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FORMULATION AND EVALUATION OF BILAYER FLOATING TABLETS OF CIPROFLOXACIN AND ALOE VERA GEL POWDER FOR TREATMENT OF GASTRIC ULCERS

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ABSTRACT

The aim of the present work was to design and develop a bilayer floating tablet of Ciprofloxacin and Aloe vera gel powder for the treatment of peptic ulcer, with the objective of retaining the dosage form in stomach for better antiulcer activity using the synthetic drug with a herbal product. Aloe vera gel powder was used for its cytoprotective action. Six Bilayer floating formulations were prepared by using direct compression method.The formulation has been developed using hydroxypropyl methyl cellulose HPMC K4M and HPMC K100M at varying concentrations. FTIR studies showed no incompatibility between the drug and excipients. The ratios of sodium bicarbonate and citric acid was adjusted to get the least possible lag time less than one minute with good matrix integrity and total floating log time greater than eight hours. Among all the six formulations F4 showed the maximum drug release of 96.018% within eight hours.

KEY WORDS
Ciprofloxacin, Aloe vera, Bilayer floating tablets, Peptic ulcer.

INTRODUCTION

Ulcer is a sore in the lining of the stomach or duodenum. These are the parts of the gut where acid bathes the surface . Gastric ulcers are closely associated with helico bacter pyroli infection and some of them may be caused by long term use of NASID's like aspirin and ibuprofen. An infected individual has an estimated life time risk of 10-20%for development of the disease. H.pyroli is a gram negative bacteria which requires low oxygen concentration & relatively high co_2 concentration for its growth. It lives in mucous layer of the stomach & sticks to stomach lining there by weakens the protective mucous layer .It allows the acid to get through the sensitive lining beneath so that it irritates and causes ulcer. It is able to survive in stomach acid because of secretion of an enzyme called urease which converts urea into bicarbonates and ammonia which are strong bases .This creates a clouds of acid neutralising chemicals around the bacteria there by protecting it. The most common symptoms is abdominal discomfort like painfull gnawing ,ache ,burning ,weight loss ,poor appetite, nausea,vomiting which occurs in 2 to 3 hours after meal and mostly during nights when stomach is empty. Chronic symptoms include bloody or black stool ,bloody vomit .This may be due to ulcer burrowing inside the stomach &bleeding occurs due to ulcer breakage into blood vessels and obstruction of the food path by ulcer. ciprofloxacin is the first generation fluoro quinolones active against a broad range of bacteria. They have relatively long post antibiotic effect and less active at acidic pH because of wide spectrum of bactericidal action ,oral efficacy and good toleribility, it is being effectively employed for blind therapy of many infections but should not be used for minor cases or where gram positive organisms

are primary causative .Therapy may be initiated by intra venous infusion and switched over to oral route based upon its effectiveness.[4] The mechanism involves as the DNA gyrase consists of 2 subunits A&B. A carries out nicking of DNA &B introduces negative super coils, Ciprofloxacin bind to A subunit with high affinity and interfere with its strand cutting & resealing function .Recent evidences indicates that in gram positive bacteria the major target of FQ's is a similar enzyme topoisomerase 4 may confer high potency against gram positive bacteria. The bactericidal action probably results from digestion of DNA by exonucleases whose product is signalled by damaged DNA.Ciprofloxacin has a good safety record but side effects occur in 10%patients but are generally mild such as nausea ,vomiting ,bad taste ,anorexia , dizziness ,insomnia ,skin rash ,photo sensitivity , swelling of lips and tendonitis etc . *Aloe barbadensis*, commonly called *Aloe vera*, is one of the most widely used healing plants in the history of mankind for thousands of years in various cultures of traditional home made remedies. *Aloe vera* upon ingestion is accomplished by inhibition of excess HCL secretion by parietal cells of stomach. They could promote the healing of burns and other cutaneous injuries and ulcer, thus improving wound healing in a dose-dependent manner and reducing edema and pain.*Aloe vera* gel has been demonstrated to protect human beings and rats against gastric ulceration. This antiulcer activity is due to its anti-inflammatory, cytoprotective, healing and mucus stimulatory effects. The adverse effects can be reduced to maximum extend with combination of aloe vera and ciprofloaxin.[2]Hence oral route is increasingly being used for the delivery of these therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. With advancement in technology and increase in awareness, towards modification in standard tablet is done to achieve better acceptability as well as bioavailability because of which newer and more efficient tablet dosage forms are being developed. In this Bilayer floating tablets are a type of multiple compressed tablets that can be a primary option to avoid chemical incompatibilities between active pharmaceutical ingredients by physical separation and to enable the development of different drug release pro-files. They remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines.[1-6]

MATERIALS AND METHODS

Materials: Ciprofloxacin was obtained as gift sample from Devis laboratories. *Aloe vera* gel powder was obtained from FDC Ltd, Mumbai .Hydroxy propyl methyl cellulose was obtained from Maple Biotech. Sodium bicarbonate , Avicel pH 102 **,** Magnesium stearate, Talc ,Citric acid was obtained from SD fine chemicals. All other ingredients used were of analytical grade.

Methodology

Standard graph preparation of Ciprofloxacin: Ciprofloxacin 100mg was dissolved in 100ml of methanol to give a solution of 1000µg/ml (solution A). 1ml was taken from solution A and transfer into the 50ml volumetric flask , volume was made upto the mark with 0.1N HCl to form a solution of 20µg/ml (solution B).

From the solution B of Ciprofloxacin, appropriate aliquots 1,2,3,4,and 5ml were pipetted out in 10 ml volumetric flasks and dilutions were made with 0.1 N HCl to obtain working standard solutions of concentrations from 2-10µg/ml. Absorbance for these solutions were measured at 254 nm in U.V spectrophotometer and standard graph was plotted.

Formulation Development

Preparation of bilayer floating tablets: Ciprofloxacin, sodium bicarbonate ($NaHCO_3$), citric acid, Avicel pH 102 and HPMC were passed from sieve # 40 and mixed for 5 min. Magnesium stearate and talc were added to the above mixture. The whole bulk of powder was then mixed thoroughly for 10 min. The powder was then compressed on multi-station rotary tabletting machine *A. vera* gel powder was added on this first layer and compressed at high pressure to obtain a bilayer tablet.

Preformulation studies

Organoleptic Properties: Colour: A small quantity of Ciprofloxacin and *aloe vera* gel powders were taken in butter paper and viewed in well-illuminated place.

Taste and odour: Very less quantity of Ciprofloxacin and *aloe vera* gel powders was used to get taste with the help of tongue as well as smelled to get the odour.

Physical Characteristics:

Solution properties: The approximate solubilities of substances were indicated by the descriptive terms in the accompanying table 2. Solvents such as methanol, alcohol, water and isopropyl alcohol , DMSO , DMF were used for the solubility studies.

Solubility studies of Ciprofloxacin and aloe vera gel powders: An excess quantity of Ciprofloxacin and

aloe vera gel powders were taken separately and added in 10ml of different solutions. These solutions were shaken well for few minutes. Then the solubility was observed.

Loss on drying studies: 1 gm of granules where weighed and kept for checking the loss on drying on a moisture sensitive balance at 105°C for 3 mins. Percentage loss of moisture content is determined.

Drug-Excipient Compatibility Studies by FTIR: All the samples were scanned at the resolution of 4 cm-1 over the wave number region 4000-400 cm-1 using KBr disk method. This KBr disks where formed by taking Drug and KBr in a ratio of 1:100 respectively. Then this mixture was mixed well in mortar for three to five min. A very small amount of this mixture was uniformly spread and sandwich between the pellets and pressed using KBr pellet press at a pressure of 20,000 psi for 1 min. The pressure was then released and pellet was placed into the pellet holder and thus scanned in the IR region.. Chemical stability was confirmed by IR spectrometry.

Pre-compression evaluation :

Bulk density: The powder sample under test was screened through sieve #18 and the sample equivalent to 10g was accurately weighed and filled in a 50ml graduated cylinder and the powder was leveled and the unsettled volume (V_0) was noted. The bulk density was calculated in g/cm^3 by the formula,

Bulk density (ρ_0) = $\frac{M}{V_0}$ Where M = mass of powder taken, V_0=apparent unstirred volume

Tapped density: The powder sample under test was screened through sieve #18 and the weight of sample equivalent to 10g was filled in 50ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a constant rate for 100 times Volume was considered as tapped volume (V_f). The tapped density was calculated in g/cm^3 by the formula,

Tapped density (ρ_t) = $\frac{M}{V_f}$ Where, M = weight of sample powder taken & V_f = tapped volume

Percentage compressibility or Carr's index: Based on the poured density and tapped density, the percentage compressibility of the granules was computed using the Carr's compressibility index by the formula,

Carr's index (%)

$$= \frac{tapped\ density - poured\ density}{tapped\ density} x\ 100$$

Hausner's ratio:

Hausner's ratio was calculated using the formula,

Hausner's ratio =tapped density/poured density

Angle of repose:

Angle of repose of the granules was determined by the height cone method. A funnel was fixed to a desired height and granules were filled in it. They were allowed to flow down on a graph paper fixed on a horizontal surface and angle of repose was calculated using the formula $\tan\theta = h/r$; $\theta = \tan^{-1}(h/r)$

Where: θ = Angle of repose , h = Height of the heap , r = Radius of the heap.

Evaluation of Post compression parameters

Hardness: The hardness of ten tablets was measured using Monsanto hardness tester. The mean and standard deviation were computed and reported. It is expressed in kg/cm^2.

Friability: The friability of the tablets was determined using electrolab friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25rpm for 4min. After 4min the tablets were weighed again. The friability was then calculated using the formula,

$$Friability\ (\%) = \frac{initial\ weight - final\ weight}{initial\ weight} x\ 100$$

Weight variation test: Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 10 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the percentage shown in table 6 and none deviate by more than twice the percentage shown.

Estimation of Drug content: Equivalent to 10mg each of aloe vera gel HCl and Ciprofloxacin HCl was accurately weighed from powdered bilayer floating tablets and it was dissolved in methanol and distilled water respectively to form a clear solution. Later it was made up to volume with methanol and distilled water respectively. One ml of the sample was withdrawn , suitably diluted with 0.1N HCl and spectrophotometrically analyzed at 269nm and 232nm respectively.

In vitro floating lag time and floating time: The time taken by the tablet to emerge onto the surface of the medium after adding to the dissolution medium is called Buoyancy lag time (BLT). Duration of time by which the dosage form constantly emerges on surface of medium called Total floating time (TFT). Both BLT & TFT were determined by placing the tablet in 900ml 0.1N HCl at temperature 37±0.5ºC, paddle rotation at 50rpm using stopwatch.

Wetting time and water absorption ratio: A piece of tissue paper folded twice was placed in a small petridish (i.d. = 6.5 cm) containing 6 ml of distilled water, a tablet was put on the paper, and the time required for complete wetting was measured. The wetted tablet was then
weighed. Three trials for each batch were performed and standard deviation was also determined. Water absorption ratio, R, was determined using equation.
$R = 100 \times (Wa - Wb) / Wb$
Where:Wb = weight of the tablet before water absorption,Wa = weight of the tablet after water absorption

***In*-vitro Drug Release studies:** The dissolution test apparatus Type II was used with 0.1N HCl as the dissolution medium(900 ml) . One tablet was placed in each dissolution bowl and the apparatus was runned for 12hrs at a speed of 50 RPM maintaining 37±0.5ºC. The sample was withdrawn at intervals like 1 to 12 hrs. Every time 5ml sample was withdrawn and 5ml of buffer(0.1N HCl) was added into the dissolution flask. The withdrawn sample filtered through membrane filter. The filtrate was collected, analysed under U.V spectrophotometer.

Release kinetics: Release data was analyzed as per zero order release, first order release Higuchi release and Korsmeyer Peppas release models to assess drug release kinetics an mechanism from Tablets.

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as:
1) Cumulative percentage drug released Vs Time (In-Vitro drug release plot)
2) Log cumulative percentage drug remaining Vs Time (First order plot)
3) Cumulative percentage drug released Vs Square root of time (Higuchi's plot)
4) Log percentage drug released Vs Log time (Peppas plot)

Stability Studies: In any rational design and evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of a drug can be defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications**.**

RESULTS AND DISCUSSIONS

Preformulation studies: All the tests mentioned in the preformulation studies were performed and the drugs shows the following results.

Ciprofloxacin Hydrochloride: Ciprofloxacin HCl raw material has been tested as per in-house specifications and the results are listed in table 7. The drug source is identified and found complying with the specifications.

Aloe vera gel : Aloe vera gel powder raw material has been tested as per in-house specifications and the results are listed in table 8 The drug source is identified and found complying with the specifications.

Drug Excipient Compatibility Studies: After the studies are completed the results prove that there is no incompatability between the drugs and excipients.

Pre compression parameters: The granules were tested for precompression parameters like bulk density, tapped density, Carr's index, Hausner's ratio and Angle of repose and the results were reported as shown in Table 9. From the results it was found that formulation powder mixture were found to be free flowing

Post compression parameters: Tablets were tested for post compression parameters like Uniformity of weight, Hardness, Friability, Thickness, Drug content, Disintegration time and the results were reported as shown in Table 10.

Results for weight variation were found to be within the limits prescribed by IP.Weight variation ranges from 850±7mg to 875±10mg.Friability test of all six formulations was also found to be within USP limit which ranges from 0.79±0.03 to 0.87±0.09%, indicating enough resistance to the mechanical shock and abrasion. Hardness of the tablet was found to between 9 and 10 kg/cm2. Drug content uniformity for ciprofloxacin was also within the acceptance criteria of the IP ranging from 98.4±1.3 to 99.0±0.9 %.Bilayer floating tablets were prepared with the aim of having maximum drug release in 8 h and with minimum floating lag time and good matrix integrity. Table 10 shows results for floating lag time, total floating time and matrix integrity. Formulations F1 to F4 containing 30 mg of citric acid and 120 mg of sodium bicarbonate (1:4) met the requirements for floating lag time and total floating time, but matrix integrity was lost in less than 8 h. To improve upon the matrix integrity,

formulations F5 and F6 were developed. Formulations F5 and F6 containing lesser amount of effervescent agents, i.e. 25 mg of citric acid and 100 mg of sodium bicarbonate (1:4) showed excellent results for matrix integrity in addition to good floating lag time and total floating time.

If the sodium bicarbonate concentration is much higher than polymer concentration in a formulation, rapid erosion of tablet occurs. This may be due to the release of carbon dioxide and its escape at a faster rate. If the polymer is in sufficient concentration, the evolved gas will get entrapped in the polymer network leading to the floating of the tablet; thus, it indicates that lower polymer levels with higher levels of sodium bicarbonate in a formulation result in erosion rather than floating. Similarly,if the polymer concentration is higher than that of sodium bicarbonate, the desired drug release profile may not be achieved as the higher polymer portions can delay the drug release. Thus, the ratio of polymer to the sodium bicarbonate concentration was altered to get lowest possible lag time with the desired drug release.

Weight Gain and WU: In weight gain study, it was observed that swelling increased up to 40% of tablet weight in 5–6 h but after that it decreased.

As water ingresses from outer side to the tablet core, the outer gel layer starts to erode and volume decreases progressively followed by reduction in tablet weight. This erosion of polymer dominates over water sorption after 6 h. The test was performed to determine the swelling of a tablet which will ensure release of drug from the dosage form.

Invitro dissolution studies: The results of drug release studies, it was found that formulations F1–F3 did not give the desired release. and thus, the formulations F1–F3,F5 were not considered for further studies. F4 showed a desirable drug release of 96.01% at the 8 h and was found to show good matrix integrity (Table 10),. The formulation F6 containing 25 mg of citric acid and 100 mg of sodium bicarbonate showed 92.4% drug release at the end of 8 h with 50% drug release within 2 h. Thus, it did not meet the criteria of controlled release matrix ,which required a drug release of 50% at the end of 3 h. In the case of formulation F4, it was observed that 96.01% drug released in 8 h and 50% drug released within 3 h as is the criteria for controlled release matrix. F4 also showed optimum floating lag time, total floating time and excellent matrix integrity. Thus, the formulation F4 was considered as the optimized formulation The optimized formulation F4 was subjected to various mathematical models to understand the release pattern.

Release kinetics: It was conducted and the formulation followed Zero order kinetics which is illustrated in table 13.

Stability studies: It is observed that there was no change in physical appearence, colour.Formulations were analysed at the end of 3 months for the assay and dissolution studies.Average drug content of the tablets were found to be 96.7±0.3% of the labelled claim. Invitro dissolution profile showed that there was no significant change in the release rate of the drug from optimised tablets at the end of 3 months.

CONCLUSION

Gastro-retentive drug delivery system (GRDDS) has gained an immense popularity in the field of oral drug delivery recently. It is a widely employed approach to retain the dosage form in the stomach for an extended period of time and release the drug slowly that can address many challenges associated with conventional oral delivery, including poor bioavailability. Six batches of bilayer floating tablets of Ciprofloxacin and aloe vera gel were successfully prepared by direct compression method optimizing the proportion of sodium bicarbonate and citric acid to get the least possible lag time with good matrix integrity and total floating time. Polymer concentration was adjusted to get the maximum release in 8 h and It was found to be 96% for the formulation F4. The most promising mechanism that the release patterns of the formulations followed was non-Fickian diffusion or anomalous diffusion. Thus, the present approach may be an alternate to treat *Helicobacter pylori*-induced peptic ulcer including an antibiotic and a herbal powder replacing a proton pump inhibitor like omeprazole.

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Table-1 : Composition of ciprofloxacin and aloe vera gel Bilayer tablets

Ingredients	F1	F2	F3	F4	F5	F6
Ciprofloxacin	500	500	500	500	500	500
HPMC K4M	80	90	70	85	80	85
HPMC K100M	20	10	30	15	20	15
$NaHCO_3$	120	120	120	120	120	120
Citric acid	30	30	30	30	25	25
Avicel pH102	50	50	50	50	50	50
Mg Stearate	15	15	15	15	15	15
Talc	10	10	10	10	10	10
Aloe vera	32	32	32	32	32	32
Avicel pH102	18	18	18	18	18	18
Colour	qs	qs	qs	qs	qs	qs

Table-2 : Solubility studies limits

Descriptive Term	Parts of Solvent Required for 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble or Insoluble	Greater than or equal to 10,000

Table-3 : Carr's index limits

Carr's index (%)	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable*
23-35	Poor
33-38	very poor
> 40	Extremely poor

Table-4 : Hausner's ratio limits

Values	Comments
Less than 1.25	Good flow
Greater than 1.5	Poor flow
Between 1.25-1.5	Glidant normally improves the flow

Table-5 : Angle of repose limits

Angle of repose (degrees)	Type of flow
< 20	Excellent
20-30	Good
30-40	Passable*
> 40	Very poor

Table-6 : Weight variation limits

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	10.0
130-324	7.5
More than 324	5.0

Table-7 : Evaluation of drug (Ciprofloxacin HCl) characterization:

Sr.No	Test	Specification	Results
1	Description	A white powder	white crystals
2	Loss on drying	Not more than 0.5%w/w	0.25 w/w
3	Solubility	Freely soluble in water , slightly soluble in alcohol	complies

Table-8 : Evaluation of Aloe vera gel powder characterization:

Sr.No	Test	Specification	Results
1	Description	white to off white	white to off white
2	Loss on drying	max 0.5%w/w	0.3% w/w
3	Solubility	Freely soluble in water , slightly soluble in methanol	complies

Table-9 : Pre-compression parameters for the powder blend F1-F6

Formulation	Bulk	Tapped	Carr's	Hausner 's	Angle of repose
F1	0.538±0.025	0.638±0.009	15.67±0.034	1.18	25.90±0.026
F2	0.694±0.019	0.754±0.016	14.54±0.027	1.24	19.85±0.021
F3	0.583±0.022	0.697±0.038	16.35±0.038	1.19	20.9±0.014
F4	0.554±0.027	0.662±0.025	16.31±0.025	1.20	25.25±0.016
F5	0.550± 0.029	0.669 ±0.047	17.78 ±0.028	1.21	25.05± 0.025
F6	0.655 ±0.017	0.780± 0.019	1.02± 0.031	1.19	19.25± 0.019

Table-10 : Post-compression parameters for the tablets F1-F6

Batch	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Uniformity Of weight(mg)	Uniformity of content(%)	Floating lag time(s)	Total floating time
F1	5.5±0.04	9±0.03	0.79±0.03	875±10	98.5±1.2	28±3	>8
F2	5.4±0.02	10±0.02	0.82±0.05	875±8	99.0±0.9	36±2	>8
F3	5.8±0.01	9.5±0.04	0.85±0.07	875±8	98.5±0.9	31±2	>8
F4	5.6±0.03	9.8±0.03	0.81±0.04	875±9	98.7±1.1	24±2	>8
F5	5.9±0.02	9.6±0.04	0.80±0.04	850±10	98.4±1.3	27±3	>8
F6	5.1±0.03	9.9±0.05	0.87±0.09	850±7	99.0±0.8	25±2	>8

Table-11: Swelling index

Batch	swelling index		
	2 hrs	4 hrs	8 hrs
A1	24.53±0.33	45.94±0.87	54.54±0.33
A2	25.92±0.78	47.36±0.65	52.60±0.81
A3	28.57±0.26	50±0.89	58.33±0.59
A4	33.33±0.33	55.55±1.09	60.25±0.40

Table-12 : In vitro dissolution studies

Time(hr)	F1(%)	F2(%)	F3(%)	F4(%)	F5(%)	F6(%)
1	12.568	13.515	14.463	15.094	13.294	14.873
2	21.985	22.906	23.954	26.168	22.873	24.903
3	31.581	32.412	34.002	38.755	32.411	35.904
4	42.365	43.644	45.874	49.390	43.958	47.155
5	53.020	54.305	56.232	61.030	55.568	57.204
6	64.685	66287	69.488	73.365	66.611	70.781
7	72.613	76.124	78.395	84.504	77.397	84.117
8	82.799	85.066	88.297	96.018	84.767	92.155

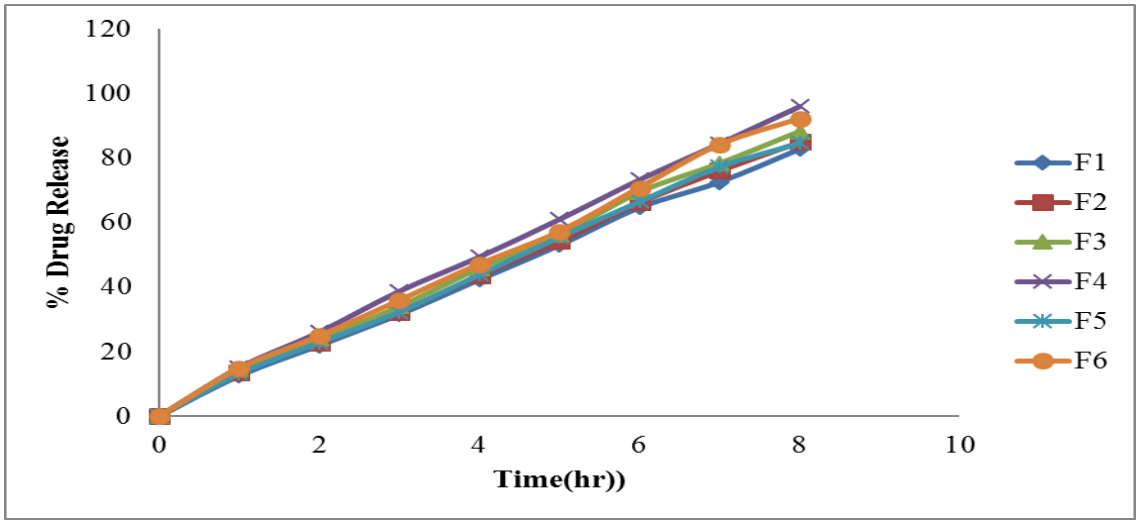

Figure-1: Graphical representation of in-vitro dissolution studies

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