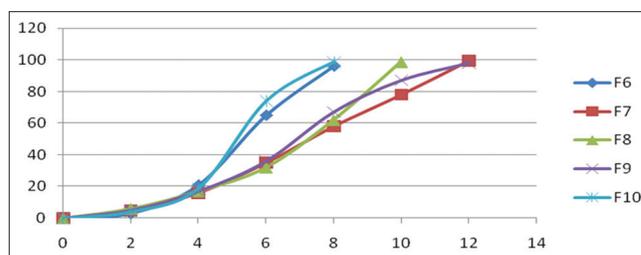
Batch code	Weight variation (mg)	Hardness (Kg/cm ²)	Friability (%)	Disintegration time (s)	Drug content (%)
C1	175±0.23	5.1	0.39	48	98.27±0.32
C2	174±0.18	5.0	0.44	44	99.23±0.27
C3	175±0.29	5.2	0.37	42	99.59±0.23

Table 5: Evaluation of compression coated tablets

Batch code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)
F1	375±0.29	4.75±0.07	9.4±0.30	0.38	98.27±0.47
F2	372±0.35	4.77±0.27	9.3±0.32	0.40	98.57±0.38
F3	377±0.26	4.76±0.17	9.7±0.19	0.32	98.15±0.57
F4	374±0.37	4.77±0.11	9.5±0.24	0.36	99.17±0.62
F5	375±0.11	4.79±0.07	9.4±0.27	0.38	99.36±0.46
F6	374±0.15	4.81±0.19	9.5±0.24	0.35	99.54±0.33
F7	377±0.23	4.74±0.23	9.6±0.18	0.33	97.59±0.24
F8	373±0.34	4.75±0.25	9.7±0.15	0.30	98.55±0.12
F9	376±0.28	4.73±0.17	9.4±0.26	0.37	98.45±0.17
F10	374±0.13	4.76±0.15	9.5±0.22	0.35	97.80±0.32
F11	377±0.24	4.77±0.11	9.3±0.32	0.41	98.68±0.27
F12	372±0.36	4.76±0.15	9.5±0.10	0.36	98.75±0.46
F13	376±0.42	4.79±0.23	9.7±0.14	0.32	97.97±0.67
F14	375±0.26	4.75±0.13	9.6±0.23	0.34	99.32±0.42
F15	374±0.17	4.77±0.09	9.4±0.16	0.36	99.56±0.23

**Figure 10: In vitro release of drug from F1 to F5**

specialized chronotherapeutic drug delivery to prevent the early morning rise in blood pressure. Candesartan cilexetil is a potent drug used in the treatment of hypertension and heart failure. Pulsatile tablet of Candesartan cilexetil was prepared with different combinations of enteric polymers and ethyl cellulose. To achieve this, F2 was selected as optimized batch which releases the drug after a predetermined lag time

**Figure 11: In vitro release of drug from F6 to F10**

when the greatest need of drug in the early morning rise in blood pressure.

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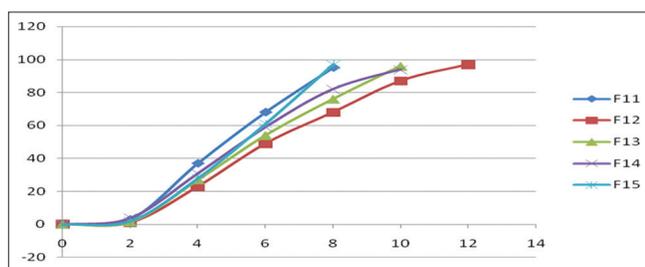


Figure 12: *In vitro* release of drug from F11 to F15

Goa, for providing ethyl cellulose as well as Evonik Degussa Pvt. Ltd., Mumbai, for gift samples of Eudragit grades.

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