**How to Cite:**
Vantimita, S. R., & Jeganath, S. (2022). Formulation and evaluation of gastro retentive drug delivery system of candesartan cilexetil. *International Journal of Health Sciences*, *6*(S1), 5093–5106. https://doi.org/10.53730/ijhs.v6nS1.6150

# Formulation and evaluation of gastro retentive drug delivery system of candesartan cilexetil

**Sarovar Reddy Vantimita**
Research Scholar, School of Pharmaceutical Sciences, Vels Institute of Science, Technology And Advanced Studies (VISTAS), Pallavaram, Chennai-600117, India

**S. Jeganath**
Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology And Advanced Studies (VISTAS), Pallavaram, Chennai-600117, India

***Abstract*---**It had became a challenging experience and effort for a formulator to develop and innovate a drug with maximum bioavailability. In the present study the focus of research is in the treatment of Hypertension, which is one of the most prevalent cardiovascular diseases in the world, affecting a big proportion of the adult and old age population. Candesartan Cilexetil angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands, used for the treatment of high blood pressure. The drug has poor bioavailability due to limited oral absorption and maximum absorption at proximal intestine. This warrants and offers the use of Gastro Retentive Drug Delivery System (GRDDS) for sustained release formulation in order to achieve prolonged action and to improve patients compliance. Wet granulation technique was selected for preparation of tablets and the drug is formulated with HPMC K100M, ethylcellulose, sodium bicarbonate, Micro crystalline cellulose, Gelucire, talc and Aerosil etc. For around twelve formulations were made and evaluated for General appearance, Thickness, Hardness or Crushing strength Test, Friability Test, Estimation of drug content, *In-vitro* buoyancy studies and *In-vitro* drug release and the results obtained for the performed tests were found with in the range of specified limits. Among all the formulations prepared, CF-10 (Gelucire 54/02 8mg, Gelucire 43/01 24mg, HPMC K100 30mg and ethyl cellulose 15mg) holds the promise for the present study.

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
***Corresponding author**: Jeganath, S.; Email: jeganaths@gmail.com*
*Manuscript submitted: 27 Feb 2022, Manuscript revised: 18 March 2022, Accepted for publication: 09 April 2022*

***Keywords*---**Candesartan Cilexetil, HPMC K100M, Gelucire 54/02, Gelucire 43/01, ethyl cellulose, *In-vitro* buoyancy studies and *In-vitro* drug release.

## Introduction

Controlled release dosage forms are the most and favorable convenient means to obtain a reduction and mitigation of daily administration of drugs with rapid absorption and elimination. Numerous controlled release systems have been developed for maintaining a therapeutically effective concentration of drug in systemic circulation for longer period of time as well as to reduce side effects. A number of dosage forms have been designed and fabricated to disintegrate or dissolve or release the drug in the stomach, after which it gets absorbed through the small intestine (Talukdar & Fassihi et al., 2004). However, gastrointestinal motility, a vigorous and variable phenomenon, presents a major impediment to the effectiveness of controlled delivery system. The real issue in the development of oral controlled release dosage form is not just to prolong the delivery of drugs for more than 12 hours but to prolong the residence time of dosage forms in the stomach or somewhere in the upper small intestine until all the drug is retained for the desired period of time. Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time (Whiteland et al., 1996). After the release of the drug, the residual system is emptied from the stomach.

## Materials and Method

Candesartan was obtained as gift sample from hetero drugs from Hyderabad, hydroxyl propyl methyl cellulose K100m from colorcon, goa, Gelucire 54/02 and Gelucire 43/01, from Gattefosse, excipients, Microcrystalline cellulose from signet Madhya Pradesh, ethylcellulose, sodium bicarbonate from Merck, Talc and Aerosil from Sd fine chemicals, Mumbai.

## Method of preparation

Gelucire (43/01 & 54/02) was melted in a large china dish at 70°C and the required quantity of CAND was added to the melted mass. Previously prepared geometric mixture of HPMC K100M, ethylcellulose and sodium bicarbonate was added to CAND - Gelucire (43/01 & 54/02) mixture and stirred well to mix (Garg R, Gupta 2008). This mass was removed from the hot plate and subjected to scrapping until it attained room temperature. The coherent mass was passed through 22 mesh and the resulting granules were reshifted using 44 mesh to separate fines. The granules were collected and mixed with talc (2%) and Aerosil (1%) as shown in table 1. The lubricated blend was compressed using round tooling on Rimek-I rotary tablet machine (Karnavati Engineering, Kadi, India) (Gupta & Robinson 1992, Park & Robinson 1984). Compression pressure was adjusted to obtain tablets with hardness in a range of 2–3 kg/cm2 (Lourdes Ochoa et al., 2005).

Table1
Composition of Candesartan Cilexetil tablets formulation

| S.No | Ingredients (mg) | Formulation code | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | CF1 | CF2 | CF3 | CF4 | CF5 | CF6 | CF7 | CF8 | CF9 | CF10 | CF11 | CF12 |
| 1 | Candesartan Cilexetil | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 |
| 2 | Gelucire 54/02 | 32 | -- | 32 | -- | 16 | 8 | 24 | 8 | 8 | 8 | 8 | 8 |
| 3 | Gelucire 43/01 | -- | 32 | -- | 32 | 16 | 24 | 8 | 24 | 24 | 24 | 24 | 24 |
| 4 | HPMC K 100 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 30 | 40 | 50 |
| 5 | Sodium bicarbonate | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 20 | 25 | 20 | 20 | 20 |
| 6 | Ethyl cellulose | -- | -- | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| 7 | Micro crystalline cellulose | 111 | 111 | 96 | 96 | 96 | 96 | 96 | 91 | 86 | 81 | 71 | 61 |
| 8 | Aerosol | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 9 | Talc | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 10 | Total weight | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

**Preformulation studies**

*Bulk density (Db):* It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml
*Tapped density (DT):* It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume (Chawla et al., 2003).
*Hausner's ratio:* Hausner's ratio is the ratio of tapped density to bulk density
*Compressibility index (I):* It indicates the ease with which a material can be induced to flow. The compressibility index (< 10) indicates excellent flow properties and above (>30) exhibits very poor flow as per I.P limits (Tao S & Desai 2005).

**Characterization of drug substances**

*Weight variation:* Twenty tablets were selected randomly in every batch and average weight was calculated (as per I.P, limit ±5% for more than 350mg tablets). Then the deviation of individual weight values from average weight and standard deviation were calibrated and checked according to the range (Jeganath et al., 2018).
*Friability:* Twenty tablets are weighed and placed in a plastic chamber and closed, which was revolved at 25rpm for 4 min. The tablets are then reweighed to % loss in weight. The friability of the tablets was determined. The value should be (<1%) as per I.P limits.
*Hardness:* The crushing strength was determined using Pfizer hardness tester. Ten tablets were randomly selected from each batch (Surana & Kotecha 2010). In

the tablets the crushing strength was additionally transformed to tensile strength. It was measured in terms of kg/cm2.
*Thickness:* Thicknesses of five randomly selected tablets from each batch were measured with a digital Vernier caliper. Then average thickness and standard deviation was calculated. Tablet thickness should be controlled with in 5% variation from standard values (Sheu et al., 2010).

**Estimation of drug content**

Twenty tablets were powdered. The powdered sample equivalent to 16 mg of drug was transferred to a 100ml volumetric flask (Vinod et al., 2010) and dissolve the drug and remaining volume was made up to 100ml with 0.1N HCl, sonicate for 60 minutes and the solution was filtered. From the filtrate, 1ml of solution was transferred to 100ml volumetric flask and the volume was made up to 0.1N HCl (Tao & Desai 2005). The sample was analyzed by using UV spectrophotometer against blank at 256nm.

In-vitro buoyancy studies: The *in-vitro* buoyancy was determined by Floating Lag Time (FLT) as per the method. The tablets were placed in a 100ml glass beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as FLT. The total floating duration was also determined (Vibin Bose et al., 2018 & Johnson 1971).
In-vitro drug release: The dissolution test was carried out using USP XXIII dissolution testing apparatus II (paddle method). The test was performed at 50 rpm paddle speed and 900 ml of dissolution medium (0.1 N HCl), at 37±0.5°C. An aliquot of 5 ml of the sample solution was withdrawn at different time intervals and the absorbance was measured by using UV-visible spectrophotometer at 256nm for CAND respectively after appropriate dilution (Mamjek & Moyer 1980).
*Drug Release Kinetics:* To determine the values of coefficient of determination (R2) and the mechanism of drug release from the formulations, the data were treated according to zero-order (cumulative percentage drug released *vs.* time, ), first order (Log cumulative percentage drug retained *vs.* Time, the Higuchi equation (Cumulative percentage drug released *vs.* square root of time) models (Urquhart & Theeuwes 1984).

**Result and Discussion**
**Characterization of blend and tablets of CAND**

The formulations CF1 to CF12 found to have varying bulk density, tapped density, compressibility index and Hausner's ratio which ranged from 0.499±0.08 gm/cc to 0.533±0.09 gm/cc, 0.615±0.06 gm/cc to 0.689±0.02 gm/cc, 17.07±0.09% to 24.09±0.09% and 1.20±0.12 to1.31±0.01 respectively. The observed values were within I.P limits and also demonstrate good flow property for the developed formulation (Table 2).

Table 2
Characterization of blend of CAND

| S.No | Formulation code | Parameters | | | |
|---|---|---|---|---|---|
| | | Bulk density(gm/cc) | Tapped density(gm/cc) | Hausner ratio | Compressibility index |
| 1 | CF1 | 0.500 ± 0.09 | 0.615 ± 0.06 | 1.23 ± 0.09 | 18.69 ± 0.1 |
| 2 | CF2 | 0.533 ± 0.08 | 0.653 ± 0.03 | 1.24 ± 0.10 | 19.9 ± 0.01 |
| 3 | CF3 | 0.523 ±0.02 | 0.689 ± 0.02 | 1.31 ± 0.01 | 24.09 ± 0.09 |
| 4 | CF4 | 0.512 ± 0.09 | 0.625 ± 0.01 | 1.22 ± 0.09 | 18.08 ± 0.08 |
| 5 | CF5 | 0.515 ± 0.07 | 0.662 ± 0.06 | 1.28 ± 0.08 | 22.20 ± 0.07 |
| 6 | CF6 | 0.521 ± 0.08 | 0.671 ± 0.04 | 1.28 ± 0.10 | 22.35 ± 0.05 |
| 7 | CF7 | 0.501 ± 0.06 | 0.625 ± 0.07 | 1.25 ± 0.01 | 20 ± 0.06 |
| 8 | CF8 | 0.519 ± 0.09 | 0.659 ± 0.09 | 1.26 ± 0.02 | 21.2 ± 0.03 |
| 9 | CF9 | 0.511 ± 0.11 | 0.625 ± 0.05 | 1.22 ± 0.09 | 18.24 ± 0.09 |
| 10 | CF10 | 0.524 ± 0.07 | 0.630 ± 0.07 | 1.23 ± 0.10 | 19.84 ± 0.01 |
| 11 | CF11 | 0.533 ± 0.09 | 0.645 ± 0.03 | 1.21 ± 0.11 | 17.36 ± 0.10 |
| 12 | CF12 | 0.499 ± 0.08 | 0.630 ± 0.02 | 1.20 ± 0.12 | 17.07 ± 0.09 |

The formulations CF1 to CF12 have varying weight variation between 197.5± 0.61mg to 204.0±0.57 mg, hardness between 2.0±0.1 kg/cm2 to 3.5±0.07 kg/cm2, percentage of friability between 0.020±0.05% to 0.92±0.036% and percentage of drug content between 96.87±0.3% to 100.7±0.78%. The results were within I.P specifications as shown in Table 3.

Table 3
Characterization of CAND Tablets

| Parameter | Weight variation(mg) | Hardnes ($kg/cm^2$) | % Friability | % Drug content |
|---|---|---|---|---|
| CF1 | 197.5 ± 0.61 | 2.0 ± 0.10 | 0.71 ± 0.030 | 96.87 ± 0.3 |
| CF2 | 202.0 ± 0.71 | 2.75±0.05 | 0.92 ± 0.036 | 97.13 ± 0.81 |
| CF3 | 201.0 ± 0.74 | 2.2 ± 0.25 | 0.87 ± 0.061 | 99.87 ± 0.63 |
| CF4 | 200.0 ± 0.62 | 2.8 ± 0.05 | 0.020 ± 0.05 | 100.7 ± 0.78 |
| CF5 | 201.0 ± 0.58 | 2.5 ± 0.30 | 0.28 ± 0.042 | 98.7 ± 0.53 |
| CF6 | 200.0 ± 0.18 | 2.0 ± 0.10 | 0.84 ± 0.064 | 99.84 ± 0.36 |
| CF7 | 200.0 ± 0.67 | 2.8 ± 0.07 | 0.58 ± 0.012 | 99.87 ± 0.83 |
| CF8 | 204.0 ± 0.57 | 2.2 ± 0.12 | 0.47 ± 0.034 | 99.48 ± 0.39 |
| CF9 | 203.0 ± 0.48 | 2.8 ± 0.77 | 0.38 ± 0.054 | 99.89 ± 0.73 |
| CF10 | 200.5 ± 0.7 | 3.1 ± 0.31 | 0.15 ± 0.065 | 99.98 ± 0.3 |
| CF11 | 199.5 ± 0.25 | 3.2 ± 0.10 | 0.68 ± 0.084 | 99.99 ± 0.43 |
| CF12 | 200.0 ± 0.56 | 3.5 ± 0.07 | 0.48 ± 0.054 | 96.98 ± 0.83 |

**FTIR Studies**

The CAND and excipients interaction was studied by comparing the FTIR spectrum of the optimized blend (F10) with that of CAND drug as shown in Fig 1-2. The comparison study demonstrates that there was no interaction between the drug and other ingredients of the formulation.

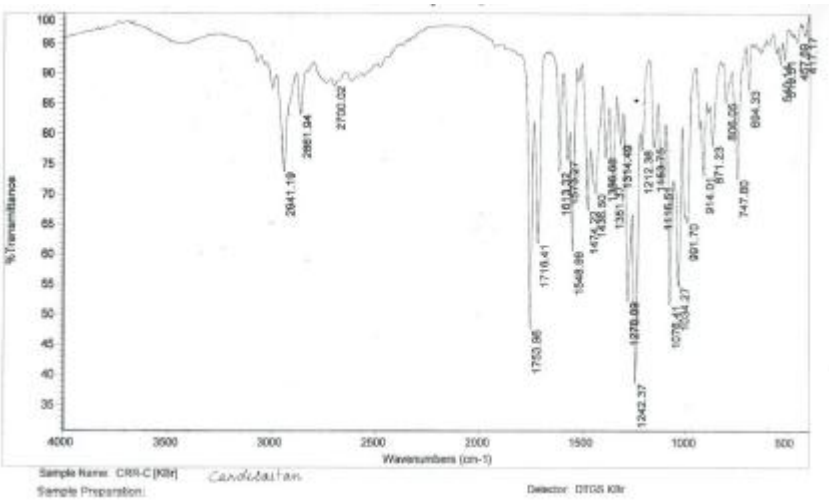


Fig. 1: FTIR of Candesartan cilexetil (CAND)

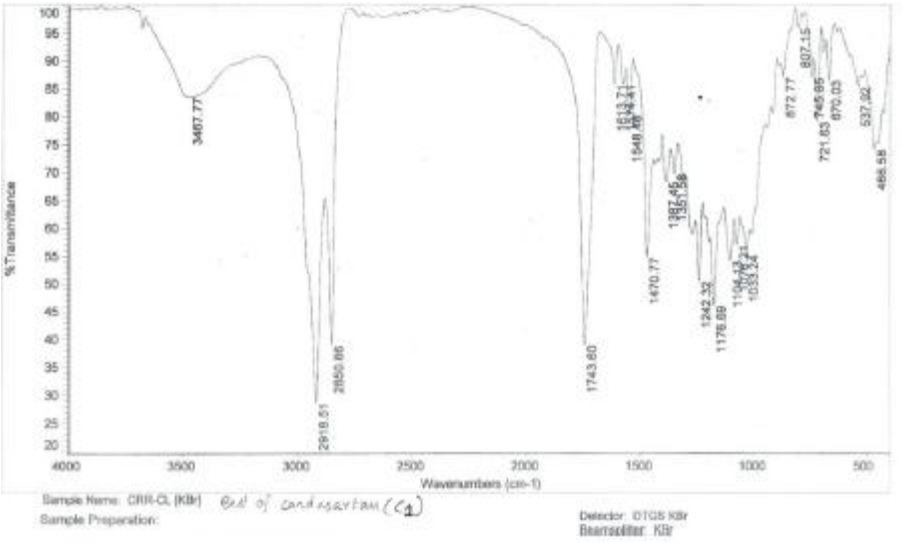


Fig. 2: FTIR of Optimized formulation blend

### *In-vitro* drug release studies of EPM: Dissolution studies

The Cumulative percentage drug release data of all formulations were shown in table 4 & 5. The formulations CF1 and CF2 were prepared using drug to lipid polymers ration of 1:2 and drug release at the end of 4hrs time were found in the range between 98 ± 0.12to 92 ± 0.06 shown in figure 3. The formulations CF3, CF4 were prepared using ethyl cellulose and drug release at the end of 8hrs time were found in the range between 96 ± 0.54 to 98 ± 1.01 shown in figure 4. The formulations CF5, CF6 and CF7 prepared with gelucire 54/02 and gelucire43/01, drug release for 10 hrs time were found to be 94 ± 0.09, 89 ± 0.19 and 92 ± 1.07 shown in figure 5. The formulations CF8, CF10, CF11 and

CF12 were prepared using HPMC K100. Among them CF10 shown desired time for total drug release of 98 ± 0.09 for 12 hrs shown in figure 6.

Table 4
Cumulative Percentage of Drug Release of Various formulations (F1-F6)

| S.No | Time (hr) | CF1 | CF2 | CF3 | CF4 | CF5 | CF6 |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 1 | 43 ± 0.06 | 36 ± 1.02 | 24 ± 0.34 | 18 ± 0.08 | 24 ± 0.05 | 16 ± 0.08 |
| 3 | 2 | 73 ± 0.04 | 70 ± 0.09 | 48 ± 0.09 | 42 ± 0.05 | 37 ± 0.03 | 23 ± 0.09 |
| 4 | 4 | 98 ± 0.12 | 92 ± 0.06 | 67 ± 0.26 | 60 ± 0.04 | 43 ± 0.09 | 36 ± 0.10 |
| 5 | 6 | - | - | 82 ± 0.09 | 81 ± 0.06 | 54 ± 1.04 | 56 ± 0.24 |
| 6 | 8 | - | - | 96 ± 0.54 | 98 ± 1.01 | 76 ± 0.08 | 75 ± 0.09 |
| 7 | 10 | - | - | - | - | 94 ± 0.09 | 89 ± 0.19 |
| 8 | 12 | - | - | - | - | - | - |

Table 5
Cumulative Percentage of Drug Release of Various formulations (F6-F12)

| S.No | Time (hr) | CF7 | CF8 | CF9 | CF10 | CF11 | CF12 |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 1 | 21 ± 0.23 | 24 ± 0.65 | 18 ± 1.02 | 20 ± 0.54 | 15 ± 0.25 | 9 ± 0.25 |
| 3 | 2 | 34 ± 0.04 | 37 ± 1.09 | 26 ± 1.03 | 37 ± 1.01 | 29 ± 0.34 | 13 ± 1.03 |
| 4 | 4 | 43 ± 0.08 | 49 ± 1.02 | 38 ± 0.29 | 48 ± 0.99 | 38 ± 0.29 | 21 ± 0.92 |
| 5 | 6 | 62 ± 0.09 | 68 ± 0.08 | 68 ± 0.08 | 53 ± 0.09 | 47 ± 0.06 | 32 ± 0.08 |
| 6 | 8 | 84 ± 1.05 | 81 ± 0.05 | 97 ± 0.32 | 69 ± 0.08 | 58 ± 0.08 | 46 ± 0.15 |
| 7 | 10 | 92 ± 1.07 | 91 ± 0.32 | - | 87 ± 0.06 | 77 ± 0.09 | 58 ± 0.25 |
| 8 | 12 | - | - | - | 98 ± 0.09 | 85 ± 1.09 | 67 ± 0.03 |

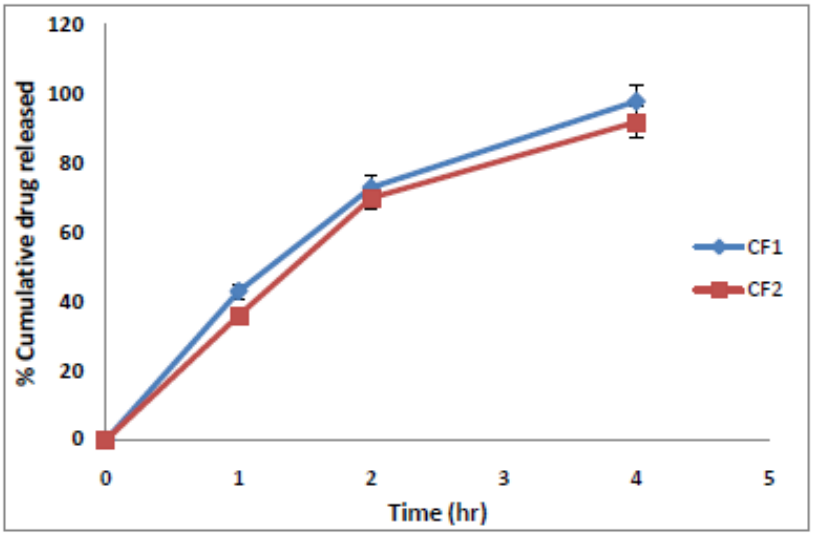


Fig 3: Cumulative percentage drug release of CF1-CF2

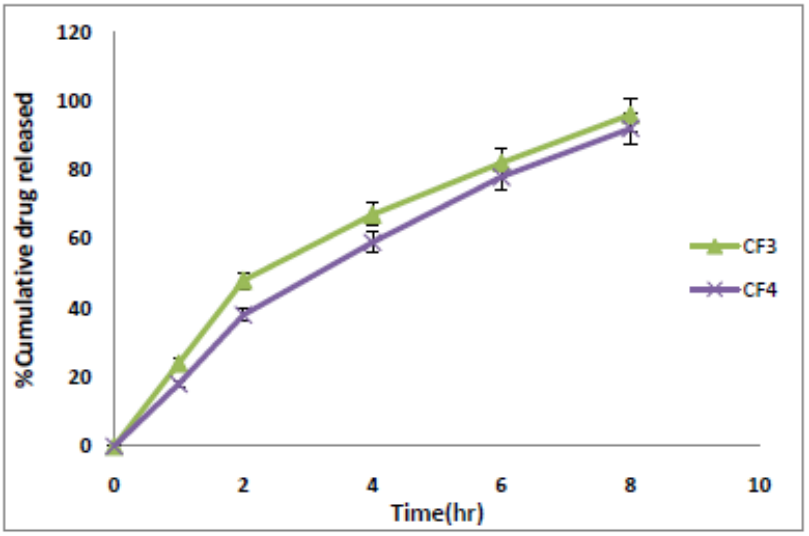


Fig 4: Cumulative percentage drug release of CF3-CF4

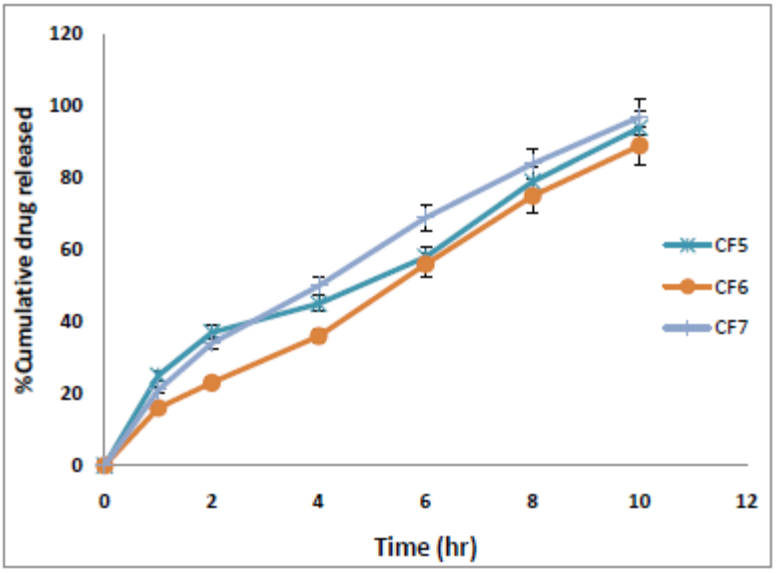


Fig 5: Cumulative percentage drug release of CF5, CF6 and CF7

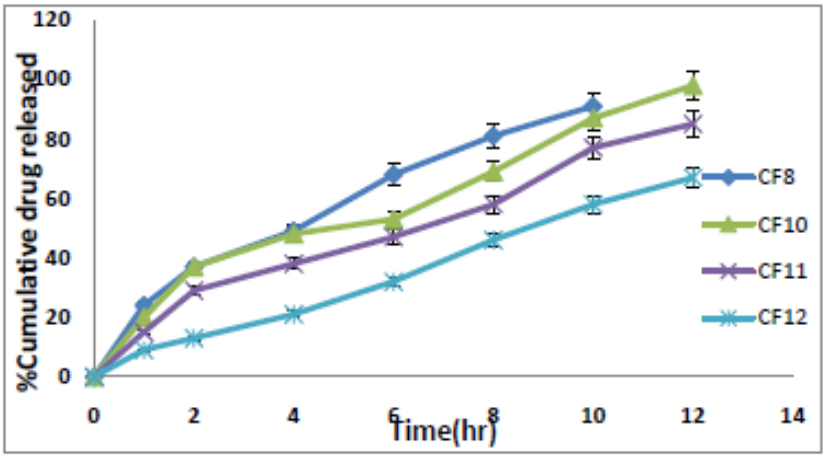


Fig 6: Cumulative percentage drug release of CF8, CF10, CF11 and CF12.

Table 6
*Invitro* drug release Kinetics data of optimized formulation of CAND (CF-10)

| Time (hrs) | Log time | SQRT of time (√t) | Cumulative %drug release | Log cumulative % drug release | Cumulative % drug remaining | Log cumulative % drug remaining |
|---|---|---|---|---|---|---|
| 0 | | 0 | 0 | 0 | 100 | 2 |
| 1 | 0 | 1 | 20 | 1.301030 | 80 | 1.903089 |
| 2 | 0.30103 | 1.41421 | 37 | 1.568201 | 63 | 1.799340 |
| 4 | 0.60206 | 2 | 48 | 1.681241 | 52 | 1.716003 |
| 6 | 0.77815 | 2.44949 | 53 | 1.724275 | 47 | 1.672097 |
| 8 | 0.90309 | 2.82842 | 69 | 1.838849 | 31 | 1.491361 |
| 10 | 1 | 3.16227 | 87 | 1.939519 | 13 | 1.113943 |
| 12 | 1.07918 | 3.46410 | 98 | 1.991226 | 2 | 0.301029 |

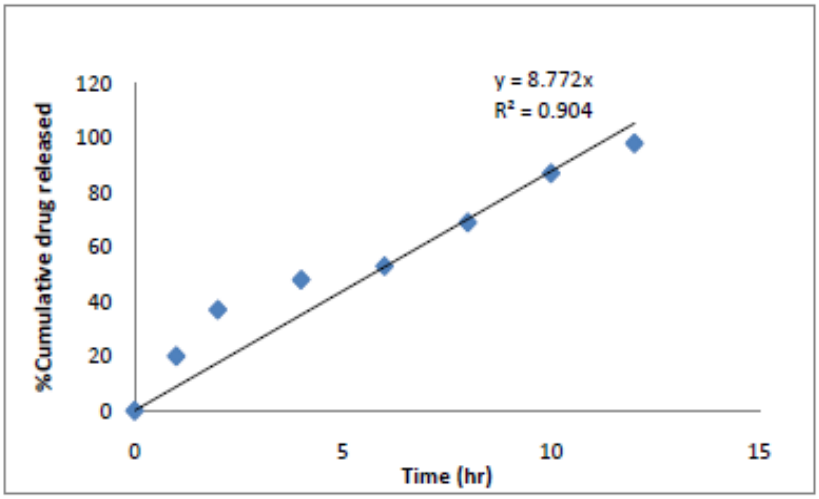


Fig. 7: Optimized formulation zero order plot of CAND (CF-10)

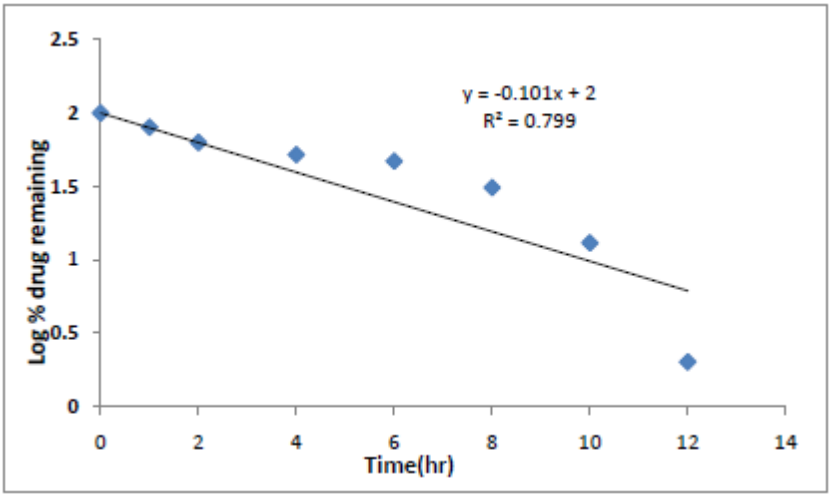


Fig. 8: Optimized formulation first order plot of CAND (CF-10)

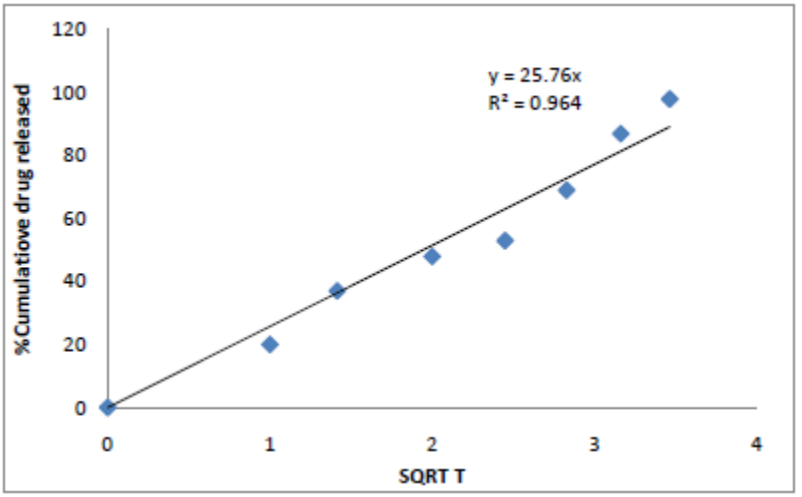


Fig. 9: Optimized formulation Higuchi plot of CAND (CF-10)

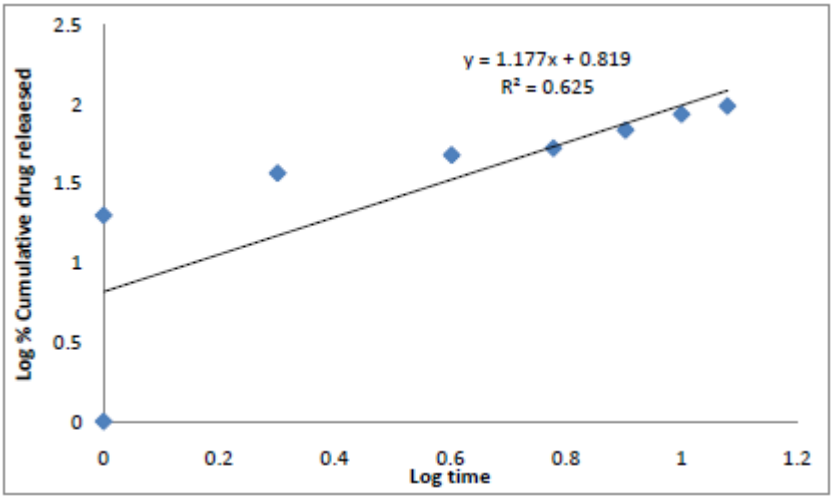


Fig. 10: Optimized formulation Peppas plot of CAND (CF-10)

Table 7
Co-efficient of determination and 'n' values of optimized formulation of CAND (CF-10)

| | $R^2$ values | | | | n values |
|---|---|---|---|---|---|
| Formulation | Zero order | first order | Higuchi | Korsmeyer peppas | Korsmeyer peppas |
| CF-10 | 0.9040 | 0.7990 | 0.9640 | 0.6250 | 0.8190 |

The optimized formulation CF-10 has coefficient of determination (R2) values of 0.9040, 0.7990, 0.9640 and 0.6250 for Zero order, First order, Higuchi and Korsmeyer Peppas respectively. A good linearity was observed with the zero order, the slope of the regression line from the Higuchi plot indicates the rate of drug release through the mode of diffusion and to further confirm the diffusion mechanism, data was fitted into the KorsmeyerPeppas equation which showed linearity with n value of 0.8190 for optimized formulation CF10 (Table 7). Thus n value indicates the coupling of diffusion and erosion mechanism. The type of drug release is called as anomalous diffusion. This indicates the drug release from the tablet follows non-Fickian diffusion mechanism. The presence of swelling and relaxation of crosslinked polymer within the matrix structure might be responsible for the drug release controlled by more than one process. Thus, the release kinetics of the optimized formulation was best fitted into Higuchi model and showed zero order drug release with non-Fickan diffusion mechanism.

**Summary**

Hypertension was one of the most common cardiovascular diseases in the world, affecting a greater proportion of the adult population. Candesartan Cilexetil angiotensin II to AT1 in many tissues including vascular smooth muscle and the adrenal glands, used for the treatment of high blood pressure. The drug has poor bioavailability due to limited oral absorption and maximum absorption at

proximal intestine. This warrants the use of GRDDS for sustained release formulation in order to get prolonged action and to improve patient compliance.

Candesartan gastroretentive tablets were prepared by melt granulation technique using different concentrations of hydrophobic (Gelucire 54/02: Gelucire 43/01) and hydrophilic polymer (HPMC k 100) minimized burst release of drug from tablet. Total twelve formulations were prepared and CF10 was optimized. Drug and polymers was subjected for compatibility study using DSC and FTIR studies, which study that there was no interaction between drug and polymers. Melt granulation method was used for preparation of different formulations and the granules were evaluated for pre compression parameters before compression of tablets. The results obtained from these studies indicated that the prepared granules had good flow properties. The prepared tablets were evaluated for physical characterisation like thickness, hardness, friability, weight variation and drug content and results comply with IP specifications. The studies showed that combination of hydrophobic and hydrophilic were suitable to get sustained drug release from gastroretentive tablets than individual polymers. The optimized formula CF10 drug release was found to be 98.0±0.09 at the end of 12hrs. The release kinetics of the optimized formulation was best fitted into Higuchi model (R2 =0.9640) and showed zero order (R2 =0.9040) drug release with non-Fickan diffusion mechanism.

**Conclusion**

The research work fabricated with the technique of melt granulation method and twelve formulations were made with all the suitable excipients with different composition and studied the evaluation ranging from preformulation studies to all the formulated ingredients. The tablets prepared were also evaluated for their suitable tests such as General appearance, Thickness, Hardness or Crushing strength Test, Friability Test, Estimation of drug content, *In-vitro* buoyancy studies and *In-vitro* drug release and the results obtained for the performed tests were found within the range of their each test specified limits. Among all the formulations prepared, CF10 (Gelucire 54/02 8 mg, Gelucire 43/01 24 mg, HPMC K100 30mg, ethyl cellulose 15mg) holds the promise for the present study and the drug release was maximum in the range at 12hr of time and the other evaluation tests results also shown as a best formulation.

**References**

Talukdar R, Fassihi R, Gastroretentive delivery systems: hollow beads, Drug Dev. Ind. Pharm 2004;30:405-12.

Whiteland L, Fell J.T, Collett J.H, Development of gastroretentive dosage form .Eur J Pharm Sci 1996;4:S182.

Lourdes Ochoa, Manuela Igartua Rosa M, Hernandez, Alicia R Gascon and Jose Luis Pedraz, Preparation of sustained release hydrophilic matrices by melt granulation in high shear mixture, *J Pharm Pharmaceut.Sci*, 08(02); 2005: 130-140.

Garg R, Gupta G, Progress in controlled gastroretentive delivery systems, Trop J Pharm Res 2008;7(3):1055-66.

Gupta P.K, and Robinson J.R, Oral Controlled- Release Delivery, in Treatise on Controlled Drug Delivery, A. Kydonieus, Eds., Marcel Dekker, New Jersey 1992: 255-310.

Park K, and Robinson J.R, Bioadhesive Polymers as Platforms for Oral- Controlled Drug Delivery: Method to Study Bioadhesion, Int J Pharm1984;19(1):107-127.

Chawla G, Gupta P, Koradia V, Bansal A. Gastroretention a Means to Address Regional Variability in Intestinal Drug Absorption. Pharm Tech 2003: 50-68.

Tao S, and Desai T. Gastrointestinal patch systems for oral drug delivery DDT 2005;10:909-915.

S. Jeganath, K. Mohammed Shafiq, P.G. Mahesh, S. Sathesh Kumar, 2018. Formulation and Evaluation of non- effervescent tablests of linagliptin using low-density carriers. Drug Invention Today. 10 (3).

Surana A. and Kotecha R. An overview on various approaches to oral controlled drug delivery system via gastroretention. IJPSRR 2010;2(2):68-72.

Sheu M, Chen R, Ho.Hsiu, Yu C, Development of swelling/floating gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose for Losartan and its clinical relevance in healthy volunteers with CYP2C9 polymorphism. European J of Pharm Sci 2010;39: 82–89.

K Vinod, Vasa Santhosh, S Anbuazaghan, Banji David, A Padmasri, S Sandhya, Approaches for gastrotentive drug delivery systems Int J of App Bio and Pharmaceutical Tech 2010;1: 589-601.

Vibin Bose R, Jeganath S, Ramya Sree K, Sherni Prithiba Jhansi Rani S. Design and Development of Gastro retentive drug Delivery System of Ciprofloxacin Hydrochloride. Asian J Pharm Clin Res 2018; 11(4):141-146.

Johnson, R.H, Rowe E.L, Medicinal dosage forms of unpolymerised thiolated gelatin with a cross linking accelerating agent providing a slowly released medication from a swollen matrix', U.S.Patient 1971;3: 574- 820.

Mamjek, R.C, Moyer, E.S, Drug Dispensing Device and Method, U.S Patient 1980;4: 207- 890.

J.Urquhart, F.Theeuwes, Drug delivery systems containing a plurality of tiny pils, U.S.Patient 1984;4:153.