RESEARCH ARTICLE

Development and Characterization of Controlled Release Tablets of Candesartan Cilexetil/ β-Cyclodextrin Inclusion Complex

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ABSTRACT

Objective: Matrix tablet approach is one of the delivery systems intended for poorly water-soluble drugs, like candesartan cilexetil (CC). CC is a class II drug used for the treatment of hypertension.

Methods: Matrix tablets from (F1x to F18z) were prepared in the presence of β-cyclodextrin. Matrix tablet formulation ensures control release of the drug and higher dissolution by β-cyclodextrin. Fourier transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC) were used to study compatibility.

Results: The angle of repose determination showed good flow for most of the formulas, besides having good compressibility. Weight variation test for all formulas showed accepted value. Drug content measurement showed accepted values. Friability and hardness of tablets were within the allowed values. Higher tablet swelling was obtained for the formulas containing hydroxypropyl methylcellulose (HPMC) K100M (F3x and F15z), in which the ratio of the polymer was 1:1 and 1:3, respectively. *In vitro* release showed that F1x to F13z were studied depends on the type and amount of polymer, i.e., 1:1, 1:2, and 1:3, respectively. F1x release after 8 hours was 95%, which contains 1:1 polymer ratio in comparison to F3x, which showed 85% after 8 hours, which includes 1:3 (drug: HPMC K100). Kinetic studies showed a zero-order model.

Conclusion: The use of β-cyclodextrin modifies the release profile of the drug, and some control the more sustained-release formulas. The lower the time of the release but in a range that a sustained release of the drug was observed in comparison with the formulas prepared without β-cyclodextrin.

Keywords: Class II drugs, Ethylcellulose, HPMC K100, Matrix tablets, Sustain release.

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INTRODUCTION

Until now, there is no pharmacological molecule meets all formulation requirements. CC is selective angiotensin II receptor antagonist. CC has unfortunately, poor oral bioavailability (less than 45%), and this due to extensive first-pass metabolism in the liver. CC is a class II drug which is a prodrug; it is entirely converted into candesartan during gastrointestinal absorption.[1] The half-life of CC is 9 to 12 hours, and peak plasma concentration (C_{max}) reaches after 4 hours, when given orally as an ordinary tablet. As the oral bioavailability is low (45%), frequent administration of the drug is intended to overcome the low bioavailability. Prolong release or sustain release dosage form is one of the approaches of drug delivery system used to decrease the frequency of the drug administration, and to improve patient compliance in comparison to the conventional tablet.[2] Matrix tablets must contain one or more polymer, which controls the release of the drug from the tablet. Polymers are biodegradable, biocompatible, and non-toxic, like HPMC and ethylcellulose.[3] CC was approved by the FDA in 2000. It is highly lipophilic drug (log P = 6.1) with low aqueous solubility of 5×10^{-5} g/L, so it was classified as a class II drug category, according to the biopharmaceutical classification system (BCS).[4] Cyclodextrins (CDs) are used in most oral pharmaceutical formulations, using inclusion complexes formation with drug. It increases the solubility, enhancement in dissolution rate, stability, and bioavailability. Drug release site and/or time profile could be modified by complex formation. Complex formation may prevent drug-drug or drug-additive interactions.[5]

The release of the drug is controlled by diffusion of the drug, or by surface erosion of the polymer in the medium, or by a combination of the two mechanisms.[6] The aim of the study is to evaluate the effect of cyclodextrin in the preparation of matrix tablets of CC on the dissolution and release profile.

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MATERIALS AND METHODS

Materials

Chemicals

CC (Micro labs, Bangalore, India). 2-hydroxyethyl-β-cyclodextrin (2-HeβCD) was procured from Lobachem Pvt. Ltd., India). HPMC K100 [Sammara Drug Industries (SDI), Iraq]. Ethylcellulose (Sigma Chemical Co., USA). PEG 6000 (Merck Pvt. Ltd., Mumbai, India). Talc (Afco., India). Polyvinylpyrrolidone (PVP K 30) (Riedel De Haen AG Seelze, Hannover, Germany). Microcrystalline cellulose (MCC) (Avecil® pH, 102) (Sigma Aldrich Co., USA). Lactose (Riedel-delta, Germany). Magnesium stearate (HiMedia Laboratories, India). Disodium hydrogen orthophosphate and potassium dihydrogen orthophosphate (S D Fine Chem Ltd., Mumbai, India). Other chemicals, solvents, and reagents used were of analytical grade.

Instruments

Tablet machine (Korsch EKO, Germany). Manual hardness tester (Stokes Monsanto Co. Ltd.). Vernier caliper (model-Triclrbrand), friabilator (Roche, Germany). UV-visible spectrophotometer (Carry win UV, Varian, Australia). pH meter (Hanna, Italy). Fourier transform infrared spectrophotometer (FTIR-8400 Shimadzu, Japan). Differential scanning calorimetry (Shimadzu, Japan). Other assistant laboratory materials and instruments used were considered official and registered.

Methods

Preliminary Study: FTIR Study

FTIR spectrum of CC, 2-HeβCD was each recorded and compared with each reference spectra of pure drug and 2-HeβCD.

Drug-Excipients Compatibility Study by DSC

Drug excipients compatibility study of pure drug was also performed to check the interaction of the pure drug with the polymers, such as, HPMC K15M and β-cyclodextrin. For the estimation of drug-polymer interaction, drug and polymer were mixed in a 1:1 ratio, and kept for study under a controlled condition, and it was examined by DSC.

Saturation Solubility of CC in Different Media

Solubility studies of CC were carried out in HCl solution (pH 1.2), buffer system (pH 6.8), HCl solution (pH 1.2) with 2-HeβCD, and buffer system (pH 6.8) with 2-HeβCD also use 0.35% tween 20 solubility study in the two media for dissolution study purpose for maintaining sink condition with appropriate concentration of tween 20.

The saturated solution was prepared by adding an excess of CC to the vehicle and shaking on the shaker for 48 hours at 37°C under constant agitation. After this period, the solutions were filtered through a 0.45 mm Millipore filter, diluted with methanol, and analyzed by UV-spectrophotometer at λ_{max} of CC. Three determinations were carried out for each sample to calculate the solubility of CC,[7,8] as shown in Table 1.

Preparation of CC, β-Cyclodextrin Inclusion Complex

It was prepared by the kneading method. For this, weigh CC and β-cyclodextrin in 1:1, 1:0.75, and 1:0.5 ratios, as shown in Table 2. β-cyclodextrin was transferred to a glass mortar, and a small quantity of water:ethanol (1:1 v/v, 3 mL) solution was added to form a homogenous paste. The drug powder was slowly added to the paste and kneaded for 45 minutes. During the kneading process, a few drops of water were also added. The resultant paste was dried and grounded well, followed by passing through a sieve. The prepared complex was stored in a desiccator to avoid humidity.[9]

Preparation of Matrix Tablets

The method used for the preparation of tablets was dry granulation technique by slugging. F1 to F6 were prepared only with the polymer without drug/ β-cyclodextrin complex, as shown in Table 3, while drug/ β-cyclodextrin complex with other components for each formula are mixed for F1x to F18z formulas, as shown in Table 4. In the two cases, the granules of each formula mixed without magnesium stearate in a bottle, and then after the mixing for 10 minutes, half of the lubricant (magnesium stearate) was added and the mixture compressed

Table 1: Saturation solubility of CC in various media

Media	*Solubility (mg/mL) (mean ± SD)*
HCl medium (pH 1.2)	0.009 ± 0.0006
Buffer medium (pH 6.8)	0.02 ± 0.004
HCl medium (pH 1.2) with 2-HeβCD	0.28 ± 0.01
Buffer medium (pH 6.8) with 2-HeβCD	0.32 ± 0.04
HCl medium (pH 1.2) with 0.35% polysorbate 20	0.093 ± 0.008
Buffer medium (pH 6.8) with 0.35% polysorbate 20	0.416 ± 0.012

n = 3; SD-standard deviation

Table 2: CC/ 2-HeβCD inclusion complex formulas according to the ratios 1:1, 1:0.75, and 1:0.5, prepared by kneading method

Ingredients (mg)	*x*	*y*	*z*
Candesartan cilexetil (CC)	8	8	8
2-HeβCD	8	6	4
Total weight	16	14	12

Table 3: Different formulas of matrix tablets without CC/ 2-HeβCD inclusion complex

	Formula tag					
Ingredients (mg)/tablet	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*
HPMC K100	16	32	48	0	0	0
Ethylcellulose	0	0	0	16	32	48
PEG 6000	10	10	10	10	10	10
Talc	5	5	5	5	5	5
PVP K 30	10	10	10	10	10	10
MCC	10	10	10	10	10	10
Lactose	71	55	39	71	55	39
Mg stearate	8	8	8	8	8	8
Total weight (mg)	130	130	130	130	130	130

Table 4: Different formulas of matrix tablets containing CC/ 2-HeβCD inclusion complex

	Formula tag																	
Ingredients (mg)/tablet	*F1x*	*F2x*	*F3x*	*F4x*	*F5x*	*F6x*	*F7y*	*F8y*	*F9y*	*F10y*	*F11y*	*F12y*	*F13z*	*F14z*	*F15z*	*F16z*	*F17z*	*F18z*
Candesartan cilexetil/ 2-HeβCD inclusion complex	16	16	16	16	16	16	14	14	14	14	14	14	12	12	12	12	12	12
HPMC K100	16	32	48	0	0	0	14	28	42	0	0	0	12	24	36	0	0	0
Ethylcellulose	0	0	0	16	32	48	0	0	0	14	28	42	0	0	0	12	24	36
PEG 6000	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
PVP K 30	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
MCC	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Lactose	55	39	23	55	39	23	59	45	31	59	45	31	63	51	39	63	51	39
Mg stearate	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Total weight (mg)	130	130	130	130	130	130	130	130	130	130	130	130	130	130	130	130	130	130

into one slug tablet by single punch tablet machine. Slug tablet then weighed and calculated the real number of tablets in which this number will help in determining the remaining amount of lubricant used. After calculating the required amount of lubricant to be used, the slug was sieved to granules by sieve, and the resulted granules were ready for the second compression by adding the calculated amount of lubricant to the granules and compressed to obtain the tablets.[10]

Tablets from F1x to F18z contained the drug/ β-Cyclodextrin complex in 1:1, 1:7.5, and 1:0.5 ratios and drug amount for all formulas were (8 mg), the polymers to be used for the study were (HPMC K100 and ethylcellulose as modifiable polymers) in the ratio 1:1, 1:2, and 1:3; the other excipients that were necessary for matrix tablet formulation were used in constant ratios for all formulas,[11] as shown in Table 4.

Evaluation of the Pre-Compressed Granules

Before compression step into tablets, the granules were evaluated for some evaluation properties,[12] like the angle of repose (Θ°), which done by funnel method, bulk density, tapped density, compressibility index, and Hausner's ratio, as shown in Tables 5 and 6. Tapped bulk density (TBD), loose bulk density (LBD), and compressibility index were calculated by using the following equations[13]:

$$\text{TBD} = \frac{\text{Weight of the powder}}{\text{Final volume}} \quad \text{Eq. 1}$$

$$\text{LBD} = \frac{\text{Weight of the powder}}{\text{Initial volume}} \quad \text{Eq. 2}$$

$$\text{Carr's compressibility index} = \left[\frac{(\text{TBD} - \text{LBD}) \times 100}{\text{TBD}}\right] \quad \text{Eq. 3}$$

$$\text{Hausner's ratio} = \frac{\text{TBD}}{\text{LBD}} \quad \text{Eq. 4}$$

Evaluation of Compressed Granules (Matrix Tablets)

The prepared tablets were evaluated by different methods like weight variation, drug content, friability, hardness, and thickness, as shown in Tables 7 and 8, swelling index (SI), as shown in Table 9, and *in vitro* dissolution test.[14]

Drug Content

An accurately weighed amount of crushed tablet of each preparation was dissolved in a small volume of methanol and further diluted in phosphate buffer with a pH of 6.8. The content of CC was determined spectrophotometrically at λ_{max} 255 nm of CC using UV-visible spectrophotometer.[15]

Weight Variation

Twenty tablets were randomly selected from each formula, and the average weight of these tablets was measured. According to the USP, not more than two of the individual weights of tablets were out of the average by more than the percentage deviation, and none deviate twice the percentage. The official limit of percentage deviation in this study is because the total weight of the tablet is which lies in the range between 130 and 324 mg.[16]

Friability, Hardness, and Thickness

Random 20 tablets were taken for evaluation from each formula. According to USP, the accepted value must be less than 1%. Friability measured by using Roche friabilator

Table 5: Evaluation of the prepared granules without CC/ 2-HeβCD inclusion complex

Formula	*Angle of repose (Θ°) (mean ± SD)*	*Flow type*	*Bulk density (g/mL) (mean ± SD)*	*Tapped density (g/mL) (mean ± SD)*	*Compressibility index (%) (mean ± SD)*	*Flow type*	*Hausner's ratio (mean ± SD)*
F1	30 ± 1.2	Excellent	0.026 ± 0.01	0.027 ± 0.01	3.7 ± 0.01	Excellent	1.06 ± 0.01
F2	30 ± 1.4	Excellent	0.023 ± 0.01	0.025 ± 0.01	8 ± 0.01	Excellent	1.08 ± 0.01
F3	31 ± 1.4	Good	0.026 ± 0.01	0.03 ± 0.01	13 ± 0.01	Good	1.13 ± 0.01
F4	31 ± 1.9	Good	0.023 ± 0.01	0.027 ± 0.01	14.8 ± 0.01	Good	1.16 ± 0.01
F5	30 ± 1.1	Excellent	0.021 ± 0.01	0.023 ± 0.01	8.7 ± 0.01	Excellent	1.08 ± 0.01
F6	31 ± 1.1	Good	0.023 ± 0.01	0.027 ± 0.01	14.8 ± 0.01	Good	1.15 ± 0.01

n = 3; SD-standard deviation

Table 6: Evaluation of the prepared granules with CC/ 2-HeβCD inclusion complex

Formula	*Angle of repose (Θ°) (mean ± SD)*	*Flow type*	*Bulk density (g/mL) (mean ± SD)*	*Tapped density (g/mL) (mean ± SD)*	*Compressibility index (%) (mean ± SD)*	*Flow type*	*Hausner's ratio (mean ± SD)*
F1x	33 ± 1.3	Good	0.018 ± 0.09	0.021 ± 0.03	16.4 ± 0.03	Good	1.16 ± 0.2
F2x	32 ± 1.4	Good	0.017 ± 0.02	0.02 ± 0.03	16.8 ± 0.06	Good	1.18 ± 0.1
F3x	32 ± 1.2	Good	0.015 ± 0.02	0.017 ± 0.02	13.9 ± 0.02	Good	1.14 ± 0.9
F4x	33 ± 1.3	Good	0.017 ± 0.01	0.019 ± 0.01	14.7 ± 0.07	Good	1.15 ± 0.4
F5x	34 ± 1.5	Good	0.014 ± 0.03	0.016 ± 0.06	14.9 ± 0.05	Good	1.14 ± 0.2
F6x	37 ± 1.7	Fair	0.013 ± 0.09	0.016 ± 0.01	22.1 ± 0.09	Fair	1.22 ± 0.1
F7y	32 ± 1.2	Good	0.017 ± 0.01	0.019 ± 0.05	13.2 ± 0.01	Good	1.13 ± 0.7
F8y	33 ± 1.1	Good	0.016 ± 0.06	0.018 ± 0.05	14.3 ± 0.01	Good	1.15 ± 0.6
F9y	32 ± 1.4	Good	0.014 ± 0.07	0.016 ± 0.02	13.4 ± 0.07	Good	1.12 ± 0.4
F10y	33 ± 1.5	Good	0.014 ± 0.01	0.015 ± 0.01	12.3 ± 0.06	Good	1.13 ± 0.4
F11y	34 ± 1.1	Good	0.014 ± 0.07	0.016 ± 0.09	14.9 ± 0.02	Good	1.14 ± 0.8
F12y	32 ± 1.1	Good	0.014 ± 0.04	0.016 ± 0.03	11.1 ± 0.03	Good	1.12 ± 0.1
F13z	31 ± 1.2	Good	0.021 ± 0.06	0.024 ± 0.03	13.4 ± 0.03	Good	1.12 ± 0.3
F14z	31 ± 1.4	Good	0.02 ± 0.01	0.023 ± 0.06	13 ± 0.04	Good	1.15 ± 0.1
F15z	31 ± 1.4	Good	0.018 ± 0.02	0.02 ± 0.09	13.4 ± 0.07	Good	1.12 ± 0.1
F16z	32 ± 1.6	Good	0.018 ± 0.01	0.021 ± 0.08	14.9 ± 0.06	Good	1.14 ± 0.2
F17z	31 ± 1.1	Good	0.02 ± 0.02	0.023 ± 0.07	13.7 ± 0.07	Good	1.16 ± 0.8
F18z	31 ± 1.1	Good	0.016 ± 0.03	0.018 ± 0.02	13.6 ± 0.02	Good	1.14 ± 0.7

n = 3; SD-standard deviation

Table 7: Evaluation parameters of matrix tablets without CC/ 2-HeβCD inclusion complex

Formula	*Weight (mg) (mean ± SD)*	*Friability (%) (mean ± SD)*	*Hardness (kg/cm^2) (mean ± SD)*	*Thickness (mm) (mean ± SD)*
F1	129.3 ± 2.3	0.2 ± 0.3	3.1 ± 0.3	3.1 ± 0.04
F2	129.9 ± 1.8	0.4 ± 0.1	3.4 ± 0.8	3.2 ± 0.06
F3	131.4 ± 2.4	0.35 ± 0.1	3.2 ± 0.4	3.4 ± 0.05
F4	128.4 ± 1.2	0.5 ± 0.6	3.1 ± 0.1	3.6 ± 0.06
F5	129.6 ± 2.7	0.3 ± 0.7	2.2 ± 0.5	3.4 ± 0.03
F6	130.5 ± 1.7	0.4 ± 0.2	2.3 ± 0.7	2.8 ± 0.05

n = 3; SD-standard deviation

(25 rpm for 4 minutes). The friability value was calculated by using the following equation[17]:

$$F\% = \frac{W\,initial - W\,final}{W\,initial} \times 100 \quad \text{Eq. 5}$$

Ten tablets were taken randomly for hardness test from each formula. The hardness was measured by using Monsanto® manual hardness tester, and the average value for the tablets was measured. Five tablets from each formula were taken randomly, and the average thickness of the tablets was calculated using vernier caliper scale.[17]

Table 8: Evaluation parameters of matrix tablets with CC/ 2-HeβCD inclusion complex

Formula	*Weight (mg) (mean ± SD)*	*Drug content of CC% (mean ± SD)*	*Friability (%) (mean ± SD)*	*Hardness (kg/cm^2) (mean ± SD)*	*Thickness (mm) (mean ± SD)*
F1x	132.4 ± 1.3	99.2% ± 0.4	0.5 ± 0.7	5.1 ± 0.6	4.2 ± 0.07
F2x	131.1 ± 1.6	98.9% ± 0.1	0.55 ± 0.2	4.6 ± 0.4	4.1 ± 0.01
F3x	132.6 ± 1.2	100.1% ± 0.3	0.75 ± 0.4	5.8 ± 0.2	4.2 ± 0.03
F4x	133.4 ± 1.1	99.8% ± 0.3	0.9 ± 0.4	5.9 ± 0.7	4.5 ± 0.08
F5x	133.3 ± 1.5	101.1% ± 0.4	0.8 ± 0.1	6.1 ± 0.5	4.1 ± 0.01
F6x	134.7 ± 1.2	100.2% ± 0.5	0.9 ± 0.1	5.5 ± 0.4	3.9 ± 0.07
F7y	131.8 ± 1.5	98.1% ± 0.1	0.9 ± 0.2	6.5 ± 0.1	4.3 ± 0.02
F8y	130.5 ± 1.6	100.5% ± 0.2	0.9 ± 0.1	3.9 ± 0.6	4.1 ± 0.03
F9y	135.1 ± 2.5	100.4% ± 0.2	0.8 ± 0.3	4.9 ± 0.3	4.1 ± 0.05
F10y	134.5 ± 1.6	99.8% ± 0.4	0.5 ± 0.1	4.7 ± 0.1	4.1 ± 0.04
F11y	133.6 ± 1.6	99.7% ± 0.4	0.4 ± 0.1	5.7 ± 0.1	4.1 ± 0.07
F12y	136.8 ± 1.2	99.6% ± 0.2	0.7 ± 0.4	6 ± 0.1	4.1 ± 0.08
F13z	131.4 ± 1.3	99.5% ± 0.3	0.3 ± 0.1	3.7 ± 0.4	4.1 ± 0.04
F14z	131.5 ± 1.2	99.6% ± 0.1	0.4 ± 0.7	4.1 ± 0.1	4.2 ± 0.02
F15z	130.6 ± 1.2	100.2% ± 0.2	0.6 ± 0.4	3.9 ± 0.9	4.1 ± 0.02
F16z	134.2 ± 1.8	98.5% ± 0.6	0.7 ± 0.1	3.9 ± 0.5	4.1 ± 0.01
F17z	133.8 ± 1.2	99.2% ± 0.5	0.6 ± 0.8	4.9 ± 0.5	4.4 ± 0.02
F18z	132.9 ± 1.2	99.9% ± 0.5	0.8 ± 0.2	5.8 ± 0.1	4.2 ± 0.05

n = 3; SD-standard deviation

Table 9: Swelling indices of matrix tablets contained drug β-cyclodextrin complex during a set of time intervals

	Swelling index (SI) (mean ± SD)			
Formula	*SI% 2 hr*	*SI% 4 hr*	*SI% 6 hr*	*SI% 8 hr*
F1x	13.3 ± 1.2	20 ± 1.7	31.2 ± 1.1	34.6 ± 1.3
F2x	16.5 ± 2.7	25 ± 1.3	35.4 ± 1.7	39.2 ± 2.1
F3x	19.6 ± 1.3	27 ± 1.7	32.8 ± 1.8	58.4 ± 2.7
F4x	13.5 ± 1.1	20.6 ± 1.2	30.3 ± 2.6	37.2 ± 2.8
F5x	13.9 ± 2.2	20.4 ± 1.5	31.6 ± 2.8	38.7 ± 2.1
F6x	13 ± 1.2	21 ± 1.1	34.4 ± 2.4	48.2 ± 1.1
F7y	16 ± 2.3	22 ± 2.3	29.9 ± 2.1	33.3 ± 1.3
F8y	19 ± 1.6	29 ± 2.1	38 ± 2.5	40.3 ± 2.5
F9y	13 ± 2.5	28.8 ± 2	32.2 ± 2.1	45.4 ± 3
F10y	12.8 ± 1.8	20.6 ± 2.8	24.8 ± 2.6	32.4 ± 3.6
F11y	13.5 ± 1.4	17 ± 2.6	29.1 ± 1.3	38.4 ± 1.3
F12y	19.3 ± 2	25.6 ± 1.5	33.3 ± 1.6	48.7 ± 1.9
F13z	12.1 ± 2.2	21.4 ± 2.8	26.9 ± 1.9	35 ± 2.4
F14z	13 ± 1.9	20.8 ± 1.1	30 ± 1.4	44.2 ± 2.5
F15z	17.8 ± 1.6	25 ± 1.8	31 ± 1.2	59.5 ± 1.4
F16z	11.5 ± 2.1	20.6 ± 1.9	24.8 ± 1.4	30.5 ± 1.6
F17z	14.7 ± 2.9	22 ± 1.6	31.5 ± 2.1	39 ± 1.8
F18z	16 ± 1	19.2 ± 1.3	29 ± 1.8	45.4 ± 1.3

n = 3; SD-standard deviation

Determination of SI

The swelling behavior of matrix tablets was determined at 37 ± 0.5ºC in phosphate buffer (pH 6.8). Three tablets from each formula were individually kept in a glass Petri dish containing 900 mL of the buffer solution. The weight of the individual tablet was taken before the swelling study (M_o). The tablet was kept in a basket. The weight of a tablet was taken at time intervals of 0.5, 1, 2, 4, 6, and 8 hours, and at the end of the interval time, the tablet was removed, polished with a filter paper, and weighed again (M_t).[18]

Percent hydration (SI) was calculated using the following formula:

$$SI = \frac{Mt - Mo}{Mo} \times 100 \quad \text{Eq. 5}$$

Where, M_t and M_o are the weight of tablet at time = t and time = 0, respectively.

In vitro Dissolution Study

In vitro dissolution of the prepared tablet was carried out using dissolution apparatus type II (paddle type), in which the paddle speed was at 50 rpm, and using 900 mL buffer solution (pH 6.8) with 0.35% tween 20, as dissolution media at 37ºC. Samples (10 mL) were withdrawn every 1-hour and replaced with the same amount of fresh buffer (pH 6.8) to maintain sink condition, and these samples were collected, and the absorbance values of the drug from those samples were measured using UV-visible spectroscopy at 255 nm for CC, and then determine the amount of drug in each sample by using the equation obtained from the calibration curve.[19]

Statistical Analysis

The one-way analysis of variance test was used to determine the significance of difference among the results obtained from the studied formulations. The level of significance was set at α = 0.05, in which less than this value was considered to be

statistically significant, and more than this was considered statistically insignificant.[10]

RESULTS

Infrared spectroscopy spectra were performed for CC pure powder and β-cyclodextrin pure powder, as shown in Figures 1 and 2, and results showed similarity to the reference infrared for both. Infrared spectroscopy (IR) spectra performed to CC/ HPMC K100 (1:1) physical mixture and for candesartan/ β-cyclodextrin complex (1:1) physical mixture, as shown in Figures 3 and 4, respectively.

Results showed absorption peaks of CC and the physical mixtures with no effects on the bands of CC and no interaction among them. This indicates good compatibility between CC, HPMC. The IR of the inclusion complex prepared by the kneading method showed the presence of characteristic peaks at the corresponding wavenumbers of both pure CC and β-cyclodextrin, thereby confirming the formation of an inclusion complex suggesting that there was no interaction between drug and β-cyclodextrin.[20]

The DSC thermogram showed a sharp characteristic endothermic peak of CC around its melting point, demonstrating a sharp characteristic endothermic peak at 172.06ºC, which is within its melting temperature range (T_m), as shown in Figure 5. Such peak indicates that CC used is in the pure crystalline state, and results showed similarity to the reference drug. A physical mixture of candesartan and HPMC K100, candesartan, and β-cyclodextrin complex were showed characteristic endothermic peaks, which correspond to the dry melting, which was appeared with small shifting and reduce in the intensity, which indicated that the drug is still in the crystal[20] form, as shown in Figures 6 and 7.

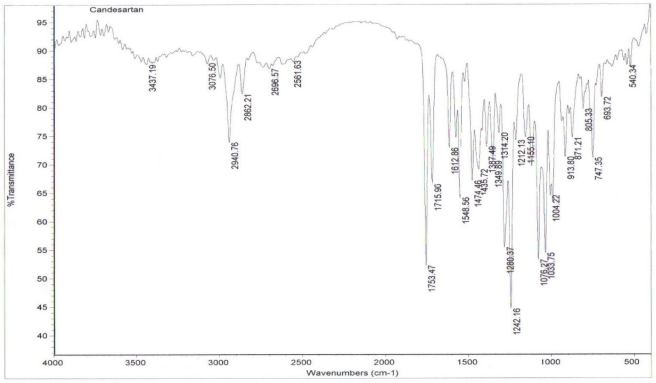

Figure 1: FTIR spectra of pure powder of CC

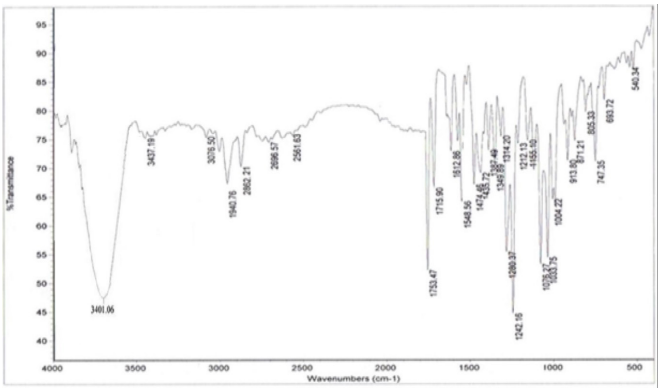

Figure 4: FTIR spectra of CC and 2-HeβCD physical mixture (1:1)

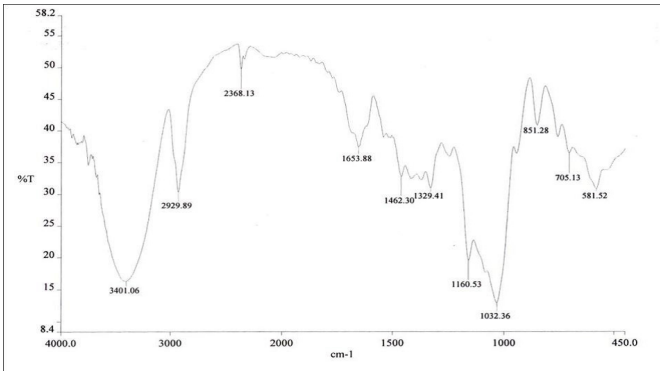

Figure 2: FTIR spectra of pure powder of 2-HeβCD

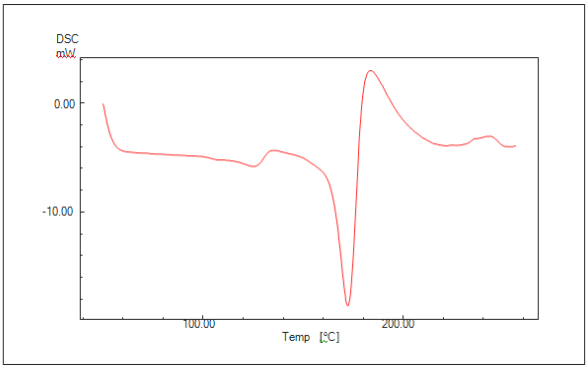

Figure 5: DSC thermogram of CC pure powder

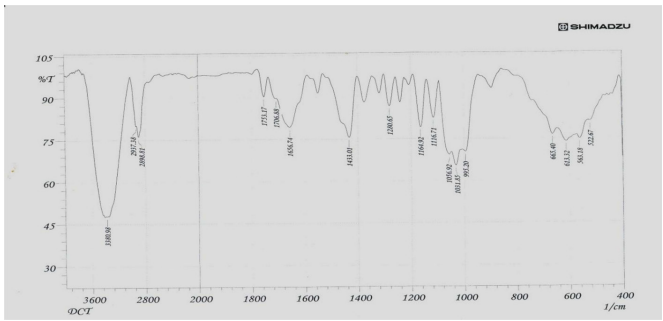

Figure 3: FTIR spectra of CC and HPMC K100 physical mixture (1:1)

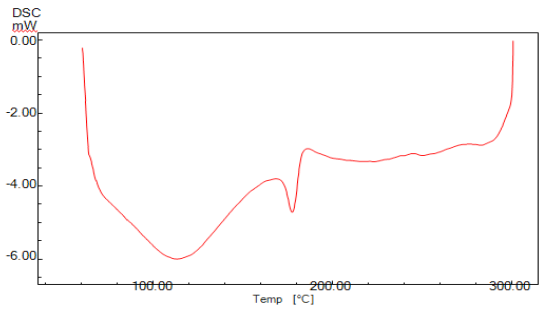

Figure 6: DSC thermogram of CC and HPMC K100M physical mixture (1:1)

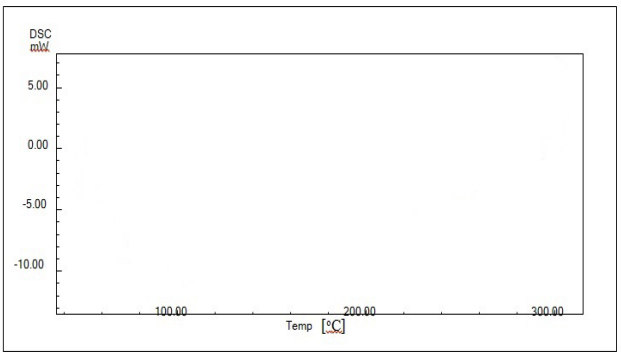

Figure 7: DSC thermogram of CC and 2-HeβCD physical mixture (1:1)

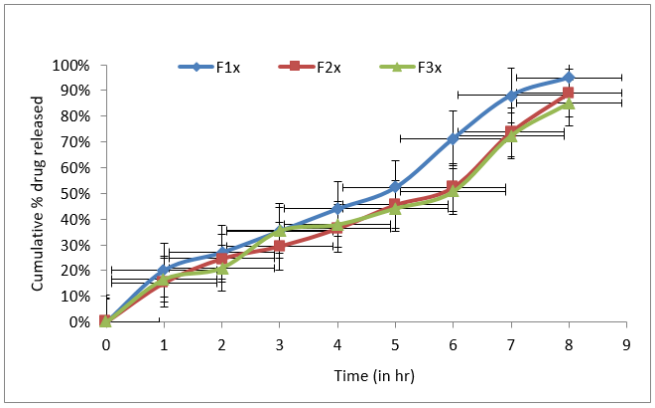

Figure 8: *In vitro* dissolution for studying the effect of ratio of polymer and β-cyclodextrin on the release profile of CC in 6.8 buffer solution; F1x contains HPMC K100 (1:1) and β-cyclodextrin (1:1); F2x contains HPMC K100 (1:2) and β-cyclodextrin (1:1); F3x contains HPMC K100 (1:3) and β-cyclodextrin (1:1); mean ± SEM; n = 3

Solubility study was done in different pH media and using β-cyclodextrin and polysorbate 20 (0.35%) in these media to study the saturation solubility of CC, and to ensure the optimum requirements in dissolution study, as shown in Table 1.

Results showed that β-cyclodextrin enhanced the solubility of CC and the same statement for polysorbate 20. *In vitro* dissolution media could be prepared by adding 35% of polysorbate 20 to achieve sink condition. Although β-cyclodextrin is increasing the solubility of poorly soluble drug CC, it had some disadvantages in which it had specific toxicity, thereby limiting their use in toxic studies. Sometimes the complex drug with cyclodextrin will not dissociate rapidly; in such cases, the pharmacokinetics of the poorly soluble drug may be altered as the release is not immediate. Thus, it is necessary to use an alternative dissolution medium to overcome these problems.[21] Polysorbate 20 is safe and non-toxic, and used in dissolution studies as solubility enhancer.[19]

CC prepared as complex with β-cyclodextrin by kneading method in three ratios (1:1, 1:0.75, and 1:0.5, respectively), as shown in Table 2. Matrix tablets prepared (F1 to F6) without candesartan/ β-cyclodextrin complex by dry granulation and these formula used to compare results between it, and in the presence of the complex (F1x to F18z) to show the effect of β-cyclodextrin on the properties of the matrix tablet, as shown in Tables 3 and 4, in the pre- and post-compression stages.

Cyclodextrin effect on the flow properties in which the angle of repose for each formula was measured, and results showed excellent and good flow. The angle of repose increases but remains in the range in which good flow obtained from granules. Compressibility decrease in the presence of β-cyclodextrin and decreases further by increasing the ratio of β-cyclodextrin and results showed excellent flow became good by presence of β-cyclodextrin as in F6, which showed good flow in the absence of the complex but became fair inflow in the presence of the candesartan/ β-cyclodextrin complex.[22]

Hausner ratio values were of less than 1.25 indicates a good flow of granules, while greater than 1.5 indicates poor flow, in which Hausner ratio is a measure of the inter-particulate friction. Lower compressibility index or lower Hausner ratios of granules indicates better flow properties than higher values.[9]

Bulk density decreased with an increase in the β-cyclodextrin amount. Post compression study of the matrix tablet showed an increase in the degree of friability, but remained in the accepted value (less than 1%) with increasing the amount of β-cyclodextrin in the tablet. Hardness and thickness remained in the accepted range for matrix tablets and no effect monitored for the presence of β-cyclodextrin. Weight variation study was considered within the accepted range, as stated by the USP for all the formulas. Drug content measurements were within the accepted values.[22] These results were shown in Tables 5 to 8, respectively.

The swelling behavior study was shown in Table 9. The SI indicates the ability of the polymer to absorb water from dissolution media and swells. The water absorption and swelling of the tablets started slowly and continued during the time of the experiment. The time was set for 8 hours and the tablet weighed every 2 hours. HPMC K100 and ethylcellulose are hydrophilic polymers, in which they absorb water and become gelled with time. β-cyclodextrin increases the SI of the matrix tablet due to the hydrophilic nature of the β-cyclodextrin.[23]

In vitro dissolution was done for the study of the effect of polymer type and the amount and the effect of the addition of β-cyclodextrin as a complex on the release profile of CC in buffer media pH 6.8, which contains 0.35% tween 20 to bypass sink condition. Increases in the amount of polymer retard the release of drugs from the matrix tablet and the presence of drugs as a complex with β-cyclodextrin had sustained the release further in respect to constant ratio of β-cyclodextrin comparing to increase in the amount of the polymer in the matrix tablet. This was observed in the release profile of F1x, F2x, and F3x in Figure 8. F1x release after 8 hours was 95%, which contains 1:1 polymer ratio in comparison to F3x, which showed 85% after 8 hours, which contains 1:3 polymer ratio of drug HPMC K100. These results were the same for ethylcellulose polymer.[24]

The effect of the amount of β-cyclodextrin added to the matrix tablet affects the release behavior of the drug due to complex formation. Differences in the drug release rate from the tablets can be attributed to the different amounts of polymers and cyclodextrin. Dissolution of pure drug-based

tablets was slower compared to the tablets containing the cyclodextrin complex. The drug complex dissolves easily in a hydrated polymeric environment, resulting in a higher diffusional driving force and faster drug release. Due to poor aqueous solubility, only a limited amount of drug can dissolve inside the hydrated polymeric matrices. Incorporation of β-cyclodextrin in the matrix improved the drug solubility and dissolution rate. The dissolved β-cyclodextrin in the gel matrix formed a complex with a drug and improved its solubility. The solubilization due to the *in situ* complex formation was the main reason for enhanced drug release from β-cyclodextrin containing polymeric matrices. Results for HPMC K100 1:1 ratio formulas showed that F1x had 95% release after 8 hours, which contained 1:1 drug/ β-cyclodextrin as shown in Figure 8, whereas F7y had 85% and F13z had 71% after 8 hours, which contained 1:0.75 and 1:0.5 drug/β-cyclodextrin, respectively, as shown in Figures 9 and 10, respectively. These were the same for ethylcellulose, as shown in Figures 11 to 13, respectively.[25]

Studying the kinetic modeling for formulas with the different β-cyclodextrin amount with constant polymer:drug

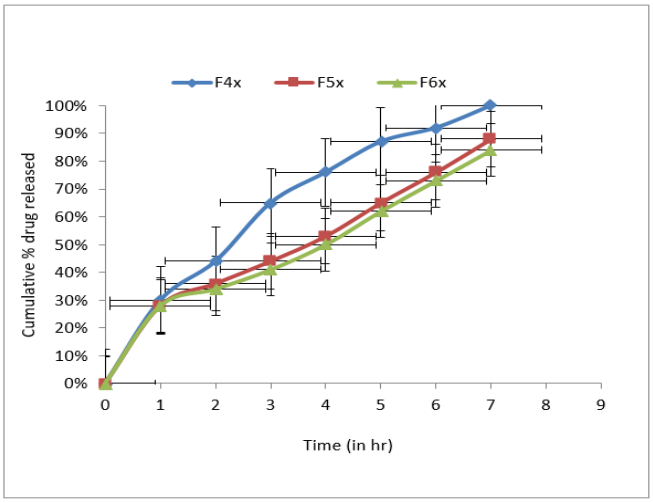

Figure 11: *In vitro* dissolution for studying the effect of ratio of polymer and β-cyclodextrin on the release profile of CC in 6.8 buffer solution; F4x contains ethylcellulose (1:1) and β-cyclodextrin (1:1); F5x contains ethylcellulose (1:2) and β-cyclodextrin (1:1); F6x contain ethyl cellulose (1:3) and β-cyclodextrin (1:1); mean ± SEM; n = 3

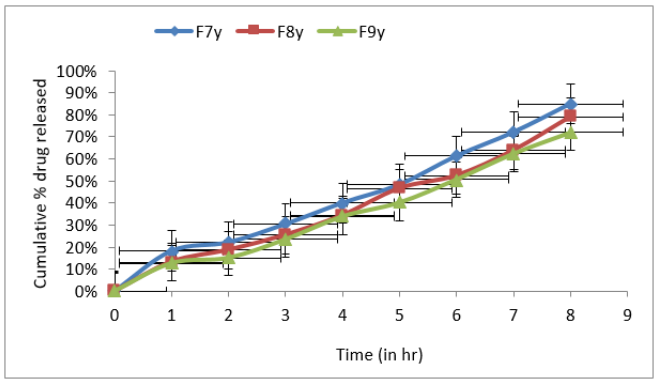

Figure 9: *In vitro* dissolution for studying the effect of ratio of polymer and β-cyclodextrin on the release profile of CC in 6.8 buffer solution; F7y contains HPMC K100 (1:1) and β-cyclodextrin (1:0.75); F8y contains HPMC K100 (1:2) and β-cyclodextrin (1:0.75); F9y contains HPMC K100 (1:3) and β-cyclodextrin (1:0.75); mean ± SEM; n = 3

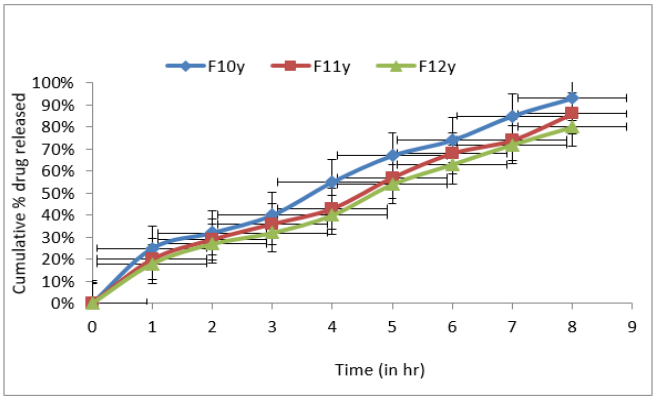

Figure 12: *In vitro* dissolution for studying the effect of ratio of polymer and β-cyclodextrin on the release profile of CC in 6.8 buffer solution; F10y contain ethylcellulose (1:1) and β-cyclodextrin (1:0.75); F11y contain ethylcellulose (1:2) and β-cyclodextrin (1:0.75); F12y contain ethylcellulose (1:3) and β-cyclodextrin (1:0.75); mean ± SEM; n = 3

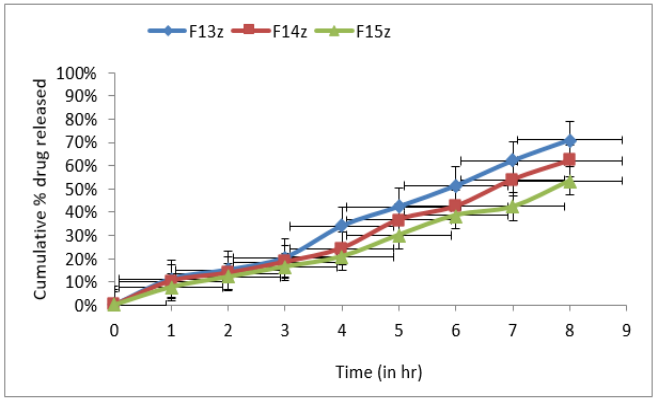

Figure 10: *In vitro* dissolution for studying the effect of ratio of polymer and β-cyclodextrin on the release profile of CC in 6.8 buffer solution; F13z contains HPMC K100 (1:1) and β-cyclodextrin (1:0.5); F14z contains HPMC K100 (1:2) and β-cyclodextrin (1:0.5); F15z contains HPMC K100 (1:3) and β-cyclodextrin (1:0.5); mean ± SEM; n = 3

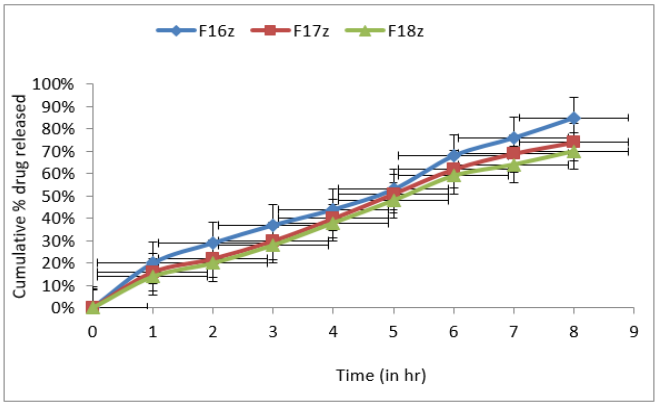

Figure 13: *In vitro* dissolution for studying the effect of ratio of polymer and β-cyclodextrin on the release profile of CC in 6.8 buffer solution; F16z contains ethylcellulose (1:1) and β-cyclodextrin (1:0.5); F17z contains ethylcellulose (1:2) and β-cyclodextrin (1:0.5); F18z contains ethylcellulose (1:3) and β-cyclodextrin (1:0.5); mean ± SEM; n = 3

Table 10: Correlation coefficients of different mathematical models for selected formulations (F1x, F7y, and F13z)

Formula	*Order*	*Correlation coefficient (R^2)*
F1x	Zero-order model	0.9693
	First-order model	0.9692
	Korsmeyer-Peppas model	0.9644
	Higuchi model	0.8001
	Hixson-Crowell model	0.9692
F7y	Zero-order model	0.9769
	First-order model	0.9769
	Korsmeyer-Peppas model	0.9754
	Higuchi model	0.8231
	Hixson-Crowell model	0.9769
F13z	Zero-order model	0.9856
	First-order model	0.9854
	Korsmeyer-Peppas model	0.9893
	Higuchi model	0.7687
	Hixson-Crowell model	0.9855

ratio showed constant mechanism as for F1x, F7y, and F13z, which contained a constant ratio of HPMC K100:drug and β-cyclodextrin in three different ratios 1:1, 1:0.75, and 1:0.5, respectively. The drug release mechanism fitted to zero-order release kinetic profile, which gave an idea about a non-Fickian diffusion-controlled mechanism.[26]

Data, as shown in Table 10, were calculated by using DDSolver add-on to calculate sample data modeling. The formulations were followed by non-Fickian diffusion kinetics in which the diffusion exponent (n) values were greater than 0.5. These results indicate that the release mechanism of the drug was shifted from diffusion-controlled to an anomalous transport (non-Fickian), in which both the diffusion and the erosion mechanisms were controlling the release.[27]

DISCUSSION

An increase in the angle of repose value was due to different reasons in which the important one is the amount of β-cyclodextrin added to form a complex. Magnesium stearate is used as a lubricant in small amount, helps in decrease the powder dust during the filling, and so will enhance granules flowability.[28]

The angle of repose test showed that the θ values increased when the ratio of the β-cyclodextrin increase was from 1:0.5 to 1:1, but remains in the range of good flowability for granules.[10]

Compressibility index related to the granular bridge strength and the stability of the bridges, as the strength increases, the compressibility index became good to excellent. Compressibility decrease in the presence of β-cyclodextrin and decrease further by increasing the ratio of β-cyclodextrin.[29]

Swelling of the polymer matrix will lead to delay in the release of CC from the tablet due to the increase in diffusion path length. The SI depends on the type of polymer used, in which swelling refers to the ability to absorb water from the buffer solution. The higher welling was obtained in the formulas containing HPMC K100M (F3x and F15z), in which the ratio of the polymer was 1:1 and 1:3, respectively, and β-cyclodextrin was 1:1 and 1:0.5, respectively.[10,30]

The mechanism of swelling was initiated with the polymer being swollen, and then a viscous gel layer was formed, and at this point, the drug started to release slowly forms the matrix system.

In vitro dissolution studies in buffer media pH 6.8, results showed that the release of the drug from the matrix system affected by different factors, like the amount of polymer used in each formula, the type of the polymer used, and the effect of drug/ β-cyclodextrin complex.[31]

The saturation solubility of CC was the main factor affecting the dissolution of the drug from the dissolution media. Different studies showed that the drug was practically insoluble in buffer solution pH 6.8, and so surfactant must be used to increase the solubility and to achieve sink condition. The solubility of the drug was differing from solvent to others, and the choice of solvent depends on the purpose of the study.[19] The solubility of the drug in various media was given in Table 1.

An increase in the pH of the medium increased the solubility of CC; this is due to CC is an acidic drug molecule. Also, the use of polysorbate 20 as a surfactant increases the solubility of CC in both HCl and buffer media. These results showed in Table 1. The solubility of candesartan was very slightly soluble in buffer solution (pH 6.8), and so tween 20 (polysorbate 20), which is safe and non-toxic with concentration (0.35% w/w) was used to increase the solubility of the drug in the dissolution media.[19,32]

The pH of the dissolution media affects the release of CC from HPMC matrix system in spite of the polymer hydration and gelling not affected by a change in the pH of the medium. The higher binding capacity of HPMC K100M to drugs leads to more sustained effect than other polymers.[10,33]

Fast release (100% in 8 hours) was obtained from the F4x matrix tablet containing ethylcellulose polymer. High aqueous solubility and hygroscopic nature of ethylcellulose and β-cyclodextrin lead to rapid drug dissolution, diffusion, and relatively fast erosion of matrix systems, and this is because of the presence of ionized carboxylic acid groups in the polymer structure. These ionized carboxylic acid groups lead to an increase in the rate and amount of water uptake by ion-pair repulsion mechanism. The break of the bonds was responsible for the gel structure is due to stretch in the gel network.[34]

IR study showed that the presence of undisturbed CC in the tablet. The IR spectra of the drug solubilized in various excipients were similar to that of the pure drug chromatograms, so there were no drug-excipients interactions,[35] as shown in Figures 3 and 4.

The data obtained from a dissolution study of some formulations (F1x, F7y, and F13z) were analyzed using various mathematical models as reported in DDSolver, which is a specialized, freely available software program developed by Zhang *et al*. to provide a tool for facilitating the parameter calculations in dissolution data analysis using nonlinear optimization model-dependent approaches.[27]

The highest correlation coefficient (R^2) resulted in a zero-order model, which indicates that the drug release is ruled by diffusion of the drug from the tablet matrix.

These results indicate that the release mechanism of the drug was shifted from diffusion-controlled to an anomalous transport (non-Fickian), in which both the diffusion and the erosion mechanisms were controlling the release.[36]

CONCLUSION

Formula F15z, which contains HPMC K100M, showed most sustain release for CC, than other studied polymers due to the higher binding and swelling of the polymer. HPMC K100M and ethylcellulose are hydrophilic polymers that absorb water from dissolution media. The use of β-cyclodextrin modify the release profile of the drug and control the sustained-release formulas. The lower the time of the release but in a range that a sustained release of the drug was observed and to minimize the longest time of some formulation due to the enhance in dissolution of poorly soluble drugs by β-cyclodextrin.

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