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Formulation and Evaluation of Fast Dissolving Tablet of Candesartan Cilexetil

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ABSTRACT

Candesartan is an angiotensin II receptor antagonist and is widely used in the management of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction following myocardial infarction, and in the management of heart failure. The fast dissolving tablets of candesartan were prepared by direct compression method using different super disintegrating agents such as crospovidone and sodium starch glycolate. The compatibility studies of drug and excipients were performed by FT-IR spectroscopy. After examining the flow properties of the powder blends the results are found to be within prescribed limits and indicated good flowing property, hence it was subjected to tablet compression. The tablets were evaluated for post compression parameters like weight variation, hardness, thickness, friability, drug content uniformity and disintegration time, *in vitro* dissolution study. All the evaluation parameters given the positive results and comply with the standards. The drug content of shown highest of 97.15 % and disintegration time shortest of 15 seconds was observed, which facilitates its faster disintegration. The best *in vitro* drug release was found to be in formulation F6 i.e.98 % at the end of 60 seconds. From the above results, it indicates that formulation F6 containing equal ratio of different super disintegrating agents (1:1) emerged as the overall best formulation based on drug release characteristics with phosphate buffer pH 6.8 as dissolution medium. Stability studies were carried out on the developed formulations indicated that the formulations were stable during the study period.

INTRODUCTION

In recent decade a variety of pharmaceutical research has been focused to develop new dosage forms with respect to considering quality of life, ease of medication or novel drug delivery systems. The dosage forms developed with respect to the concept of ease of medication, the fast dissolving tablets stands one of the most widely accepted commercial products. Conventional solid unit dosage forms such as tablets & capsules posses one important drawback of dysphasia or chewing in some patients particularly in paediatric & geriatric patients. The problem of swallowing is common phenomenon in geriatric patients due to fear of chocking, hand tremors & in young patients due to underdeveloped muscular & nervous system & in schizophrenic patients which leads to poor patient compliance.

Fast dissolving Tablets (FDT) has taken much attention, because it avoids the problem of dysphasia & improves patient compliance. FDT is solid dosage form that disintegrates & dissolves in mouth without water. Further they are absorbed faster when compared to conventional tablets or chewable tablets and elicit the early therapeutic benefit. As they are absorbed in oral cavity they must include some substances to mask the taste of active ingredient if it is non aggreable[1].

Candesartan cilexetil commonly known as candesartan belongs to the class of angiotensin receptor antagonist and acts by binding selectively and non-competitively to angiotensin II receptor type 1, thus preventing actions of angiotensin II. The drug finds most significant clinical uses in the treatment of hypertension of all grades. Candesartan cilexetil is an ester prodrug of its active metabolite Candesartan, to which it owes its therapeutic effect. Candesartan cilexetil is white to off-white crystalline powder having melting point of 157-160°C, and is water insoluble[2]. Candesartan acts by inhibits the binding of angiotensin II to the AT1-Receptor. Candesartan cilexetil is hydrolyzed to candesartan during absorption from gastrointestinal tract. It is used in the management of hypertension and may also be used in heart failure in patients with impaired left ventricular systolic function, either when ACE inhibitors are not tolerated, or in addition to ACE inhibitors. Candesartan cilexetil is widely used for the treatment of hypertension and heart failure in clinical application. It is available in 4 mg, 8 mg, 16

mg, 32 mg and can be used in the dose range of 8-32 mg/day[3,5].

Hence, in the present study the main aim is to develop and evaluate the fast dissolving tablets of candesartan for the treatment of hypertension.

MATERIALS AND METHODS

Materials:

Candesartan cilexetil was obtained as gift sample from Micro labs, Bengaluru, India. Crospovidone was obtained from Balaji drugs. Lactose, Magnesium stearate were obtained from Leo chem, S.Puram, Bengaluru. Sodium starch glycolate, Microcrystalline cellulose, Talc, Saccharin sodium were obtained from S.D fine chemicals limited, Mumbai.

Methods:

The compatibility studies of drug and excipients were determined by FTIR studies. Both pure drug and excipients were individually analysed and further the physical mixture and formulations were also studied.

Preparation of Fast dissolving tablet of Candesartan cilexetil by direct compression:

Fast dissolving tablet of Candesartan cilexetil were prepared by direct compression method by using different super disintegrants such as crospovidone and sodium starch glycolate, lactose as diluent, saccharin sodium as sweetening agent, magnesium stearate as lubricant, talc used as glidant, microcrystalline cellulose as disintegrant. The drug, diluent, superdisintegrants and sweetener were passed through sieve #40 and all the ingredients were properly mixed together to form initial mixture. Talc and magnesium stearate were passed through sieve #80 and mixed well to form secondary mixture. Then the secondary mixture was blended with initial mixture until uniform mixing is achieved and carried out various pre-compression parameters. Before compression, hardness was adjusted and compressed into 150 mg each tablets using tablet compression machine equipped with 5 mm flat faced beveled edge punches on 12 station rotary tablet machine and same hardness was used for the required number of tablets. The various formulations designed were shown in Table 1[1].

Pre-compression parameters

The various Pre-compression parameters like Angle of repose, Bulk density, Tapped density, compressibility index, Hausner's ratio and Carr's index were studied[1,4].

Angle of Repose: The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\text{Tan } \theta = h/r$$

Where *h* and *r* are the height and radius of the powder cone.

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 and is given by

$$\text{Db= Mass powder/Volume}$$

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. It is expressed in gram/ml and is given by

$$Dt=M/Vt$$

Where, M - Mass of the powder

Vt – Tapped volume of the powder.

Compressibility index (I) and Hausner's ratio: Carr's index and Hausner's ratio measure the propensity of granule to be compressed and the flow ability of granule. Carr's index and Hausner's ratio were calculated using following formula.

$$C.I = (Dt - Db)100/Dt$$

Where, Dt – Tapped density of the powder

Db – Bulk density of the powder

Post-Compression Parameters

The Candesartan cilexetil tablets prepared were evaluated for the following various post compression parameters:

Organoleptic Characters

Organoleptic characters properties such as colour, odour, taste, were evaluated for tablets from each batch were randomly selected and taste tested, colour visually compared and odour checked.

Weight variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The weight variation test is done by selecting 20 tablets randomly from each formulation after compression, weighed individually using a "Electronic weighing balance" and average weight was determined. The individual weights are compared with the average weight for the determination weight variation[1].

Tablet hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using "Monsanto hardness tester". The hardness was measured in terms of kg/cm^2.

Friability

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. The friability was determined by using roche friabilator[4].

Tablet thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using "Vernier Callipers". It was determined by checking the thickness of ten tablets of each formulation[4].

Drug content uniformity

The tablets were tested for their drug content uniformity. At randomly selected 6 tablets from each formulation were finely powdered and dissolved in 100 ml of phosphate buffer solution at

pH 6.8. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman filter paper No. 41 and the concentration of drug was determined spectrophotometrically by using SHIMADZU UV 1800 at 277 nm[4].

Disintegration time

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in "LABINDIA disintegration test apparatus". It consists of 6 glass tubes which are 3 inches long, open at the top and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 litter beaker containing phosphate buffer pH 6.8 as medium. The volume of medium was 900 ml and temp was 37°C ± 0.2°C[4].

***In vitro* Dissolution Studies**

Dissolution testing of Fast dissolving tablet of Candesartan cilexetil was carried out with "Paddle type-II USP dissolution test apparatus" at rpm 50 and temperature 37±0.5°C by using both dissolution media and water. At each specified intervals of time 5 ml sample was withdrawn and replaced by fresh media. The samples were analytically tested to determine the concentration by UV spectroscopy method at wavelength of 277 nm. The % drug release was calculated using an equation obtained from the calibration curve[6].

Dissolution Test Parameters:	
Dissolution test apparatus	USP type II
Speed	50 rpm
Stirrer	Paddle type
Volume of medium	900 ml
Volume withdrawn	5 ml
Medium used	phosphate buffer pH 6.8
Temperature	37±0.5ºC
λ_{max}	277 nm

Further the cumulative amount of drug released from the formulations at different time intervals were subjected to various kinetic models such as zero order, first order, higuchi and korsmeyer-peppas model to characterize mechanism of drug release[10].

Stability Studies

Stability can be defined as the capacity of drug product to remain within specifications established to ensure its identity, strength, quality, and purity. The formulation was subjected to short term stability studies. The formulations were packed in aluminium foil in tightly closed container. They were then stored at 30ºC/65% RH and 40ºC/75% RH for two months and evaluated for their post compression studies[5].

RESULTS AND DISCUSSION

The compatibility studies revealed both drugs and excipients were compatible after FTIR studies, the results shown in Figure 1.

Pre-compression evaluation parameters

For each type of formulation blends of active pharmaceutical ingredients and excipients were prepared and evaluated for various parameters as explained earlier. Bulk density was found in the range of 0.476-0.529 g/cm^3 and the tapped density between 0.555 - 0.632 g/cm^3. Using the above two density data, Carr's compressibility index were calculated. The compressibility index was found between 14.23-17.24% and the compressibility and flowability data indicated good flow properties of all powder blends. The better flow property of all powder blends was also evident from angle of repose. The angle of repose was in the range of 26.21°-28.56°. Angle of repose below 30º indicates good flow property. In the present study all powder blends showed good flow property. The results are shown in Table 2.

Post- Compression evaluation parameters organoleptic characters:

Various organoleptic properties *viz*. taste, colour and odour performed on all the formulations, the results found that all the formulations were sweet in taste, white in colour and odourless.

Thickness

Thickness of all the formulations was evaluated as per the procedure and the average values was ranges between minimum of 3.12 mm to maximum of 3.32 mm and found to be within the

allowed limit of deviation i.e. 5% of the standard value. Also the crown diameter of all the formulation was 6 mm and the results are shown in Table 3.

Hardness

All the tablet formulations were evaluated for their hardness as per procedure and the results were shown in Table 3. All the formulations have an average hardness in between 4.30 to 4.10 kg/cm^2 which was found to be acceptable.

Friability

All the Fast dissolving tablets were evaluated for their percentage friability as per the procedure and the results are shown in Table 3. The average percentage friability for all the formulations was found between 0.39 % to 0.77 %, which is observed to be within the limit as per the standard (i.e. maximum 1 %). So the maximum friability was 0.77 % observed for F3 and the minimum friability 0.39 % observed for F1 formulations.

Weight Variation

All the Fast dissolving tablet formulations were evaluated for their uniformity of weight according to the procedure and the results were shown in Table 3. The maximum weight of 152.2 mg for F3 and the minimum weight of 147.1 mg for F2 formulations were observed. The maximum allowed percentage weight variation for tablets 150 mg by Indian pharmacopoeia is 7.5% and no formulations were exceeded the limit. Thus all the formulations were found to be complying with the standards given in IP.

Drug Content

All the Fast dissolving tablet formulation was evaluated for their uniformity of drug content according to the procedure and results were shown in Table 3. The percentage drug content of all formulations was found in the range of 95.51 to 97.15% w/w. The maximum drug content of 97.15% w/w for F6 and the minimum of 95.51% w/w for F2 formulations were observed.

Disintegration time

Disintegration is the first and important step for drug absorption from a solid dosage form after oral administration. All the formulations were evaluated for their disintegration time according to the procedure and the results were shown in Table 3. An important factor affecting the

disintegration is the hardness and definitely has an influence on the disintegration time as it affects the porosity of the matrix and accordingly the ability of water to penetrate through the matrix. The average disintegration time for all the formulations was in the range of 15 to 170 seconds. The maximum *in vitro* disintegration time of 170 sec and minimum *in vitro* disintegration time of 15 seconds were shown by F1 and F6 respectively.

***In vitro* dissolution studies**

Dissolution studies on all the six formulations of fast dissolving tablet of Candesartan cilexetil were carried out using a USP type II (paddle type) dissolution test apparatus by using phosphate buffer pH 6.8 as the dissolution medium. The amount of drug released from formulations F1, F2, F3, F4, F5, F6 were 86.47%, 94.16%, 95.12%, 97.12%, 98.74% 99.59%, respectively at the end of 80 seconds. Results in Figure 2, showed that the drug release from the formulations decreased with increase in the amount of excipients added in each formulation. Formulation F6 shows fast drug release compared to all formulations. The formulation F6 containing equal ratio of super disintegrants such as sodium starch glycolate : crospovidone: (1:1). The release data was fitted to various mathematical models such as zero order, first order, Higuchi, Korsmeyer-peppas and it was found that the drug release follows first order kinetics.

Stability studies

The formulations subjected to the stability studies and the evaluation parameters performed after the study period was shown no significant changes with respect to the initial observations. Further the results were compared and all the formulations found to be stable during the study period.

CONCLUSION

Fast dissolving tablets of Candesartan cilexetil were prepared using different super disintegrants, such as crospovidone, sodium starch glycolate by direct compression method. A total of six formulations were prepared. The powder properties like angle of repose, bulk density, tapped density; Hausner's ratio and Carr's index of all the formulations were found to be within the standard limits. All the post compression characteristics of the formulations like thickness, weight variation, hardness, friability, drug content and disintegration time were found to be well within the limits of official standards. The dissolution studies showed that the formulations were

suitable for the fast release of the drug from the formulations for the instant therapeutic actions. The release data was fitted to various mathematical models showed that the drug release follows first order kinetics. All the formulations subjected for the stability studies showed there were significant changes in the parameters even after the period of 60 days. From these results, it was concluded that, the candesartan is suitable to develop in to fast dissolving tablets, further clinical trials and commercial exploitation is needed for the better usefulness in the intended therapeutic treatment.

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Table 1: Formulation development of Fast dissolving tablet of Candesartan cilexetil

INGREDIENTS	F1	F2	F3	F4	F5	F6
Candesartan cilexetil	4	4	4	4	4	4
Sodium starch glycolate	15	30	-	-	7.5	15
Crospovidone	-	-	15	30	7.5	15
Microcrystalline cellulose	50	35	50	35	50	35
Magnesium stearate	4	4	4	4	4	4
Talc	2	2	2	2	2	2
Saccharin sodium	20	20	20	20	20	20
Lactose	55	55	55	55	55	55
Total weight	150	150	150	150	150	150

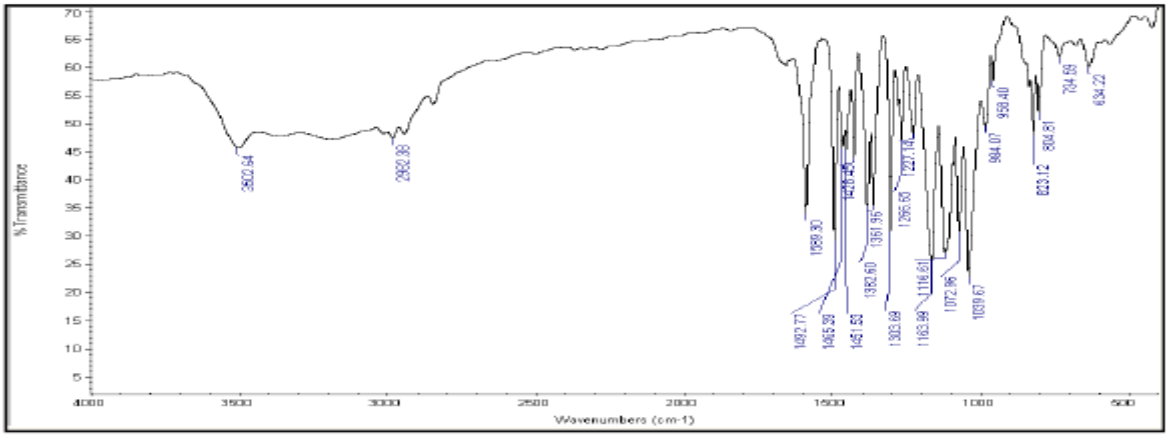
All quantities are in milligrams (mg).

Table 2: Pre-compression Parameter

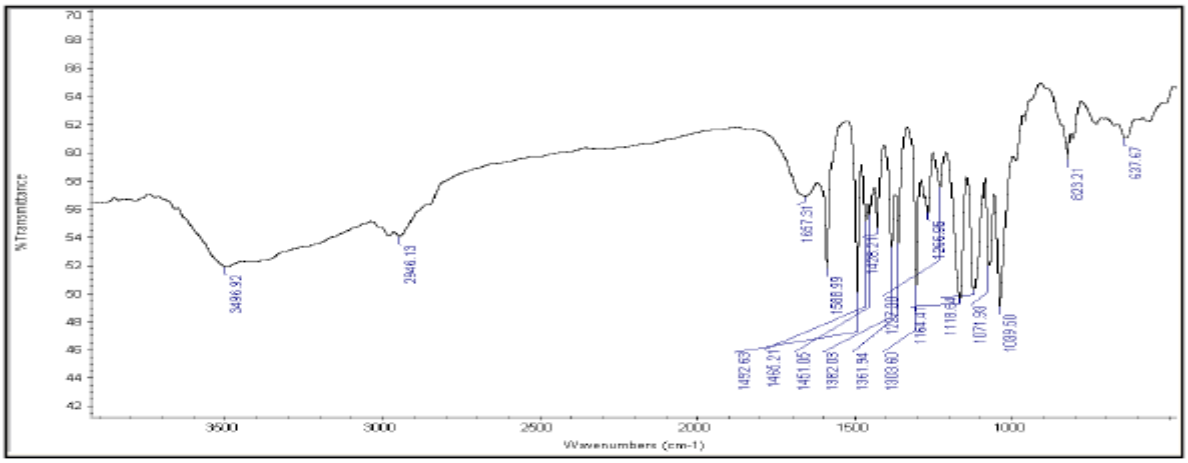
Code	Bulk density g/cm^3	Tapped density g/cm^3	Carr's index%	Hausner's ratio	Angle of repose(°)
F1	0.521±0.094	0.625±0.120	16.64±0.03	1.19	28.56±0.04
F2	0.529±0.101	0.626±0.034	15.49±0.094	1.18	28.19±0.067
F3	0.528±0.074	0.620±0.069	14.83±0.065	1.17	27.89±0.051
F4	0.523±0.089	0.632±0.091	17.24±0.074	1.20	26.21±0.079
F5	0.521±0.093	0.623±0.113	16.37±0.093	1.19	27.97±0.084
F6	0.476±0.112	0.555±0.108	14.23±0.034	1.16	27.61±0.099

Table 3:Post- compression evaluation parameter

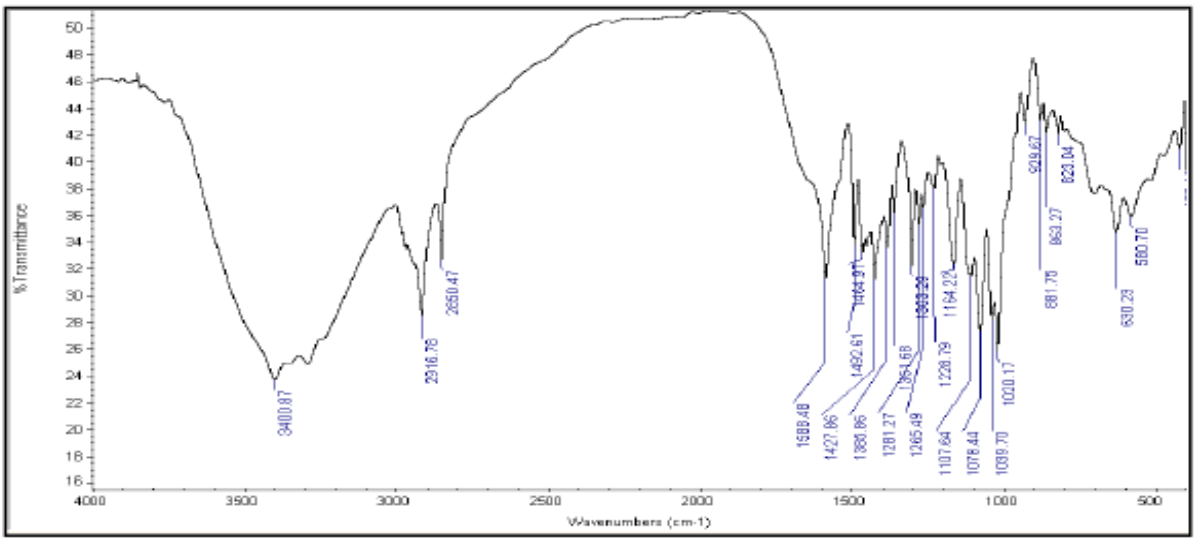
Code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)	Disintegration Time (Sec)
F1	148.91±0.22	4.30±0.10	3.12±0.01	0.39±0.15	95.51±0.50	170
F2	147.10±0.22	4.10±0.09	3.15±0.03	0.56±0.11	95.00±0.40	90
F3	152.20±0.49	4.10±0.04	3.18±0.03	0.77±0.09	96.85±0.32	23
F4	150.10±0.41	4.20±0.07	3.12±0.02	0.43±0.62	95.79±0.27	30
F5	148.20±0.32	4.20±0.05	3.32±0.01	0.42±0.44	97.01±0.89	20
F6	148.30±0.91	4.10±0.03	3.19±0.04	0.62±0.53	97.15±0.42	15



A. Pure Drug Candesartan cilexetil



B. Drug with Crospovidone



C. Formulation F6.

Figure 1: FTIR studies of pure drug, with excipients and formulation

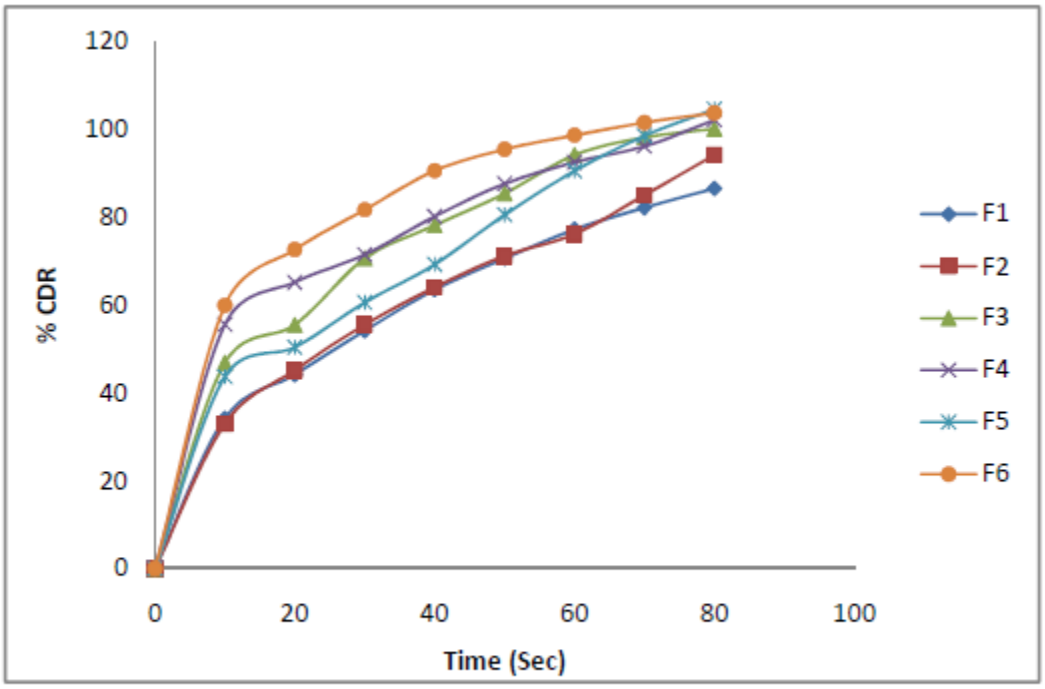


Figure 2: *In-vitro* drug release studies