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Formulation and evaluation of gastroretentive tablets of Furosemide (Evaluation based on drug release kinetics and factorial designs)

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ABSTRACT

Gastroretentive floating drug delivery systems (GFDDS) of furosemide, an loop diuretic drug, with an oral bioavailability of only 50% (because of its poor absorption from lower gastrointestinal tract) have been designed and optimized using 3^2 full factorial design. Hydroxypropyl methyl cellulose of different viscosity grades (K4M and K100M) was used as the polymers and sodium bicarbonate as gas generating agent to reduce floating lag time. The tablets were prepared by direct compression method. Estimation of furosemide in the prepared tablet formulations was carried out with 0.1N HCl and measuring the absorbance at 271 nm. The prepared formulations were further evaluated for hardness, friability, weight variation, drug content uniformity, swelling index, In-vitro drug release pattern, short-term stability and drug excipient interactions. Majority of the designed formulations displayed nearly first order release kientics, releasing more than 80% drug in 10 hours and remained buoyant more than 24 hours. The optimized formulation containing furosemide 80 mg, HPMC (K4M) 100 mg and sodium bicarbonate 30 mg has displayed almost zero order release kinetics with a floating lag time of only 2.9 minutes. This formulation released more than 90% drug in 9 hours. This study proves that GFDDS of furosemide can be designed using HPMC K4M as matrix polymer, which provides nearly zero order release kinetics and thus possible enhancement of oral bioavailability of the drug.

Keywords: Furosemide; Gastroretentive floating drug delivery systems; Hydrodynamically balanced systems; Hydroxypropyl methyl cellulose; 3^2 factorial design.

INTRODUCTION

Controlled Release Through Gastric Retention:[7,9,10,13]
During the last decade, many studies have been performed concerning the sustained release dosage forms of drug, which have aimed at the prolongation of gastric emptying time (GET).The GET has been reported to be from 2 to 6 hours in humans in the fed state [7]. Accordingly, when a sustained release dosage form is administered orally, sufficient bio-availability and prolongation of the effective plasma level occasionally can't be obtained. Also reflected in the recent scientific patent literature, an increased interest in novel dosage forms which possess not only a mechanism for controlled release of the drug but also controlled GI transit time exists today in academic and industrial research groups[8]. Retention of drug delivery systems in the stomach prolongs overall gastro intestinal transit time, thereby resulting in improved bioavailability.

In the design and development of Hydrodynamically Balanced Systems (HBS), anatomical and physiological factors of the stomach play an important role.

Basic Gastrointestinal Tract Physiology
Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions[10].

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the two states. During the fasting state an interdigestive series of electrical events take place, which cycle goes through stomach and intestine every 2 to 3 hours [11]. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following four phases as described by Wilson and Washington[12].

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of two consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state, onset of MMC is delayed resulting in slowdown of gastric emptying rate[13].

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications that of short gastric residence time and unpredictable gastric emptying rate.

Approaches to Increase Gastric Retention:
Various approaches have been worked out to improve the retention of oral dosage form in the stomach.
Swelling and expanding.
Altered density dosage forms.
Low-density or floating drug delivery.

Intragastric Floating Drug Delivery System (IGFDDS):
A IGFFDS can be made to float in the stomach by incorporating a floatation chamber, which may be a vacuum, filled with air or a harmless gas.
Inflatable Gastrointestinal Delivery System;

The residence time of the drug delivery device in the stomach can also be sustained by incorporation of an inflatable chamber, which contains liquid (e.g., ether) that gasifies at body temp to cause the chamber to inflate in the stomach.
Intragastric Osmotically Controlled Drug Delivery System;

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device.

Depending on the mechanism of buoyancy, two distinctly different methods like effervescent and non-effervescent systems have been used in the development of floating drug delivery systems (FDDS).

Non-Effervescent FDDS:
The commonly used excipients in this type of drug delivery system are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonates, polyacrylates, etc. In one approach, gel forming hydrocolloid swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and the bulk density of less than unity within gastric environment [22].

Sheth and Tossounian developed a hydrodynamically balanced system (HBS) which when comes in contact with an aqueous medium, imbibes water and starts to hydrate, thereby forming a gel at the surface [23]. The drug in the dosage form dissolves in and diffuses out with the diffusing solvent forming a receding boundary within the gel structure. Jain NK et al have studied the formulation and performance evaluation of hydrodynamically balanced capsules of diazepam for oral controlled release and studied the buoyancy characteristics of capsules in the stomach [24]. Capsules remained buoyant in simulated gastric fluid and the integrity of the matrix was maintained in vitro for more than 12hours.

Effervescent FDDS:
These buoyant drug delivery systems utilize matrices prepared with swellable polymers such as Methocel® or polysaccharides, e.g., chitosan and effervescent components, e.g., sodium bicarbonate and citric acid and tartaric acid [25]. These matrices are formulated in a way that upon arrival in the

stomach, CO_2 is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid, which causes an upward movement of the dosage form and maintains its buoyancy. Stockwell et al prepared floating capsules by milling with a mixture of sodium alginate and sodium bicarbonate [26]. The systems were shown to float during *in vitro* tests as a result of generation of CO_2 that has trapped in the hydrating gel.

It was also observed that the addition of carbonates to the dosage form not only imparts buoyancy to these forms but they also provide the initial alkaline micro environment for polymers to gel [21].

The ability to float relies on the hydration state of the dosage form. In order to keep these tablets floating *in vivo*, intermittent administration of water (a tumbler full, every 2 hours) is beneficial [43]. The ability of drug to remain in the stomach depends upon the subject being positioned upright [44]. FDDS are not suitable for the drugs that have solubility or stability problems in the gastric fluid [33]. Drugs like nifedipine, which is well absorbed along the entire GIT and which undergoes significant first pass metabolism, may not be desirable candidates for FDDS since the slow gastric emptying may lead to the reduced systemic bio-availability [33].

Optimization [45, 84**]**

In today's industrialized society almost every product that eventually reaches the market has a long lineage of testing and modification to its design before it sees the light of the day. So "success is the most difficult commodity" to come out, especially with time frame imposed, which is structured by a customer need or by a competitive threat. This leads to experimenters or researchers to find the most efficient schemes of formulating, testing and applying such schemes as broad a gamut of application required, to make a successful product.

The word 'optimize' is defined as, to make as perfect, effective or functional as possible and optimization may be interpreted as the way to find those values of the dependent variable. The application of formulation optimization techniques is relatively new to practice of the pharmacy, when used intelligently, with common sense, these "statistical" methods will broaden the perspective of the formulation process. Before any experiment is conducted at the pre-formulation stage, certain problems arise. It is often known beforehand which variables will significantly influence the response(s). Using screening designs and ANOVA can solve the problem.

A second serious complication may arise with new exipients and new process factors, for which qualitative or quantitative effects are not known and nor they are predictable. Before choosing design, following question must be answered. Which part of the factor space should be chosen for experiments, are these constraints to be put on the levels of the variables. The third complication is that, formulated products, in particular, dosage forms have to conform to several requirements, very often competing. The formulator has to trade off objectives and choose a compromise. A fourth problem is the lack of insight in the balance between the needed and prior knowledge to perform an adequate optimization study and the gain in knowledge obtained by this study. It should be emphasized that in the performance of an optimization study, the development scientist can also be a factor, reliable prior experience and knowledge is a pre-requisite.

Terms used in Optimization:

Variables*:* These are the measurements, values, which are characteristics of the data. There are two types of variables, dependent and independent variables. Independent variables are the variables, which are not dependent on any other value e.g., lubricants concentration, drug to polymer ratio, etc. Dependent variables are dependent on the concentration of independent variable used.

Factor*:* Factor is an assigned variable such as concentration, temperature, lubricating agent, drug-to-polymer ratio, polymer-to-polymer ratio or grade. A factor can be qualitative or quantitative. A quantitative factor has a numerical value to it e.g., concentration (1%, 2%…… so on), drug to polymer ratio (1:1, 1:2……etc). Qualitative factors are the factors, which are not numerical. For e.g. Polymer grade, humidity condition, type of equipment etc. These are discrete in nature.

Levels*:* The levels of a factor are values or designation assigned to the factor. For e.g., concentration (factor) 1% will be one level, while 2% will be another level. Two different plasticizers are levels of grade factor. Usually levels are indicated as low, middle or high level. Normally for ease of calculation the numeric and discrete levels are converted to –1 (low level) and +1 (high level).
The general formula for this conversion is

$$\text{Level} = \frac{\text{X} - \text{the average of the two levels}}{\text{Half the difference of levels}}$$

Where 'X' is the numeric value.

Response*:* Response is mostly interpreted as the outcome of an experiment. It is the effect, which we are going to evaluate i.e., disintegration time, duration of buoyancy, thickness, $t_{1/2}$ etc.

Effect*:* The effect of a factor is the change in response caused by varying the levels of the factor. This describes the relationship between factors and levels.

Interaction*:* It is also similar to effect, which gives the overall effect of two or more variables (factors) of a response. For example, the combined effect of lubricant (factor) and glidant (factor) on hardness (response) of a tablet.

From the optimization we can draw conclusion about Effect of a factor on a response i.e., change in dissolution rate as the drug to polymer ratio changes.
The relationship between various factors and response i.e., quantitative change of a response as we change the factors and its levels.
The contribution effect i.e., whether two factors are contributing additively or antagonistically for a response. E.g., any relationship between lubricant concentration and glidant concentration on hardness of the tablet or flow property of the granules.
The best formulation (according to our need).

Optimization Process:

In general the optimization process involves the following steps:
Based on the previous knowledge or experience or from literature, the independent variables are determined or set in the beginning.
Selection of a model based on the results of the factor screening.
The experiments are designed and are conducted.

The responses are analyzed by ANOVA, test on lack of fit, to get an empirical mathematical model for each individual response.

The responses are screened by using multiple criteria to get the values of independent variables. For example restriction of hardness to 6-8 kg/cm² and disintegration time < 5 min for a tablet formulation to get the most probable values of the independent variables like lubricant type or its concentration, disintegrating agent, etc.

Experimental Designs:
Experimental design is a statistical design that prescribes or advises a set of combination of variables. The number and layout of these design points within the experimental region depend on the number of effects that must be estimated. Depending on the number of factors, their levels, possible interactions and order of the model, various experimental designs are chosen. Each experiment can be represented as a point within the experimental domain, the point being defined by its co-ordinate (the value given to variables) in the space.

Factorial Design:
It is an experimental design, which uses dimensional factor space at the corner of the design space. Factorial designs are used in experiments where the effects of different factors or conditions on choice for simultaneous determination of the effect of several factors and their interaction. The simplest factorial design is the two factorial designs, where two factors are considered each at two levels, leads to four experiments, which are situated in 2-dimensional factor space at the corners of a rectangle.
If there are three factors, each at two levels, eight experiments are necessary which are situated at the corners of an orthogonal cube on a 3 dimensional space. The number of experiments is given by 2^n, where 'n' is the number of factors.

If the number of factors and levels are large, then the number of experiments needed to complete a factorial design is large. To reduce the number of experiments, fractional factorial design can be used (i.e., ½ or ¼ of the original number of experiments with full factorial design).

The fitting of an empirical polynomial equation to the experimental result facilitates the optimization procedure. The general polynomial equation is as follows:
$Y = B_0 + B_1X_1 + B_2 X_2 + B_3 X_3 + \ldots\ldots\ldots + B_{12} X_1X_2 + B_{13}X_1X_3 + B_{23}X_2X_3 + \ldots\ldots + B_{123} X_1X_2 X_3$.
Where Y is the response.
Where X_1, X_2, X_3 are the levels (concentration) of the 1, 2, 3 factor.
B_1, B_2, B_3, B_{12}, B_{13}, B_{23}, B_{123} are the polynomial coefficient
B_0 is the intercept (which represents the response when the level of all factors is low).

EXPERIMENTAL SECTION

Preparation of Standard Calibration Curve of Furosemide:
Method:
100mg of Furosemide was accurately weighed and transferred into 100ml volumetric flask. It was dissolved and diluted to volume with 0.1N HCl to give stock solution containing 1000µg/ml.

Table-1: Materials Used

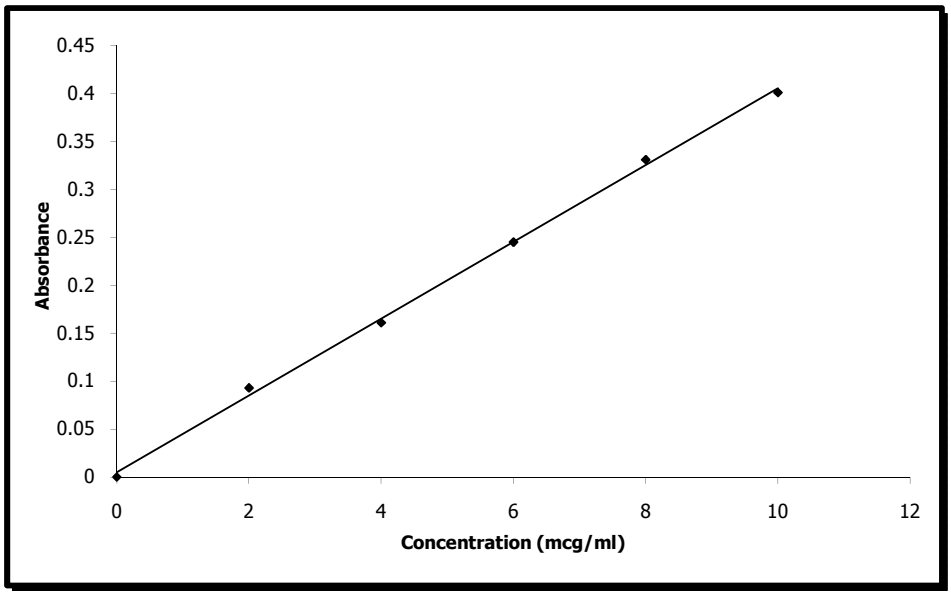
Materials	Source
Furosemide	Modern Labs, Indore
HPMC K4M	Colorcon Asia Pvt. Ltd., Goa
HPMC K100M	Colorcon Asia Pvt. Ltd., Goa
Sodium bicarbonate	Modern Labs, Indore
Avicel PH-102	Modern Labs, Indore
Talc	S.D. Fine Chem. Ltd.
Magnesium Stearate	S.D. Fine Chem. Ltd.
Hydrochloric acid LR	S.D. Fine Chem. Ltd.

Table-2: Standard calibration curve of furosemide (λ_{max}=271 nm)

Sl. No.	Concentration (mcg/ml)	Absorbance (mean±SD)
1.	Blank	0.00±0.0000
2.	2	0.093±0.0031
3.	4	0.161±0.0025
4.	6	0.245±0.0020
5.	8	0.331±0.0030
6.	10	0.401±0.0035

The standard stock solution was then serially diluted with 0.1N HCl to get 1 to 10µg/ml of furosemide. The absorbances of the solution were measured against 0.1N HCl as blank at 271 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Figure-1: **Standard calibration curve of furosemide (λ_{max}=271 nm)**



Formulation Table-3: Preliminary Trial Formulations

Ingredient	T_1	T_2	T_3	T_4	T_5	T_6
Furosemide (mg)	80	80	80	80	80	80
HPMC (K100M) (mg)	50	100	150	--	--	--
HPMC (K4M) (mg)	--	--	--	50	100	150
$NaHCO_3$ (mg)	25	37	50	25	37	50
Avicel PH-102	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium stearate (mg)	1.42	1.42	1.42	1.42	1.42	1.42
Talc (mg)	2.85	2.85	2.85	2.85	2.85	2.85

Table-4: Factorial Design Formulations

Ingredient	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Furosemide(mg)	80	80	80	80	80	80	80	80	80
HPMC (K4M) (mg) (X_1)	100	100	100	125	125	125	150	150	150
$NaHCO_3$ (mg) (X_2)	15	30	45	15	30	45	15	30	45
Avicel PH-102	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium stearate (mg)	1.42	1.42	1.42	1.42	1.42	1.42	1.42	1.42	1.42
Talc (mg)	2.85	2.85	2.85	2.85	2.85	2.85	2.85	2.85	2.85

All the batches contained 2% w/w talc and 1% w/w magnesium stearate.
Each tablet contains uniform weight of 280 mg.

Preparation of gastro retentive floating tablets

In this work, direct compression method has been employed to prepare HBS of furosemide with hydroxypropyl methyl cellulose (HPMC) of two different grades (HPMC K4M and HPMC K100M).

Procedure:

All the ingredients were accurately weighed and passed through mesh # 60. In order to mix the ingredients thoroughly drug and polymer were blended geometrically in a mortar and pestle for 15 minutes then sodium bicarbonate, talc and magnesium stearate were mixed one by one. After thoroughly mixing these ingredients, the powder blend was passed through # 44 mesh. Tablets were compressed on a single punch tablet machine (Cadmach India) using 8 mm flat round punches.

Compatibility studies:

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. Drug- excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. From the figure no: 2,3,4 it has been observed that there is no chemical interaction between Furosemide and the polymers used. It was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymer.

The peaks obtained in the spectra's of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

Fig. No. 2. IR. Sepectra of Furosemide (Pure drug)

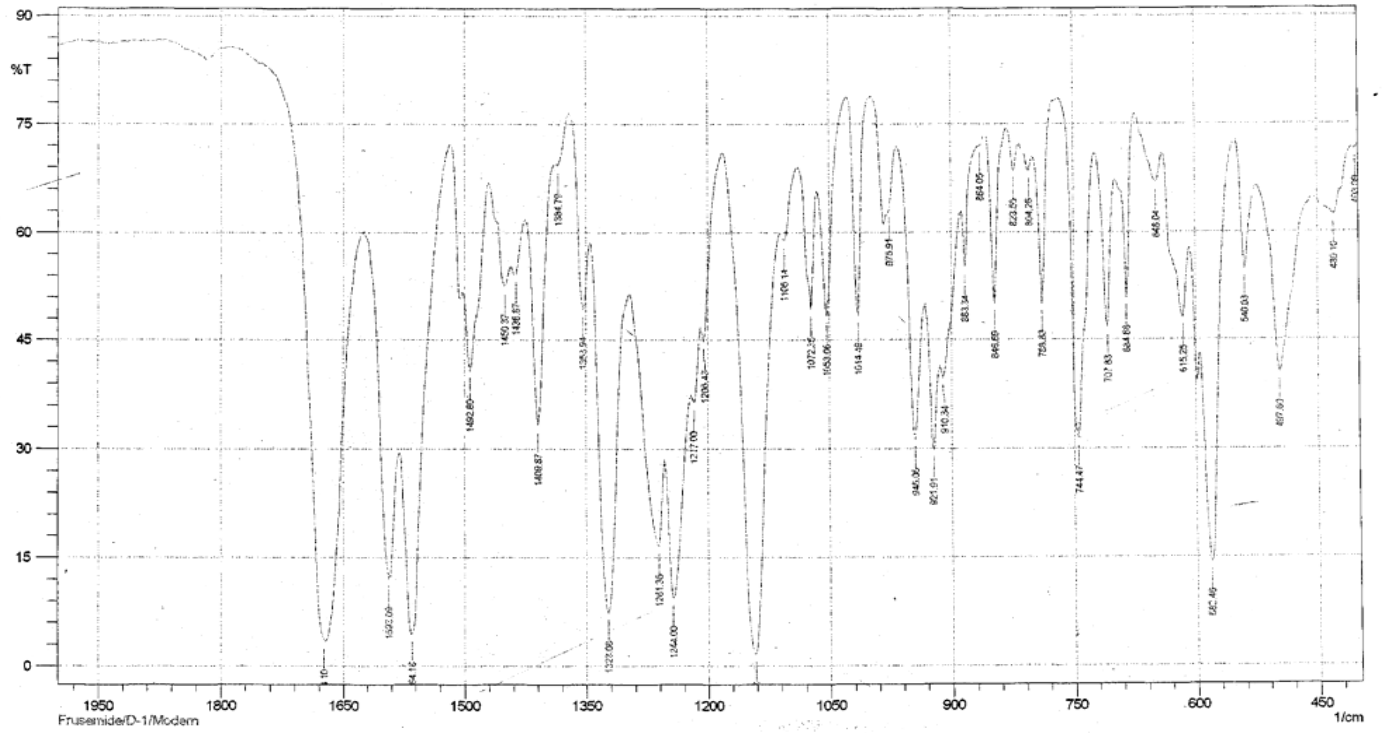


Fig. No. 3. IR. Sepectra of Furosemide + HPMC K100M

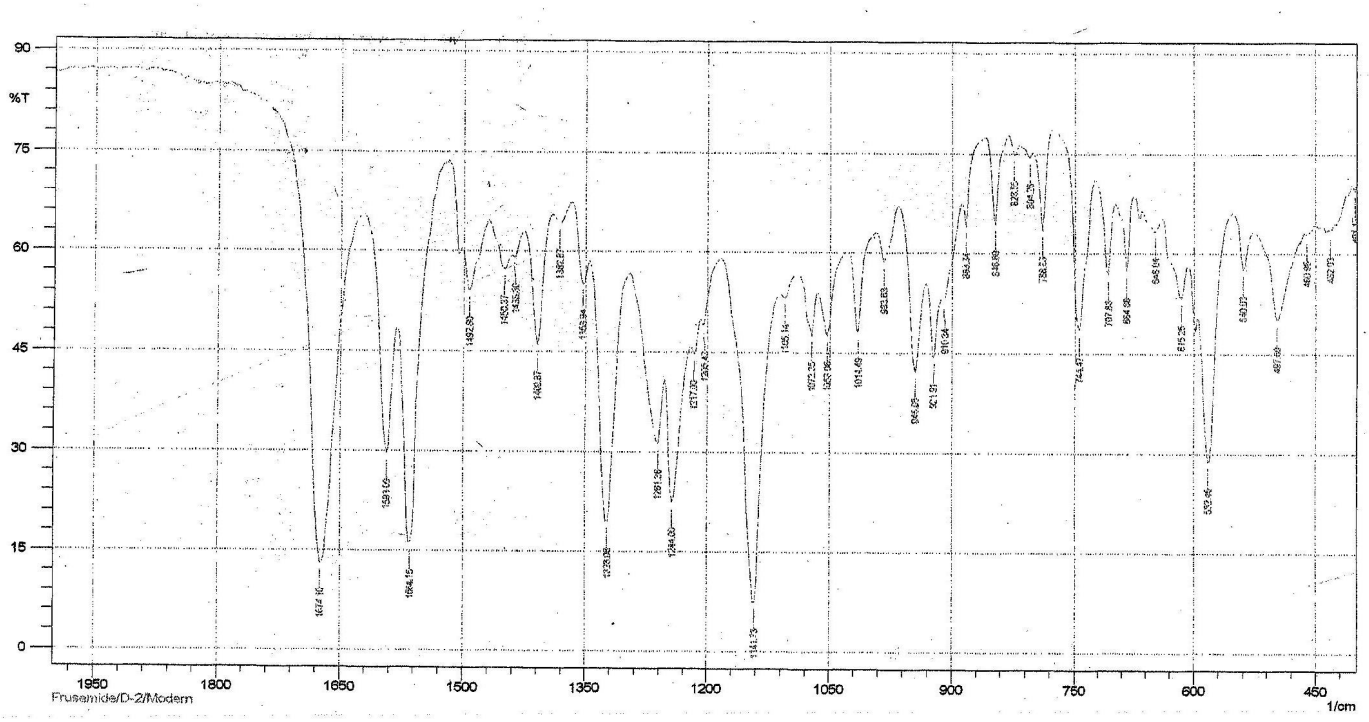


Fig No.4. IR. Spectra of Furosemide + HPMC K4M

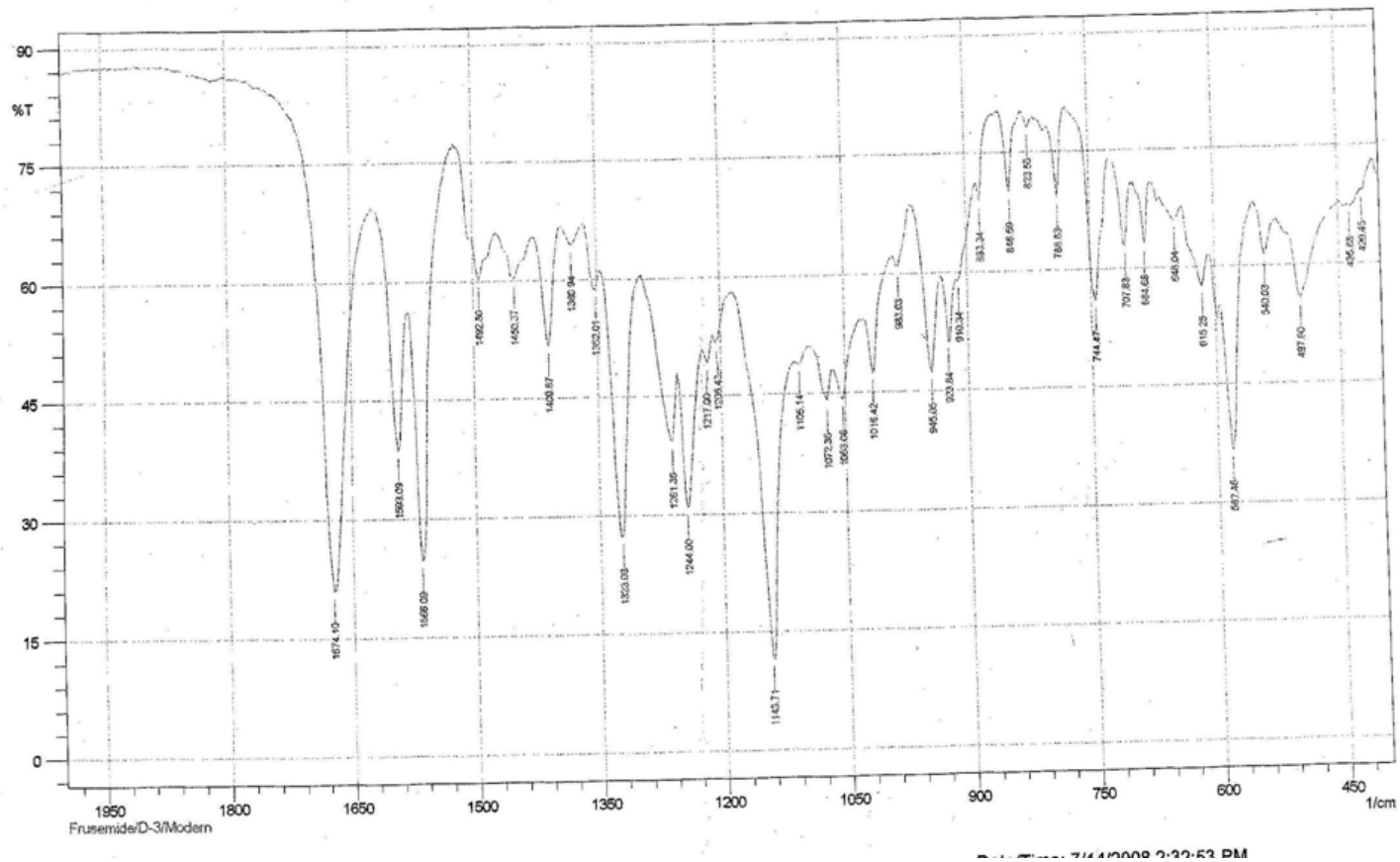


Fig. No. 5. IR. Sepectra of Furosemide + $NaHCO_3$ + Avicel PH-102

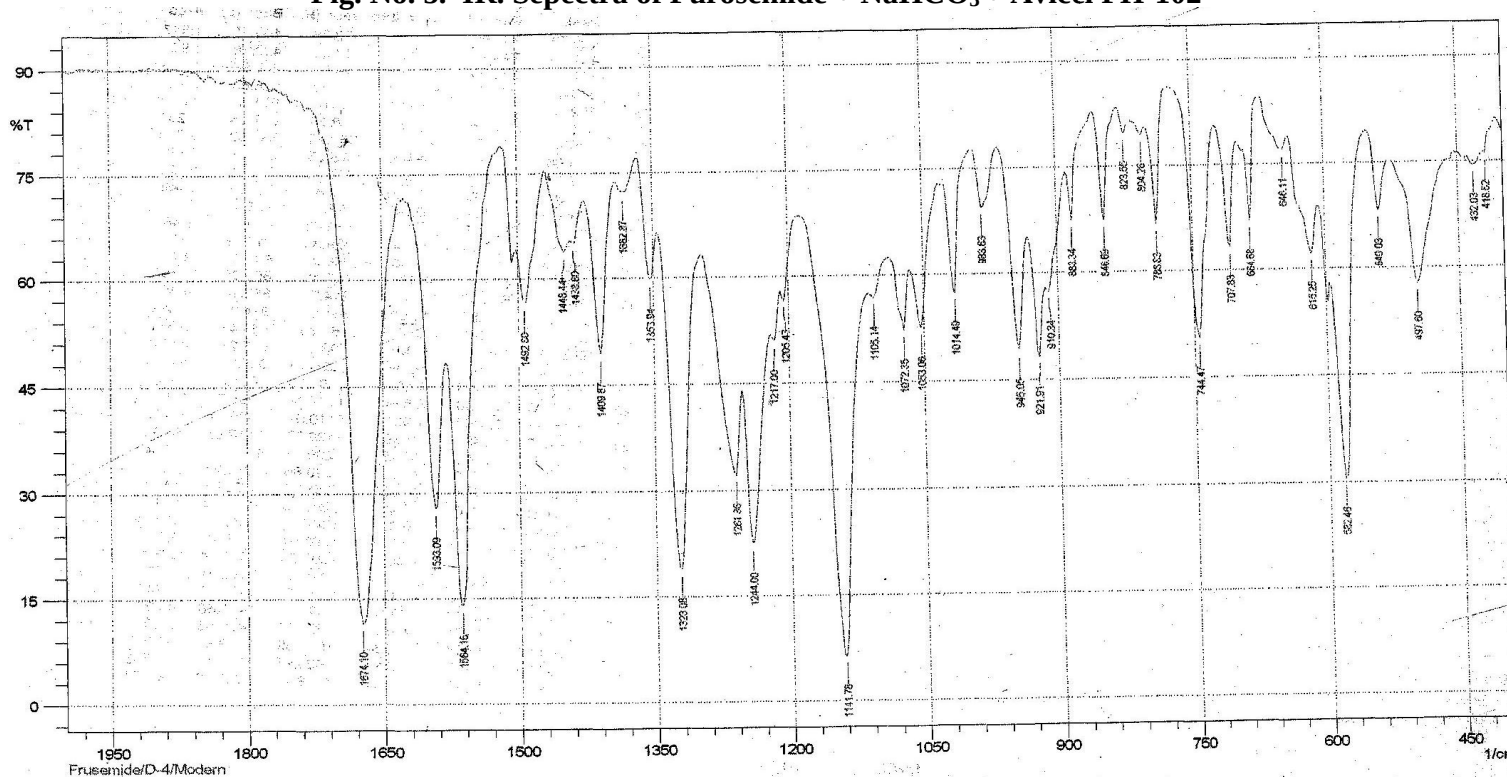
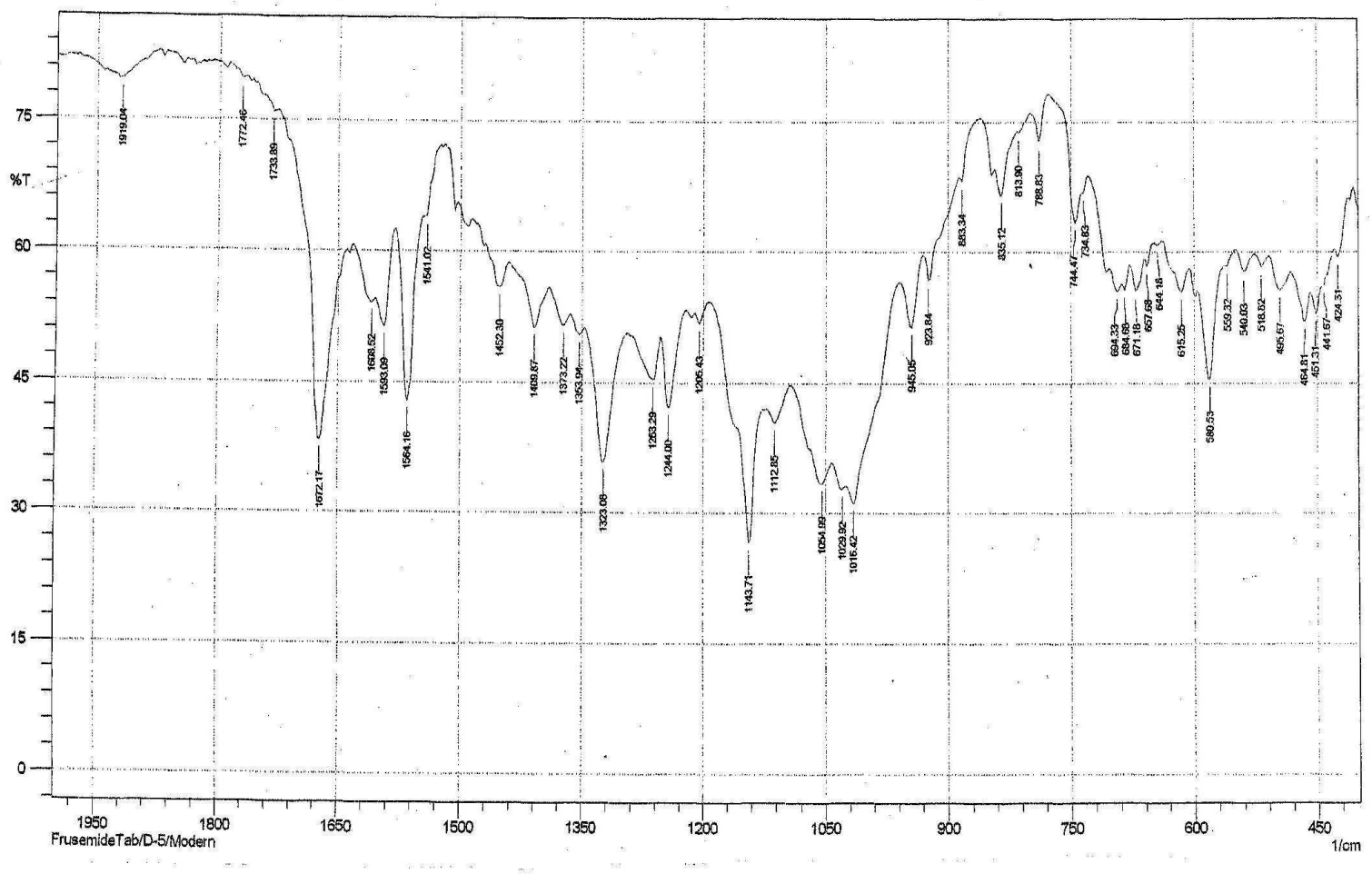


Fig No. 6 IR. Spectra of best Formulation (F-2)



Angle of repose
Bulk density
Compressibility Index
Total Porosity

Table 5 → Micromeritic properties of trial formulations (Powder blend)

Powder blend	Angle of Repose (^{0})	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Compressibility Index (%)	Total Porosity (%)
T1	24°.30'	0.130	0.155	16.13	15.78
T2	25°.30'	0.114	0.135	14.30	12.50
T3	28°.56'	0.105	0.126	16.30	26.31
T4	29°.88'	0.129	0.146	15.41	27.77
T5	28°.88'	0.106	0.120	15.91	10.00
T6	26°.47'	0.132	0.148	12.76	35.00

Table 6→ Micromeritic properties of factorial design formulations(Powder blend)

Powder blend	Angle of Repose (^{0})	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Compressibility Index (%)	Total Porosity (%)
F1	26°.77'	0.110	0.130	15.67	20.00
F2	28°.88'	0.106	0.120	15.91	10.00
F3	28°.56'	0.105	0.126	16.30	26.31
F4	29°.88'	0.129	0.146	15.41	27.77
F5	25°.30'	0.114	0.135	14.30	12.50
F6	26°.47'	0.132	0.148	12.76	35.00
F7	24°.28'	0.135	0.154	13.47	13.04
F8	26°.56'	0.144	0.162	12.34	20.83
F9	25°.28'	0.090	0.102	14.48	37.50

Evaluation of tablets

Weight variation test [71]
Hardness
Thickness
Friability Test
Drug content [72]
In-vitro buoyancy studies [73]

Swelling index [74]

Table-7: Evaluation of trial Formulations

Formulation Code	Mean Hardness Kg/ cm²	Friability % W/W	Weight variation test (%)	Thickness (mm)	Mean Drug Content %±SD	Swelling Index±SD	Floating Lag Time (min)	Floating time(hrs)
T1	4.18	0.51	±3.52	3.12 ±0.06	96.30±1.17	5.26±0.152	3.5	24
T2	4.59	0.54	±1.42	3.16 ±0.011	94.92±3.10	14.33±0.251	2.7	24
T3	4.77	0.57	±1.56	3.18 ±0.012	97.71±1.69	40.50±1.470	0.7	24
T4	3.92	0.64	±3.54	3.15 ±0.010	96.60±1.02	8.60±0.257	3.1	24
T5	4.46	0.61	±2.04	3.10 ±0.012	94.49±0.54	22.36±1.150	2.2	24
T6	4.65	0.56	±2.11.	3.20±0.011	93.65±1.72	65.33±0.321	0.4	24

The in-vitro buoyancy was determined by floating lag time method described by Dave B.S.[60]The tablets were placed in 250 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

Table-8: Evaluation of factorial design Formulations

Formulation Code	Mean Hardness Kg/ cm²	Friability % W/W	Weight variation test (%)	Thickness (mm)	Mean Drug Content %±SD	Swelling Index±SD	Floating Lag Time (min)	Floating time (hrs)
F1	4.54	0.55	±3.52	3.12 ±0.06	96.83±1.32	17.81±0.83	3.8	24
F2	4.49	0.61	±2.04	3.20±0.011	97.09±1.34	17.37±1.25	2.9	24
F3	4.42	0.68	±1.56	3.18 ±0.012	94.57±0.77	19.14±1.42	0.3	24
F4	4.62	0.53	±3.54	3.15 ±0.010	97.15±2.05	28.47±1.24	4.1	24
F5	4.59	0.65	±1.42	3.10 ±0.012	95.70±4.08	35.33±2.25	3.2	24
F6	4.51	0.69	±2.11.	3.16 ±0.011	93.49±1.49	66.69±1.322	0.9	24
F7	4.69	0.57	±1.89	3.08 ± 0.2	95.42±0.68	28.39±1.27	4.3	24
F8	4.67	0.62	±2. 56	3.16±0.01	95.77±1.79	33.49±0.87	3.5	24
F9	4.66	0.64	±2.15	3.14±0.012	95.55±2.42	64.31±0.85	1.1	24

Figure-8: In vitro floating study

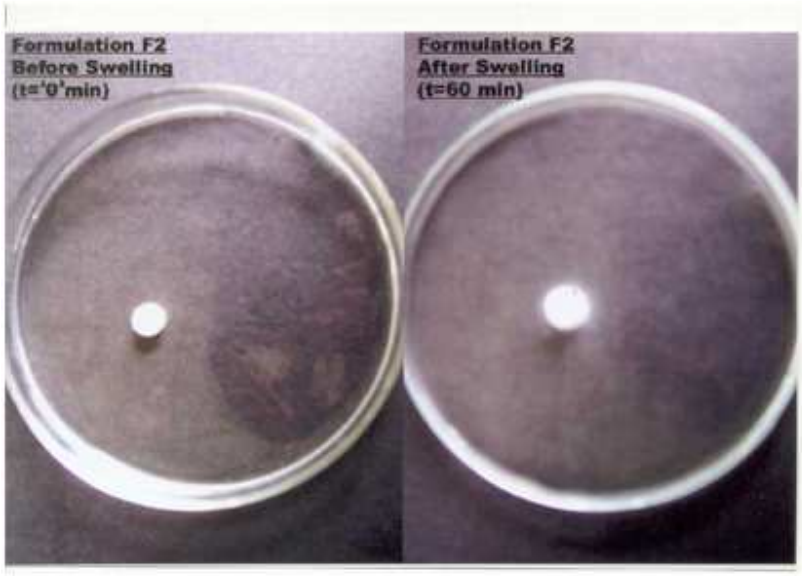


Figure-9: Determination of swelling index

In-vitro dissolution studies [71]
The release rate of Furosemide from floating tablets was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 75 rpm A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 271 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

In-vitro Dissolution Study and Kinetic modeling of drug release;
All the formulation of prepared floating tablets of Furosemide were subjected to invitro release studies these studies were carried out using dissolution apparatus, 0.1N HCL (PH 1.2) The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

Cumulative percent drug released vs. time (zero order rate kinetics)
Log cumulative percent drug retained vs. time (First Order rate Kinetics)
Log cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
Log of cumulative % release Vs log time (Peppas Exponential Equation)

Zero Order Kinetics: A zero-order release would be predicted by the following equation.

$$A_t = A_0 - K_0 t$$

Where:

A_t = Drug release at time 't'
A_0 = Initial drug concentration
K_0 = Zero-order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

First Order Kinetics: A first-order release would be predicted by the following equation

$$\text{Log } C = \text{Log } C_0 - \frac{K_t}{2.303}$$

Where:

C = Amount of drug remained at time‘t’

C_0 = Initial aSmount of drug

K = First-order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follows First-order kinetics. The constant ‘K’ can be obtained by multiplying 2.303 with slope values.

Higuchi’s Model: Drug released from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation.

$$Q = \left[\frac{D\varepsilon}{\tau}(2A - \varepsilon C_S) C_S t\right]^{½}$$

Where:

Q = Amount of drug released at time‘t’

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

C_S = The solubility of the drug in the diffusion medium

ε = Porosity of the matrix

τ = Tortuosity

t = Time (hrs) at which ‘Q’ amount of drug is released.

Equation-3 may be simplified if one assumes that D, C_S and A are constant. Then equation-3 becomes:

$$Q = Kt$$

When the data is plotted according to equation-4 i.e., cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism[78, 79]. The slope is equal to ‘K’.

Korsmeyer and Peppas Model: The release rates from controlled release polymeric matrices can be described by the equation (5) proposed by korsmeyer et al [80].

$$Q = K_1 t^n$$

Q is the percentage of drug released at time ‘t’, K is a kinetic constant incorporating structural and geometric characteristics of the tablets and ‘n’ is the diffusional exponent indicative of the release mechanism [81].

For Fickian release, n=0.45 while for anomalous (Non-Fickian) transport, n ranges between 0.45 and 0.89 and for zero order release, n = 0.89 [80].

The results of in vitro drug release studies of all the formulations are shown in Tables-11 to 29. In Vitro floating studies were performed by placing tablets in USP XXIII dissolution the apparatus-II containing 900 ml of 0.1N HCl maintained at a temperature of 37±0.5ºC. The floating lag time and floating time was noted visually. The results are given in Tables-10&11. For all (trial and factorial) formulations, lag time is in the range of 0.3 min to 4.3 min.With formulations containing the same amount of polymer of the same grade, floating lag time decreased with increase in concentration of sodium bicarbonate. For formulation F3, it is lowest (0.3 min) as the drug-polymer (HPMC K4M) ratio is 1:2 and sodium bicarbonate is in highest proportion among all formulations and the tablet bursts into pieces within 30 minutes, while for formulation F7, lag time is highest (4.3 minutes) as drug-polymer ratio is 1:3 and $NaHCO_3$ is in lowest proportion (15 mg) among all formulations. All the designed formulations have displayed a floating time of more than 24 hours.

In vitro drug release study was performed using USP XXIII dissolution test apparatus-II at 50 rpm using 900 ml of 0.1N HCl maintained at 37±0.5ºC as the dissolution medium. The results were shown in Tables-11 to 25. From the above data, it is evident that as the proportion of polymer in the formulation increases, cumulative percent drug release in 10 hours decreases, and as the proportion of the gas generating agent increases, the drug release increases. Among the six trial batches, formulations T1 to T3 have released only 67 to 76% drug in 10 hours, whereas formulations T4 to T6 have released 81 to 95% during the same period. Among these six formulations, T5 formulation has shown promising dissolution parameters ($t_{50\%}$=4.8 hours, $t_{70\%}$=6.4 hours and $t_{90\%}$=8.2 hours) and shorter lag time (<3 min).

Optimization using Factorial Design Method [63-67]**:**
Optimization has been done by using 3^2 full factorial designs, where amount of HPMC K4M (X_1) and amount of sodium bicarbonate (X_2) were taken as independent variables and $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ taken as independent variables.

Table-9: Factorial Design Batches of Furosemide HBS

Variable	Batch										
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**C1**	**C2**
X_1	-1	-1	-1	0	0	0	+1	+1	+1	-0.5	+0.5
X_2	-1	0	+1	-1	0	+1	-1	0	+1	-0.5	+0.5

Table-10: Coded Values and Actual Values for the Independent Variables

Coded Values	Actual Values (mg)	
	X_1	X_2
–1	100	15
0	125	30
+1	150	45
–0.5	112.5	22.5
+0.5	137.5	37.5

Step-wise backward linear regression analysis was used to develop polynomial equations for the dependent variables $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ values by using PCP Disso 2000 V3 software. The

validity of the developed polynomial regression equations was verified by preparing two check point formulations (C_1 and C_2), as shown in Tables- 8&9 below.

Table-11: In vitro drug release data of trial Formulation T1

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	15.72±0.16	1.1965	84.28	1.9257
2	2	1.4142	0.3010	23.94±0.07	1.3791	76.06	1.8812
3	3	1.7320	0.4771	36.70±0.28	1.5647	63.30	1.8014
4	4	2.0000	0.6021	39.82±0.28	1.6001	60.18	1.7795
5	5	2.2360	0.6990	50.63±0.27	1.7044	49.37	1.6935
6	6	2.4494	0.7782	60.01±0.16	1.7782	39.99	1.6020
7	7	2.6457	0.8451	68.31±0.28	1.8345	31.69	1.5009
8	8	2.8284	0.9031	72.50±0.27	1.8603	27.50	1.4393
9	9	3.0000	0.9542	74.82±0.39	1.8740	25.18	1.4011
10	10	3.1622	1.0000	76.44±0.29	1.8833	23.56	1.3722

** Average of three determinations*

Table-12: In vitro drug release data of trial Formulation T2

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	16.39±0.09	1.2146	83.61	1.9223
2	2	1.4142	0.3010	45.14±0.51	1.6546	54.86	1.7393
3	3	1.7320	0.4771	46.20±0.08	1.6646	53.80	1.7308
4	4	2.0000	0.6021	46.50±0.44	1.6675	53.50	1.7284
5	5	2.2360	0.6990	48.01±0.36	1.6813	51.99	1.7159
6	6	2.4494	0.7782	60.70±0.29	1.7832	39.30	1.5944
7	7	2.6457	0.8451	64.04±0.20	1.8065	35.96	1.5558
8	8	2.8284	0.9031	66.59±0.27	1.8234	33.41	1.5239
9	9	3.0000	0.9542	70.45±0.14	1.8479	29.55	1.4706
10	10	3.1622	1.0000	72.67±0.29	1.8614	27.33	1.4366

** Average of three determinations*

Table-13: In vitro drug release data of trial Formulation T3

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	6.79±0.13	0.8319	93.21	1.9695
2	2	1.4142	0.3010	12.99±0.07	1.1136	87.01	1.9396
3	3	1.7320	0.4771	24.46±0.14	1.3885	75.54	1.8782
4	4	2.0000	0.6021	38.72±0.27	1.5879	61.28	1.7873
5	5	2.2360	0.6990	46.11±0.05	1.6638	53.89	1.7315
6	6	2.4494	0.7782	54.47±0.27	1.7362	45.53	1.6583
7	7	2.6457	0.8451	59.88±0.27	1.7773	40.12	1.6034
8	8	2.8284	0.9031	63.08±0.28	1.7999	36.92	1.5673
9	9	3.0000	0.9542	64.82±0.28	1.8117	35.18	1.5463
10	10	3.1622	1.0000	67.19±0.21	1.8273	32.81	1.5160

** Average of three determinations*

Figure-10: Cumulative Percent Drug Released Vs Time Plots (Zero Order) of Formulations T1, T2 and T3

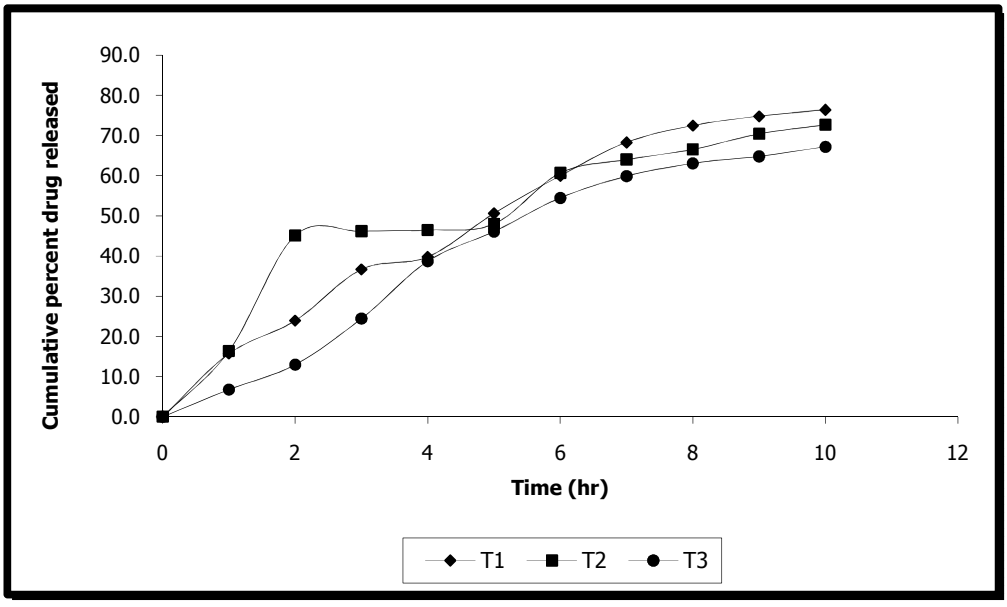


Figure-11: Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of Formulations T1, T2 and T3

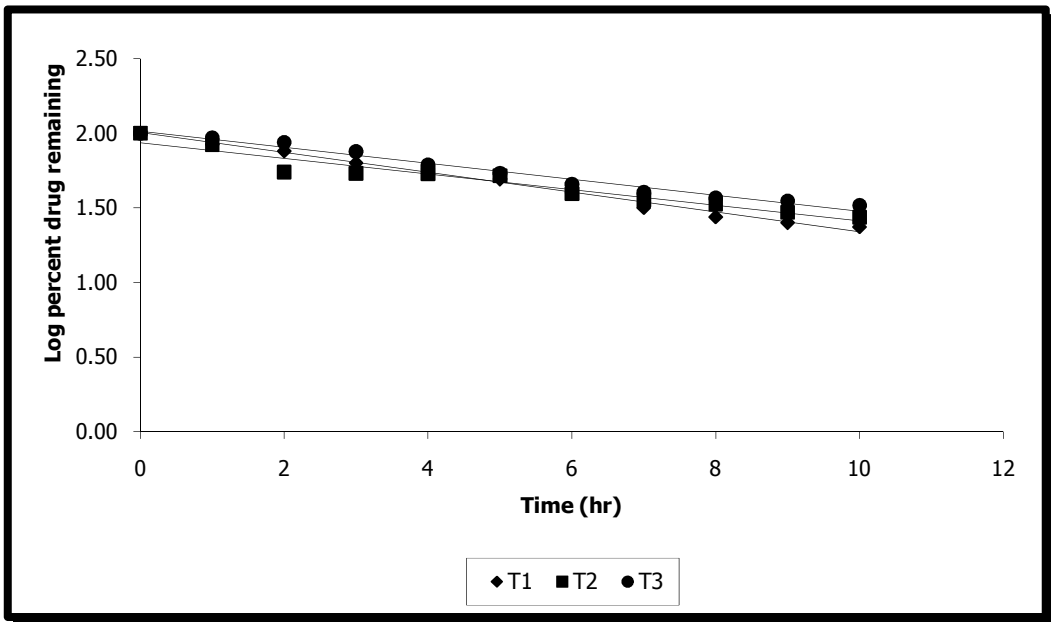


Figure-12: Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of Formulations T1, T2 and T3

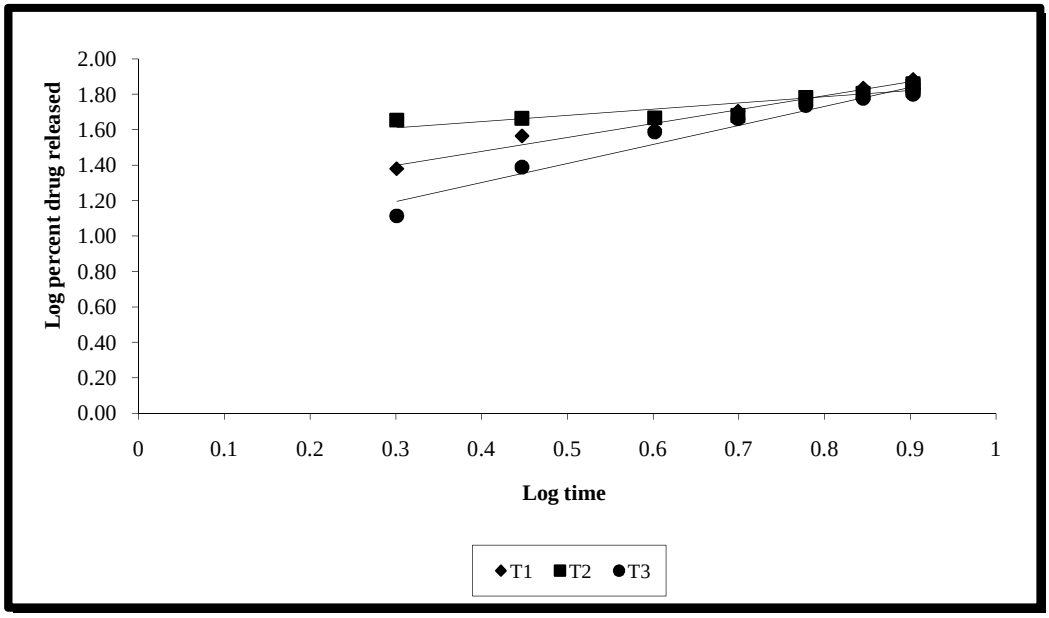


Figure-13: Log Cumulative Percent Drug Released Vs Log Time (Peppas Plots) of Formulations T1, T2 and T3

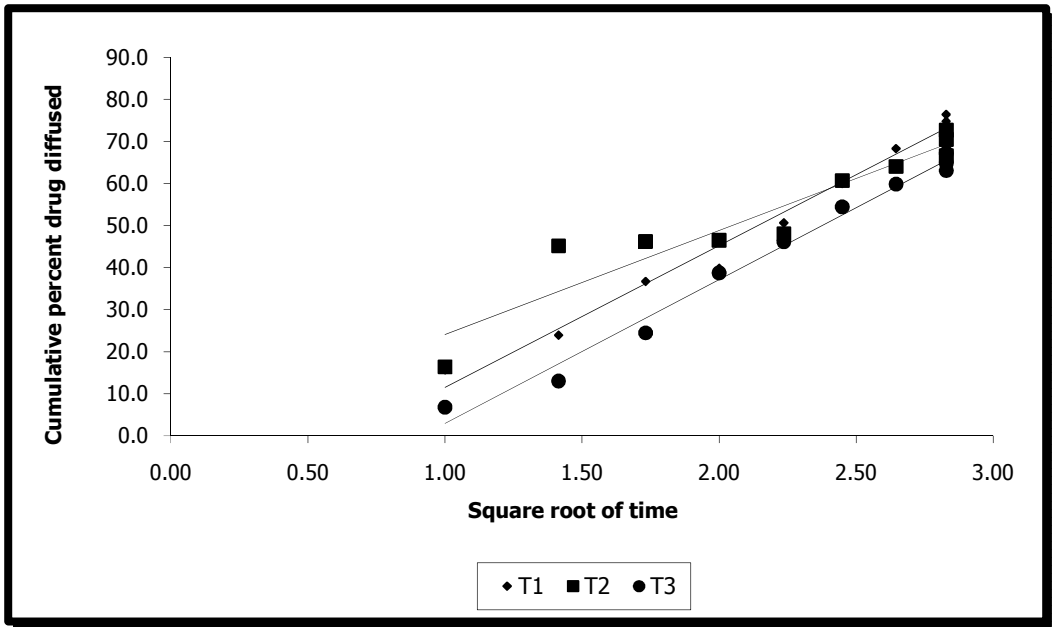


Table-14: In vitro drug release data of trial Formulation T4

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	23.48±0.04	1.3707	76.52	1.8838
2	2	1.4142	0.3010	59.23±0.21	1.7725	40.77	1.6103
3	3	1.7320	0.4771	63.06±0.21	1.7998	36.94	1.5675
4	4	2.0000	0.6021	66.99±0.91	1.8260	33.01	1.5186
5	5	2.2360	0.6990	70.20±0.34	1.8463	29.80	1.4742
6	6	2.4494	0.7782	76.42±0.35	1.8832	23.58	1.3725
7	7	2.6457	0.8451	78.93±0.34	1.8972	21.07	1.3237
8	8	2.8284	0.9031	81.00±0.40	1.9085	19.00	1.2788
9	9	3.0000	0.9542	84.81±0.45	1.9284	15.19	1.1816
10	10	3.1622	1.0000	95.21±0.27	1.9787	4.79	0.6803

** Average of three determinations*

Table-15: In vitro drug release data of trial Formulation T5

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	17.53±0.07	1.2438	82.47	1.9163
2	2	1.4142	0.3010	24.04±0.09	1.3809	75.96	1.8806
3	3	1.7320	0.4771	51.92±0.21	1.7153	48.08	1.6820

4	4	2.0000	0.6021	64.69±0.20	1.8108	35.31	1.5479
5	5	2.2360	0.6990	76.44±0.27	1.8833	23.56	1.3722
6	6	2.4494	0.7782	77.65±0.23	1.8901	22.35	1.3493
7	7	2.6457	0.8451	79.65±0.22	1.9012	20.35	1.3086
8	8	2.8284	0.9031	83.22±0.22	1.9202	16.78	1.2248
9	9	3.0000	0.9542	86.96±0.34	1.9393	13.04	1.1153
10	10	3.1622	1.0000	90.65±0.67	1.9574	9.35	0.9708

** Average of three determinations*

Table-16: In vitro drug release data of trial Formulation T6

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	14.24±0.04	1.1535	85.76	1.9333
2	2	1.4142	0.3010	18.46±0.07	1.2662	81.54	1.9114
3	3	1.7320	0.4771	29.20±0.09	1.4654	70.80	1.8500
4	4	2.0000	0.6021	46.59±0.09	1.6683	53.41	1.7276
5	5	2.2360	0.6990	49.81±0.09	1.6973	50.19	1.7006
6	6	2.4494	0.7782	52.78±0.09	1.7225	47.22	1.6741
7	7	2.6457	0.8451	60.98±0.36	1.7852	39.02	1.5913
8	8	2.8284	0.9031	65.48±0.27	1.8161	34.52	1.5381
9	9	3.0000	0.9542	70.28±0.14	1.8468	29.72	1.4730
10	10	3.1622	1.0000	81.34±0.20	1.9103	18.66	1.2709

** Average of three determinations*

Figure-14: Cumulative Percent Drug Released Vs Time Plots (Zero Order) of Formulations T4, T5 and T6

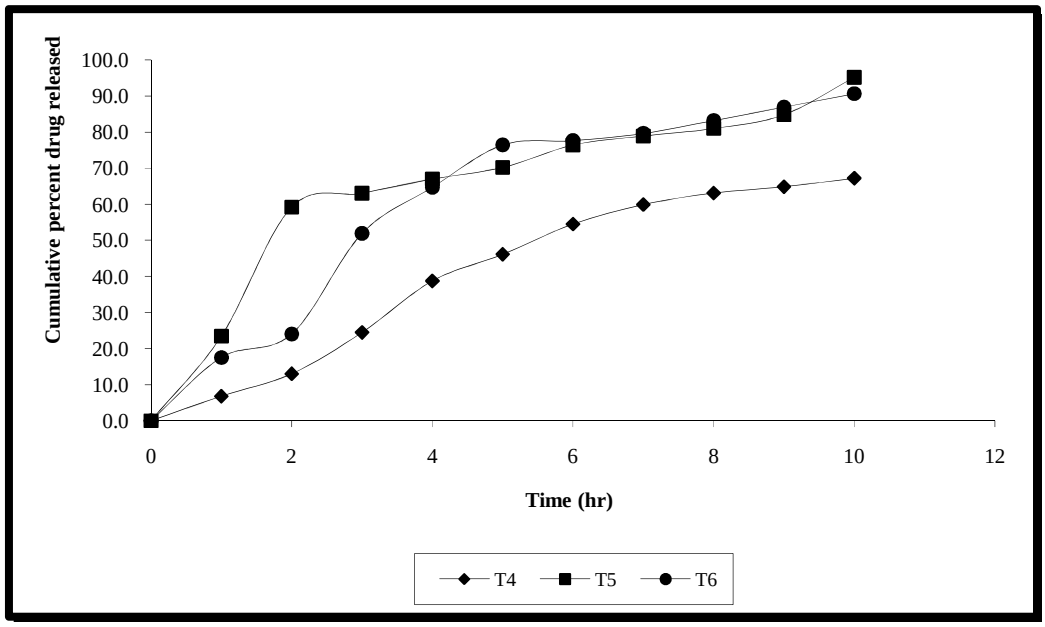


Figure-15: Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of Formulations T4, T5 and T6

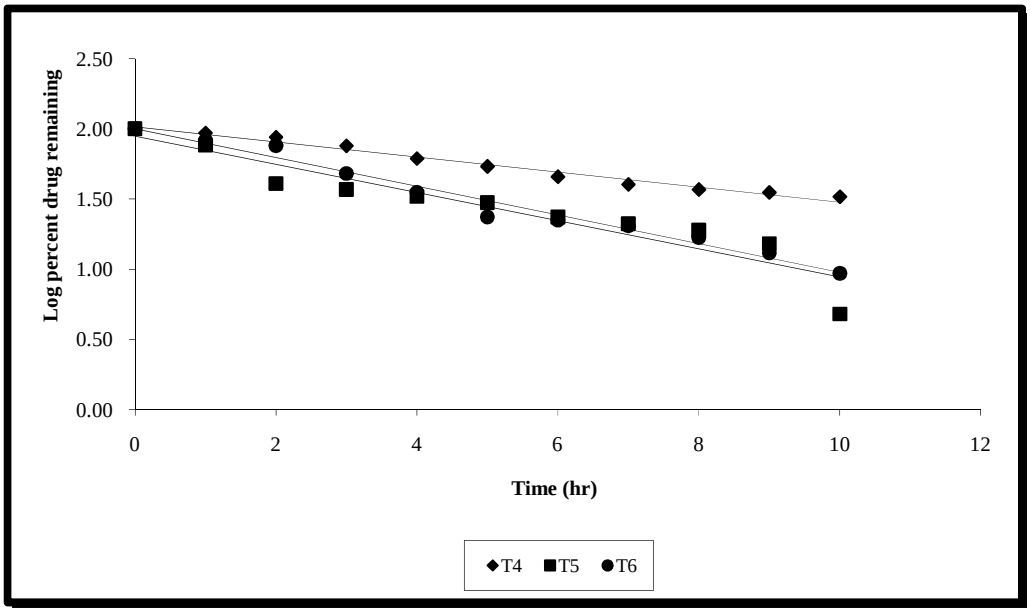


Figure-16: Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of Formulations T4, T5 and T6

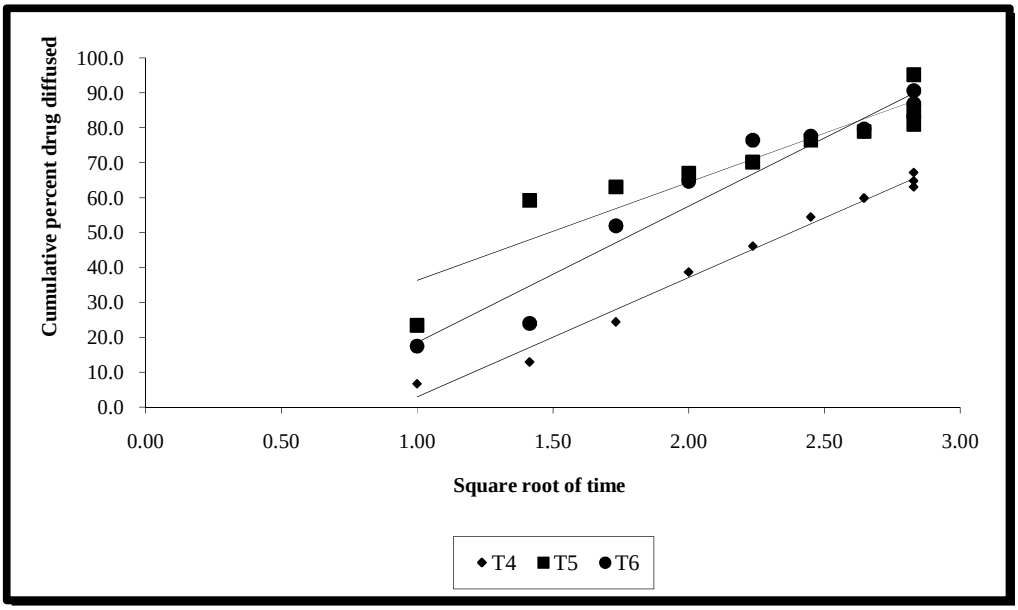


Figure-17: Log Cumulative Percent Drug Released Vs Log Time (Peppas Plots) of Formulations T4, T5 and T6

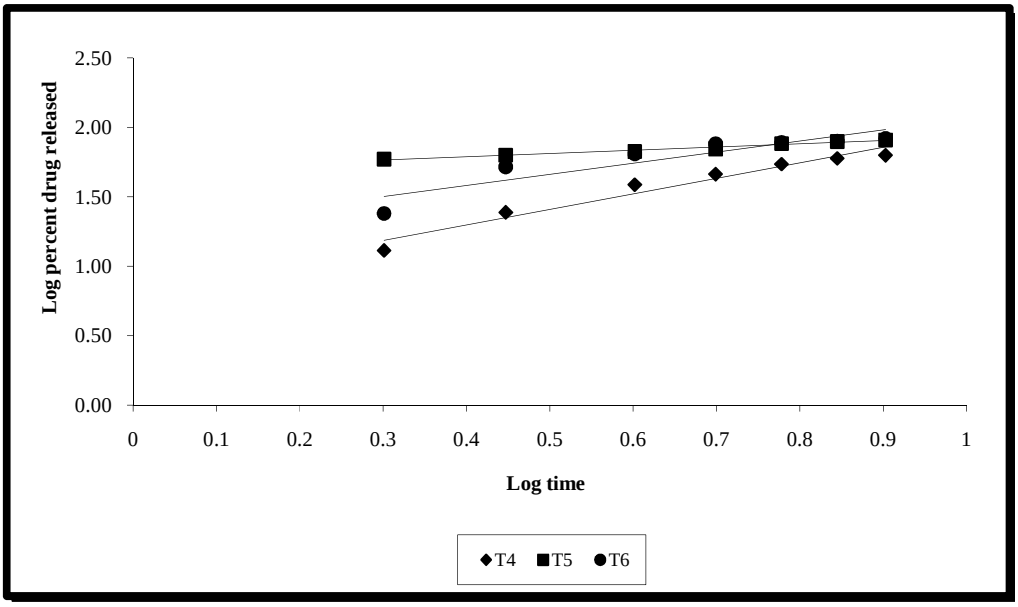


Table-17: In vitro drug release data of factorial Formulation F1

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	22.50±0.59	1.3522	77.50	1.8893
2	2	1.4142	0.3010	38.55±0.73	1.5860	61.45	1.7885
3	3	1.7320	0.4771	51.30±1.27	1.7101	48.70	1.6875
4	4	2.0000	0.6021	56.94±0.59	1.7554	43.06	1.6341
5	5	2.2360	0.6990	67.50±0.57	1.8293	32.50	1.5119
6	6	2.4494	0.7782	73.35±0.51	1.8654	26.65	1.4257
7	7	2.6457	0.8451	76.98±0.20	1.8864	23.02	1.3621
8	8	2.8284	0.9031	81.98±1.00	1.9137	18.02	1.2558
9	9	3.0000	0.9542	90.05±1.23	1.9545	9.95	0.9978
10	10	3.1622	1.0000	93.85±1.03	1.9724	6.15	0.7889

** Average of three determinations*

Table-18: In vitro drug release data of factorial Formulation F2

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	23.04±0.73	1.3625	76.96	1.8863
2	2	1.4142	0.3010	44.69±0.89	1.6502	55.31	1.7428
3	3	1.7320	0.4771	52.75±0.68	1.7222	47.25	1.6744
4	4	2.0000	0.6021	59.44±0.64	1.7741	40.56	1.6081
5	5	2.2360	0.6990	72.00±0.71	1.8573	28.00	1.4472
6	6	2.4494	0.7782	74.56±0.27	1.8725	25.44	1.4055
7	7	2.6457	0.8451	79.09±1.48	1.8981	20.91	1.3204
8	8	2.8284	0.9031	83.97±0.76	1.9241	16.03	1.2049
9	9	3.0000	0.9542	90.61±0.94	1.9572	9.39	0.9727
10	10	3.1622	1.0000	94.56±0.57	1.9757	5.44	0.7356

** Average of three determinations*

Table-19: In vitro drug release data of factorial Formulation F3

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	0.25	0.5000	-0.6021	50.39±0.47	1.7023	49.61	1.6956
2	0.5	0.7071	-0.3010	54.20±0.68	1.7340	45.80	1.6609
3	0.75	0.8660	-0.1249	65.84±0.96	1.8185	34.16	1.5335
4	1	1.0000	0.0000	71.91±0.90	1.8568	28.09	1.4486
5	2	1.4142	0.3010	75.35±0.55	1.8771	24.65	1.3918
6	3	1.7320	0.4771	78.59±1.22	1.8954	21.41	1.3306
7	4	2.0000	0.6021	81.67±0.82	1.9121	18.33	1.2632
8	5	2.2360	0.6990	85.43±0.71	1.9316	14.57	1.1635
9	6	2.4494	0.7782	87.51±0.43	1.9421	12.49	1.0966
10	7	2.6457	0.8451	93.38±0.74	1.9703	6.62	0.8209
11	8	2.8284	0.9031	100.46±1.22	2.0020	-0.46	
12	9	3.0000	0.9542	101.07±0.28	2.0046	-1.07	

** Average of three determinations*

Figure-18: Cumulative Percent Drug Released Vs Time Plots (Zero Order) of Formulations F1, F2 and F3

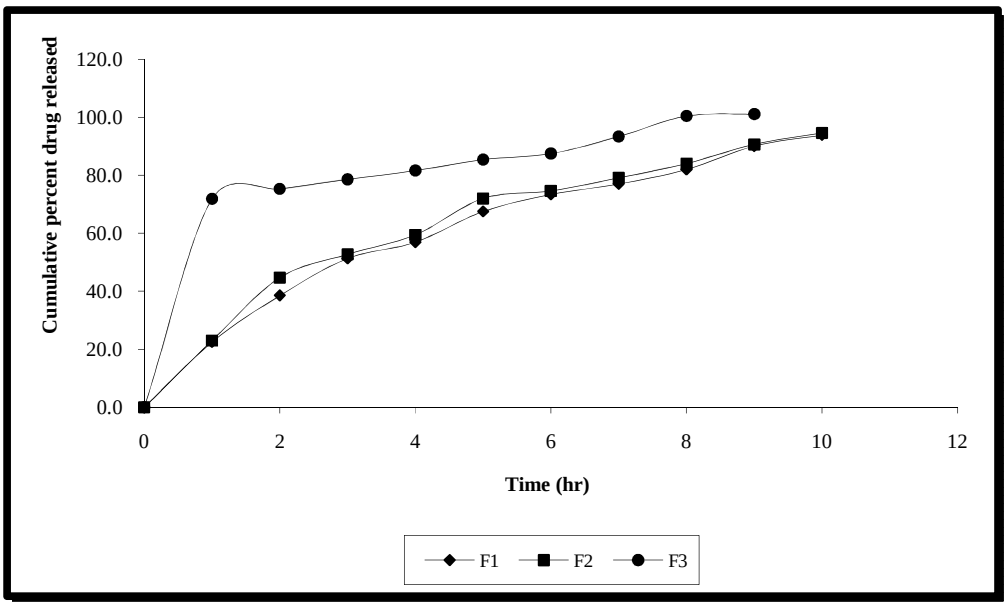


Figure-19: Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of Formulations F1, F2 and F3

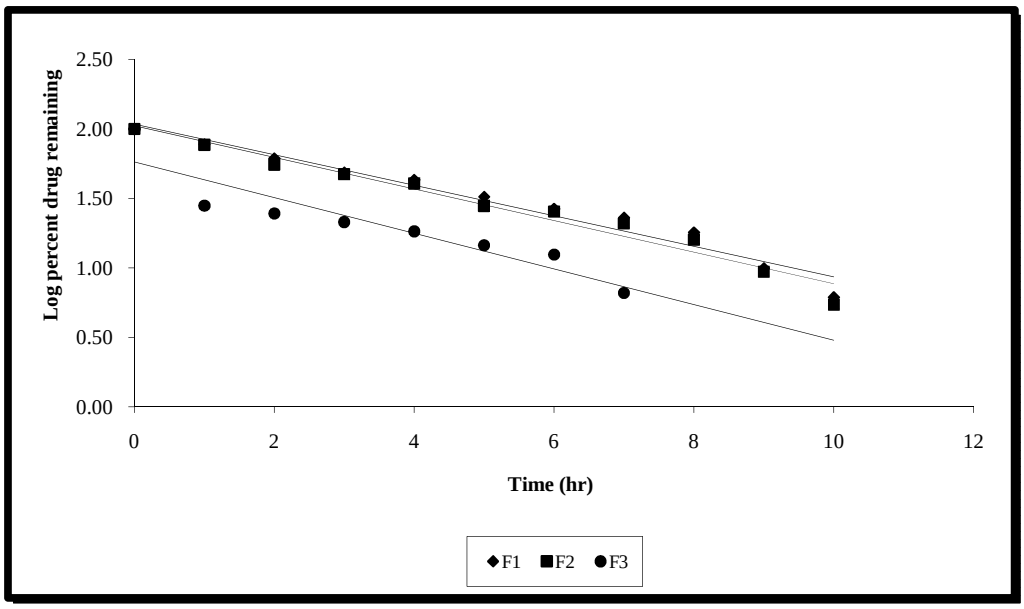


Figure-20: Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of Formulations F1, F2 and F3

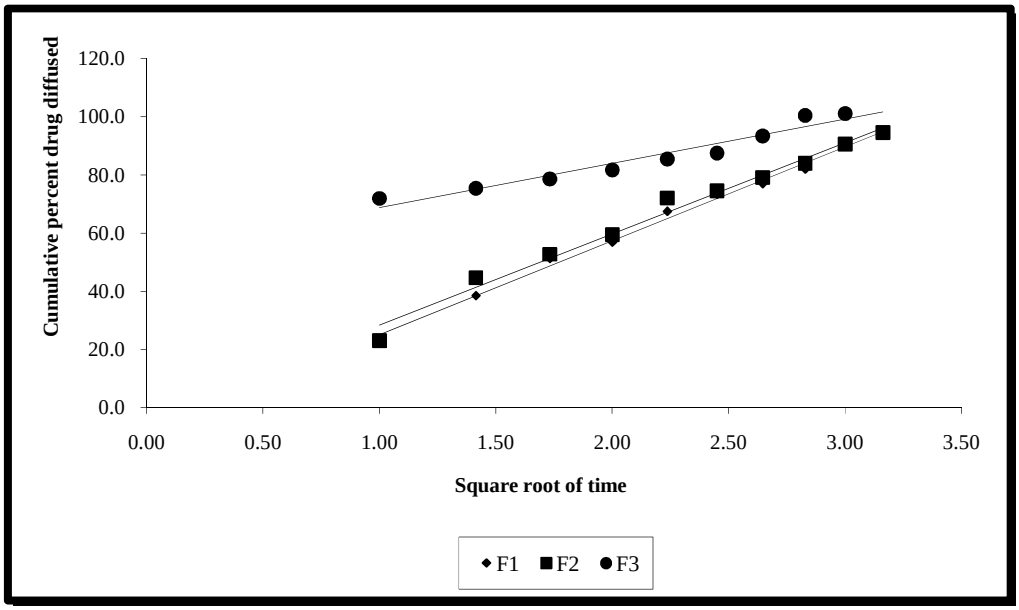


Figure-21: Log Cumulative Percent Drug Released Vs Log Time (Peppas Plots) of Formulations F1, F2 and F3

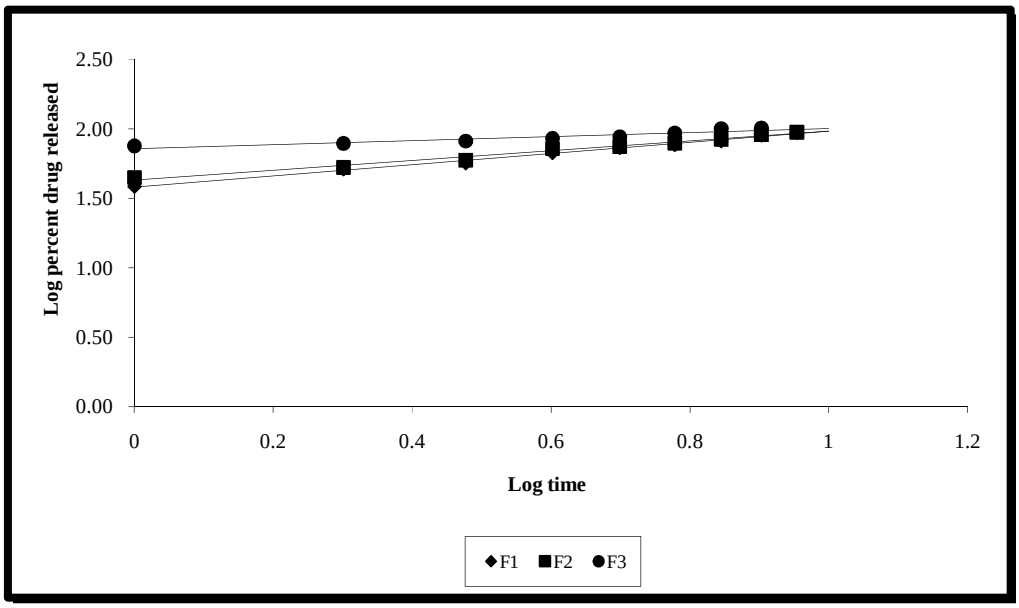


Table-20: In vitro drug release data of factorial Formulation F4

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	13.30±1.11	1.1239	86.70	1.9380
2	2	1.4142	0.3010	28.13±0.82	1.4492	71.87	1.8565
3	3	1.7320	0.4771	37.07±1.26	1.5690	62.93	1.7989
4	4	2.0000	0.6021	53.58±1.22	1.7290	46.42	1.6667
5	5	2.2360	0.6990	56.93±0.92	1.7553	43.07	1.6342
6	6	2.4494	0.7782	60.03±1.87	1.7784	39.97	1.6017
7	7	2.6457	0.8451	65.74±0.62	1.8178	34.26	1.5348
8	8	2.8284	0.9031	70.41±1.59	1.8476	29.59	1.4711
9	9	3.0000	0.9542	75.19±0.64	1.8762	24.81	1.3946
10	10	3.1622	1.0000	78.29±1.32	1.8937	21.71	1.3367

** Average of three determinations*

Table-21: In vitro drug release data of factorial Formulation F5

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	15.36±0.31	1.1864	84.64	1.9276
2	2	1.4142	0.3010	29.03±0.07	1.4628	70.97	1.8511
3	3	1.7320	0.4771	48.02±1.12	1.6814	51.98	1.7158
4	4	2.0000	0.6021	52.44±0.90	1.7197	47.56	1.6772
5	5	2.2360	0.6990	54.26±0.79	1.7345	45.74	1.6603
6	6	2.4494	0.7782	60.54±0.91	1.7820	39.46	1.5962
7	7	2.6457	0.8451	67.88±0.74	1.8317	32.12	1.5068
8	8	2.8284	0.9031	72.97±0.62	1.8631	27.03	1.4318
9	9	3.0000	0.9542	76.32±0.60	1.8826	23.68	1.3744
10	10	3.1622	1.0000	79.38±0.79	1.8997	20.62	1.3143

** Average of three determinations*

Table-22: In vitro drug release data of factorial Formulation F6

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	19.86±0.82	1.2980	80.14	1.9038
2	2	1.4142	0.3010	30.95±0.16	1.4907	69.05	1.8392
3	3	1.7320	0.4771	52.59±0.95	1.7209	47.41	1.6759
4	4	2.0000	0.6021	57.46±1.04	1.7594	42.54	1.6288
5	5	2.2360	0.6990	61.24±1.51	1.7870	38.76	1.5884
6	6	2.4494	0.7782	69.95±1.43	1.8448	30.05	1.4778
7	7	2.6457	0.8451	78.38±0.98	1.8942	21.62	1.3349
8	8	2.8284	0.9031	79.30±1.26	1.8993	20.70	1.3160
9	9	3.0000	0.9542	86.02±1.25	1.9346	13.98	1.1455
10	10	3.1622	1.0000	88.72±0.47	1.9480	11.28	1.0523

** Average of three determinations*

Figure-22: Cumulative Percent Drug Released Vs Time Plots (Zero Order) of Formulations F4, F5 and F6

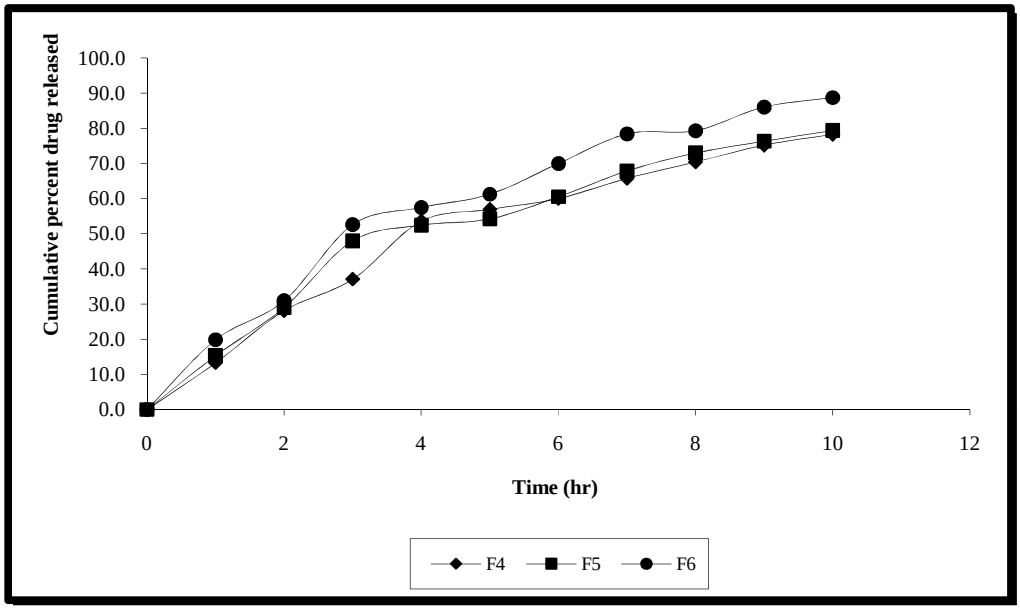


Figure-23: Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of Formulations F4, F5 and F6

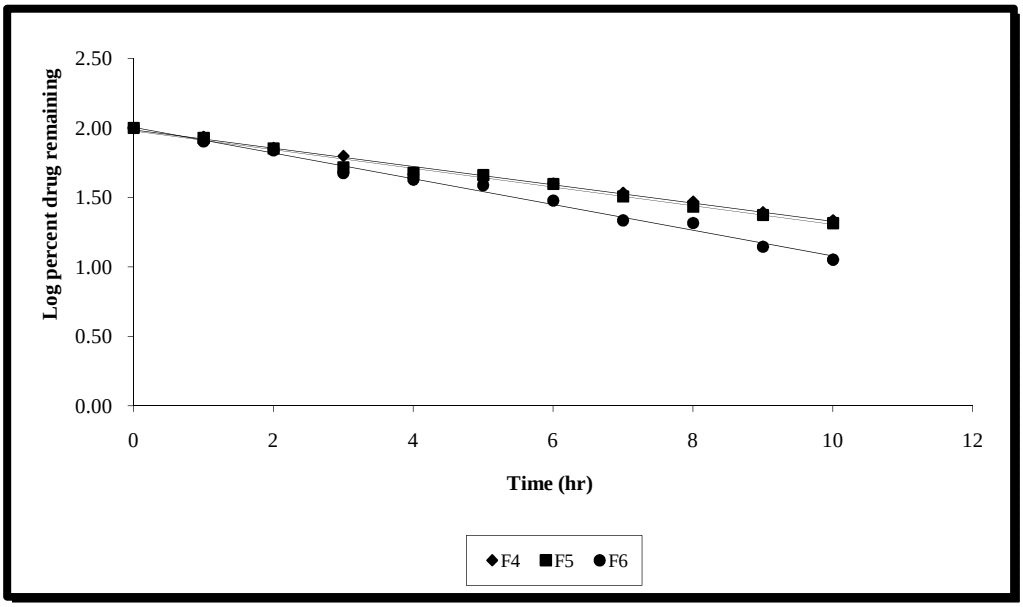


Figure-24: Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of Formulations F4, F5 and F6

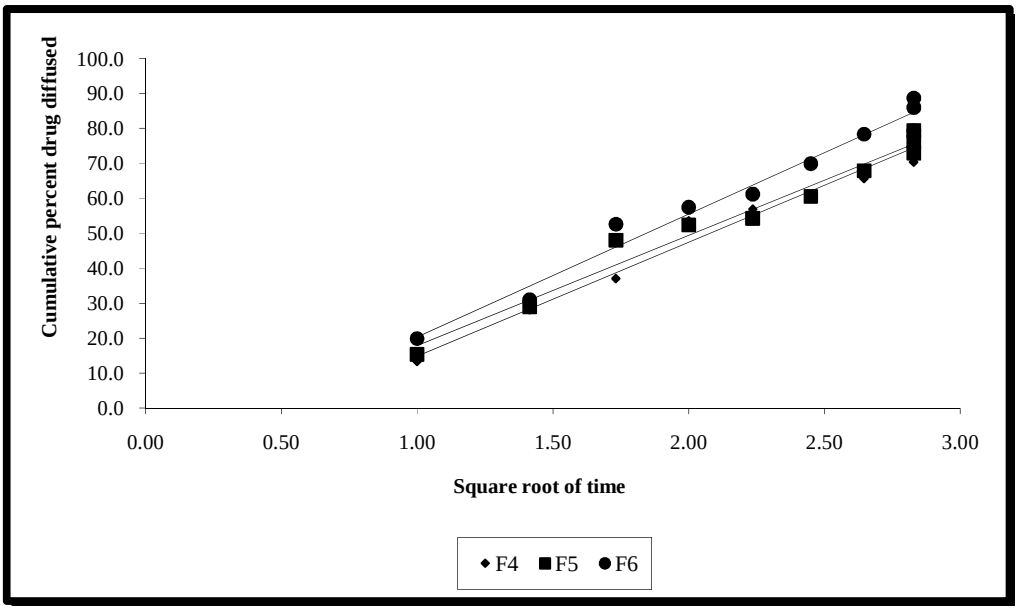


Figure-25: Log Cumulative Percent Drug Released Vs Log Time (Peppas Plots) of Formulations F4, F5 and F6

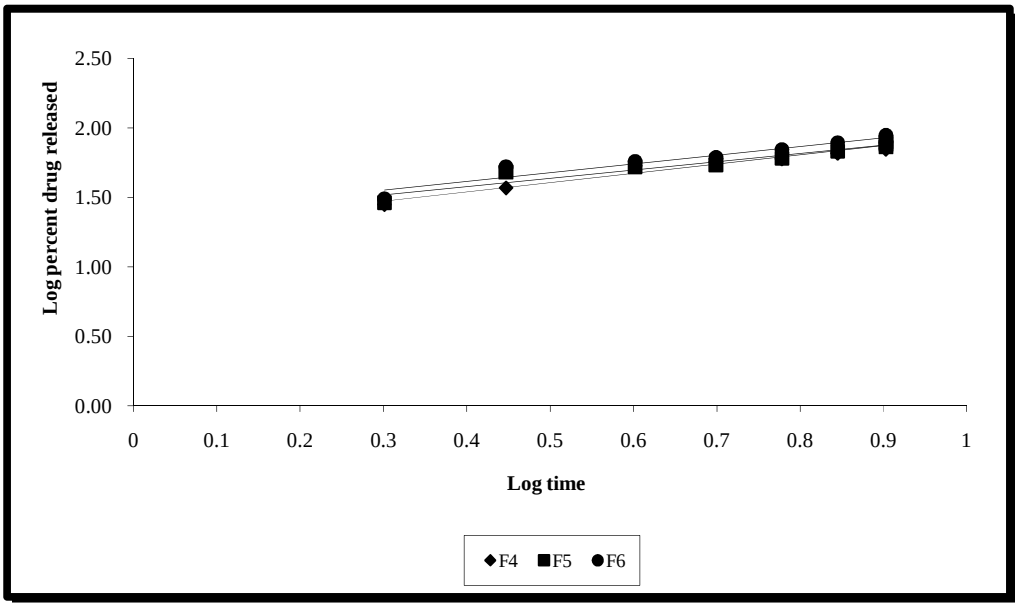


Table-23: In vitro drug release data of factorial Formulation F7

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	16.34±1.08	1.2133	83.66	1.9225
2	2	1.4142	0.3010	24.52±0.72	1.3895	75.48	1.8778
3	3	1.7320	0.4771	36.02±1.04	1.5565	63.98	1.8060
4	4	2.0000	0.6021	42.23±0.23	1.6256	57.77	1.7617
5	5	2.2360	0.6990	52.55±1.16	1.7206	47.45	1.6762
6	6	2.4494	0.7782	57.06±1.07	1.7563	42.94	1.6329
7	7	2.6457	0.8451	63.29±0.41	1.8013	36.71	1.5648
8	8	2.8284	0.9031	68.49±1.24	1.8356	31.51	1.4984
9	9	3.0000	0.9542	72.45±1.24	1.8600	27.55	1.4401
10	10	3.1622	1.0000	74.14±1.23	1.8701	25.86	1.4126

** Average of three determinations*

Table-24: In vitro drug release data of factorial Formulation F8

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	16.74±0.72	1.2238	83.26	1.9204
2	2	1.4142	0.3010	26.52±1.07	1.4236	73.48	1.8662
3	3	1.7320	0.4771	38.22±0.50	1.5823	61.78	1.7908
4	4	2.0000	0.6021	48.39±0.73	1.6848	51.61	1.7127
5	5	2.2360	0.6990	53.08±0.87	1.7249	46.92	1.6714
6	6	2.4494	0.7782	58.29±0.90	1.7656	41.71	1.6202
7	7	2.6457	0.8451	64.08±1.07	1.8067	35.92	1.5553
8	8	2.8284	0.9031	70.85±0.39	1.8503	29.15	1.4646
9	9	3.0000	0.9542	73.3±0.77	1.8651	26.70	1.4265
10	10	3.1622	1.0000	77.28±0.27	1.8881	22.72	1.3564

** Average of three determinations*

Table-25: In vitro drug release data of factorial Formulation F9

Sl. No.	Time (Hrs)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release±SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	1	1.0000	0.0000	19.63±1.05	1.2929	80.37	1.9051
2	2	1.4142	0.3010	27.95±0.63	1.4464	72.05	1.8576
3	3	1.7320	0.4771	38.72±0.16	1.5879	61.28	1.7873
4	4	2.0000	0.6021	54.40±0.62	1.7356	45.60	1.6590
5	5	2.2360	0.6990	58.50±0.89	1.7672	41.50	1.6180
6	6	2.4494	0.7782	62.42±1.56	1.7953	37.58	1.5750
7	7	2.6457	0.8451	68.59±1.01	1.8363	31.41	1.4971
8	8	2.8284	0.9031	75.88±0.66	1.8801	24.12	1.3824
9	9	3.0000	0.9542	77.46±0.55	1.8891	22.54	1.3530
10	10	3.1622	1.0000	81.60±0.35	1.9117	18.40	1.2648

** Average of three determinations*

Figure-25: Cumulative Percent Drug Released Vs Time Plots (Zero Order) of Formulations F7, F8 and F9

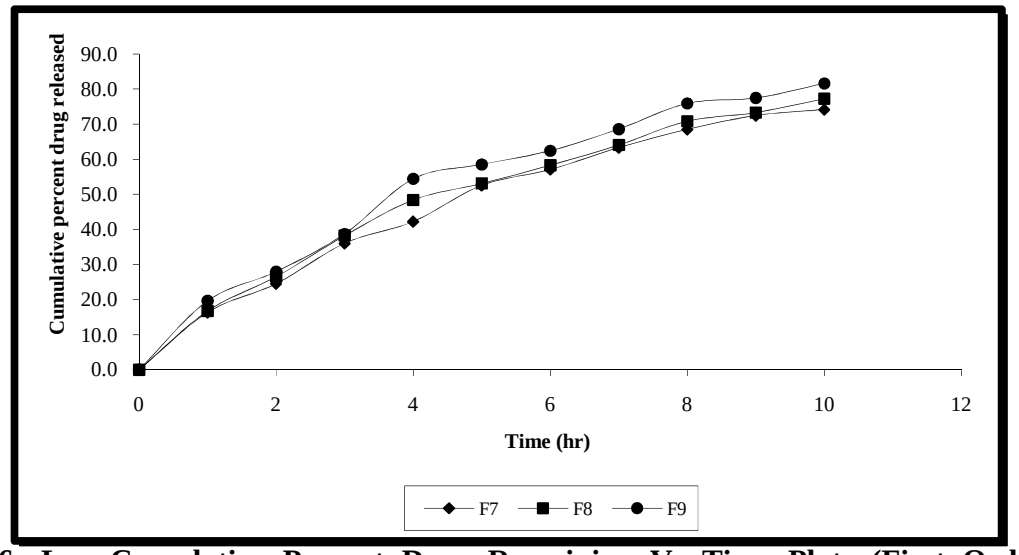


Figure-26: Log Cumulative Percent Drug Remaining Vs Time Plots (First Order) of Formulations F7, F8 and F9

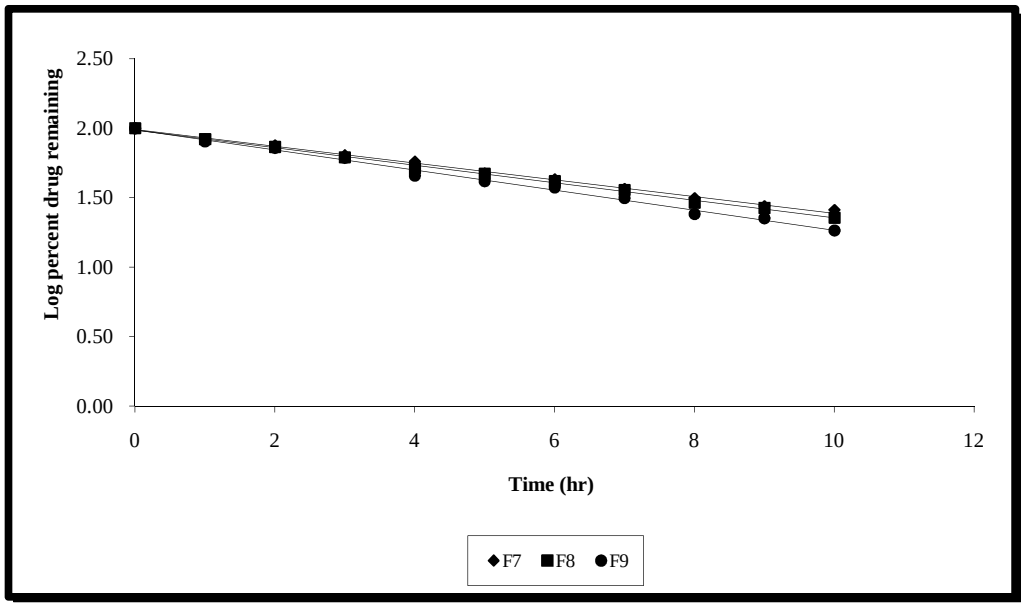


Figure-27: Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots) of Formulations F7, F8 and F9

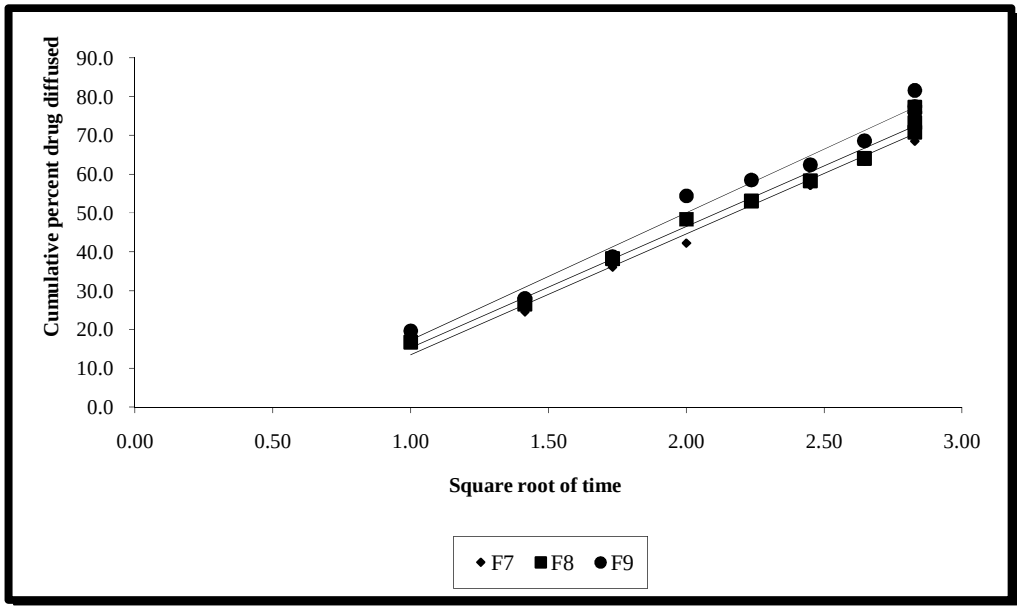


Figure-28: Log Cumulative Percent Drug Released Vs Log Time (Peppas Plots) of Formulations F7, F8 and F9

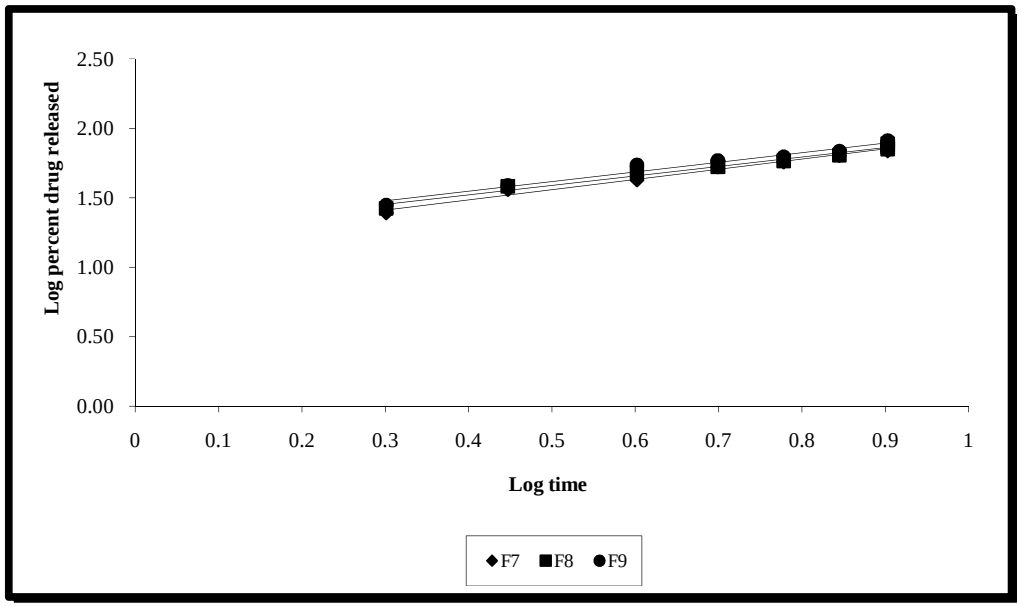


Table-26: Dissolution Parameter for the Trial Formulations

Sl. No.	Formulation Code	$t_{50\%}$ (hours)	$t_{70\%}$ (hours)	$t_{90\%}$ (hours)	Cumulative percent drug release in 10 hours
1.	T1	4.9	7.6	>10	76.44
2.	T2	5.2	8.9	>10	72.67
3.	T3	5.5	>10	>10	67.19
4.	T4	4.5	6.2	8.0	95.21
5.	T5	4.8	6.4	8.2	90.65
6.	T6	5.9	8.2	>10	81.34

Table-27: Dissolution Parameters for 3^2 Full Factorial Design Batches

Batch Code	Variable level in Coded Form		$t_{50\%}$ (hours)	$t_{70\%}$ (hours)	$t_{90\%}$ (hours)	Cumulative percent drug release in 10 hours
	X_1^*	$X_2^\#$				
F1	-1	-1	2.90	5.40	9.40	93.85
F2	-1	0	2.70	4.85	8.90	94.56
F3	-1	1	0.24	0.95	5.10	101.07
F4	0	-1	3.80	8.00	13.60	75.19
F5	0	0	3.50	7.50	12.80	79.38
F6	0	1	2.90	6.20	10.40	88.72
F7	1	-1	4.75	8.50	15.20	74.14
F8	1	0	4.40	7.90	14.20	77.28
F9	1	1	3.70	7.20	12.40	81.60
C1	-0.5	-0.5	2.90	5.80	9.9	91.49
C2	+0.5	+0.5	3.65	6.90	11.3	87.69

C_1, C_2 check point batches.

$t_{90\%}$ analyzed by matrix model fitting using PCP Disso V3 Software

* For HPMC K4M (X_1) transformed levels in mg are: –1=100; '0'=125, +1=150, –0.5=112.5, +0.5=137.5

For $NaHCO_3$ (X_2) transformed levels in mg are: –1=15; '0'=30, +1=45, –0.5=22.5, +0.5=37.5

All the batches contained 80 mg of furosemide 1% talc and 0.5% magnesium stearate.

Table-28: Kinetic Data of Trial Formulations

Batch	Zero Order	First Order	Higuchi's Equation	Peppas Equation	
	R	0.9798	-0.9919	0.9823	0.9945
T1	A	8.6400	2.0060	-7.9368	1.1924
	B	7.7062	-0.0669	27.0450	0.7220
	R	0.9185	-0.9714	0.9751	0.9292
T2	A	17.2527	1.9016	1.2920	1.3343

	B	6.3074	-0.4735	23.2690	0.5559
	R	0.9742	-0.9858	0.9657	0.9836
T3	A	3.2768	2.0200	-11.6286	0.8621
	B	7.3175	-0.5430	25.2148	1.0547
	R	0.8891	-0.7715	0.9689	0.9125
T4	A	25.9400	1.8920	5.2363	1.5022
	B	7.5259	-0.0840	28.4053	0.4813
	R	0.9336	-0.9871	0.9710	0.9605
T5	A	14.9350	1.9933	-6.2388	1.2654
	B	8.8811	-0.1029	32.1101	0.7584
	R	0.9861	-0.9762	0.9786	0.9851
T6	A	4.7137	2.0313	-6.7894	1.1144
	B	7.8644	-0.6660	25.7071	0.7890

Table-29: Kinetic Data of Factorial Formulations

Batch		Zero Order	First Order	Higuchi's Equation	Peppas Equation
	R	0.9638	-0.9688	0.9969	0.9931
F1	A	16.7500	2.0529	-3.2300	1.3894
	B	8.5230	-0.1099	30.6400	0.5971
	R	0.9515	-0.8946	0.9955	0.9930
F2	A	19.1227	1.4960	-1.3700	1.3893
	B	8.4429	-0.0549	30.7007	0.5970
	R	0.7780	-0.9679	0.9061	0.6561
F3	A	47.4400	1.6533	31.2830	1.9250
	B	7.3431	-0.1058	25.4186	8.2930
	R	0.9634	-0.9625	0.9879	0.9817
F4	A	11.2572	2.0463	-5.8963	1.2013
	B	7.5414	-0.0728	26.8830	0.7299
	R	0.9579	-0.9924	0.9902	0.9778
F5	A	13.2172	1.9693	-7.0649	1.2557
	B	7.4858	-0.6643	26.7697	0.6848
	R	0.9600	-0.9900	0.9913	0.9820
F6	A	15.0600	2.0050	-4.0981	1.1957
	B	8.2489	-0.0909	29.5917	0.7441
	R	0.9777	-0.9980	0.9913	0.9965
F7	A	9.8936	1.9875	-5.9711	1.2125
	B	7.2400	-0.0597	25.5038	0.6863

	R	0.9737	-0.9982	0.9935	0.9953
F8	A	11.1900	1.9320	-5.2217	1.2386
	B	7.3383	-0.0624	26.1200	0.6745
	R	0.9676	-0.9954	0.9414	0.9917
F9	A	12.7000	1.9847	-2.1400	1.2904
	B	7.7346	-0.0717	24.8500	0.6459

Stability studies

Statistical analysis was performed on the drug content data and drug release parameters by using 't' test. The 't' value for the drug content was found to be 3.97 against the table value of 4.3. For $t_{50\%}$ and $t_{70\%}$ the 't' values were found to be 0.95 and 0.83 respectively ($p<0.05$). These results indicate that there were no significant changes in drug content and dissolution profile of the formulation F2 during storage at 45ºC for after two months. The data of dissolution and in vitro floating studies are shown in Tables-32 to 34.

Table-32.1: Drug Content Data of Stability Formulation (F2)

Sl. No.	Trial No.	1st Day (%)	20th Day (%)	40th Day (%)	After two months (%)
1.	I	95.57	95.51	95.40	95.02
2.	II	98.13	98.02	97.96	97.92
3.	III	97.59	97.39	97.22	96.70
4.	Mean ($\overline{X}$)	97.09	96.97	97.22	96.70
5.	SD	1.35	1.30	1.31	1.50

Table-32.1: Statistical Analysis of Drug-Content Data for the Stability Formulation (F2)

Sl. No.	Trial No.	A	B	A – B
1.	I	95.57	95.02	0.55
2.	II	98.13	97.92	0.21
3.	III	97.59	97.18	0.41
4.	Mean ($\overline{X}$)	97.09	96.70	0.39
5.	SD	1.35	1.50	0.17

't' = 3.97 ($p<0.05$)

Table-33: In vitro Release Data of the Stability Formulation (F2)

Sl. No.	Time (Hrs)	Cumulative* Percent Drug Released±SD at 45±1ºC	
		1st Day	After two months
1.	01	23.04±0.73	21.35±0.07
2.	02	44.69±0.90	41.15±0.54
3.	03	52.75±0.68	49.71±1.20

4.	04	59.44±0.64	57.47±1.60
5.	05	72.00±0.71	68.69±1.02
6.	06	74.56±0.27	73.19±0.99
7.	07	79.09±1.48	75.16±0.81
8.	08	83.97±0.76	31.38±1.12
9.	09	90.61±0.94	87.48±1.24
10.	10	94.56±0.57	92.67±0.42

** Average of three determinations*

Table-34: Statistical Analysis of Dissolution Parameters ($t_{50\%}$, $t_{70\%}$) of Stability Formulation (F2)

Trial	$t_{50\%}$ values		A – B	$T_{70\%}$ values		A – B
	1st Day (A)	After two months (B)		1st Day (A)	After two months (B)	
I	2.60	2.55	0.05	4.96	4.98	–0.03
II	2.90	2.91	–0.01	4.77	4.76	0.01
III	2.60	2.59	0.01	4.82	4.84	–0.02
Mean	2.70	2.68	0.017	4.85	4.86	–0.01
SD±	0.173	0.197	0.031	0.0984	0.11135	0.021
t=0.95; (p<0.05)				t=0.83 (p<0.05)		

RESULT AND DISCUSSION

In the present study, hydrodynamically balanced systems of furosemide were prepared by using different viscosity grades of hydroxy propyl methyl cellulose (HPMC) viz., K4M and HPMC K100M, at different drug to polymer ratios along with a gas generating agent, sodium bicarbonate.

The prepared HBS tablets were evaluated for hardness, friability, uniformity of weight, uniformity of drug content, swelling index, floating lag time, in vitro floating time, in vitro dissolution, short-term stability and drug-polymer interaction.

Formulation optimization has been done by using 3^2 full factorial designs after evaluating the preliminary data obtained from six batches of formulations (T_1 to T_6). Polynomial equations were derived for $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ values by backward stepwise linear regression analysis using 'PCP Disso 2000 V3 software'. Validity of the derived equations was verified by preparing two check point formulations of intermediate concentrations (C_1 and C_2).

The hardness of the prepared HBS of furosemide was found to be in the range of 3.9 to 4.8 Kg/cm². The friability of all tablets was less than 1% i.e., in the range of 0.51 to 0.69%. The percentage deviation from the mean weights of all the batches of prepared HBS was found to be within the prescribed limits as per IP. The low values of standard deviation indicates uniform drug content in all the batches prepared as observed from the data given in tables-9 & 10.

The swelling index of the tablets increases with an increase in the polymer content as can be seen from the data given in tables-9 & 10. In vitro floating studies were performed by placing tablets in USP XXIII dissolution the apparatus-II containing 900 ml of 0.1N HCl maintained at a temperature of 37±0.5ºC. The floating lag time and floating time was noted visually. The results are given in tables-9 & 10. For all (trial and factorial) formulations, lag time is in the range of 0.3 min to 4.3 min. With formulations containing the same amount of polymer of the same grade, floating lag time decreased with increase in concentration of sodium bicarbonate. For formulation F3, it is lowest (0.3 min) as the drug-polymer (HPMC K4M) ratio is 1:2 and sodium bicarbonate is in highest proportion among all formulations and the tablet bursts into pieces within 30 minutes, while for formulation F7, lag time is highest (4.3 minutes) as drug-polymer ratio is 1:3 and $NaHCO_3$ is in lowest proportion (15 mg) among all formulations. All the designed formulations have displayed a floating time of more than 24 hours.

In vitro drug release study was performed using USP XXIII dissolution test apparatus-II at 50 rpm using 900 ml of 0.1N HCl maintained at 37±0.5ºC as the dissolution medium. The results were shown in tables-11 to 25. From the above data, it is evident that as the proportion of polymer in the formulation increases, cumulative percent drug release in 10 hours decreases, and as the proportion of the gas generating agent increases, the drug release increases. Among the six trial batches, formulations T1 to T3 have released only 67 to 76% drug in 10 hours, whereas formulations T4 to T6 have released 81 to 95% during the same period. This increased drug release from these formulations can be attributed to the lower viscosity grade (HPMC K4M) of HPMC. Among these six formulations, T5 formulation has shown promising dissolution parameters ($t_{50\%}$=4.8 hours, $t_{70\%}$=6.4 hours and $t_{90\%}$=8.2 hours) and shorter lag time (<3 min).

Factorial Design:

Based on the composition of T5 formulation, we have fixed the constraints for the levels of independent variables (X_1 and X_2) i.e., 100 to 150 mg for HPMC K4M (X_1) and 15 to 45 mg for $NaHCO_3$ (X_2) in designing the formulations of 3^2 full factorial design. In this 3^2 full factorial design, two factors (proportion of matrix polymer and gas generating agent) are evaluated, each at three levels and experiments are performed on all nine possible combinations. Dissolution parameters i.e., $t_{50\%}$, $t_{70\%}$, and $t_{90\%}$ values were selected as dependent variables. Formulation codes of the nine batches of factorial formulations along with dissolution parameter values ($t_{50\%}$, $t_{70\%}$ and $t_{90\%}$) and cumulative percent drug released in 10 hours were shown in table-27. From the data in the above table, it is evident that formulation F2 has shown highly satisfactory values for dissolution parameters ($t_{50\%}$=2.7 hours; $t_{70\%}$=4.85 hours and $t_{90\%}$=8.9 hours) and has released approximately 95% drug in 10 hours. Hence, formulation F2 may be considered as the optimized furosemide gastric floating drug delivery system for improved bioavailability.

Drug Release Kinetics:

In vitro drug release data of all the HBS formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in tables-28 and 29 and plots shown in figures-6 to 25. From the above data, it can be seen that except formulation T4, all the trial formulations have displayed first order release kinetics ('r' values in the range of 0.9714 to 0.9933). From Higuchi and Peppas data, it is evident that the drug is released by non-fickian diffusion mechanism (n=0.48 to 0.79) except formulation T3 (n=1.05). From the kinetic data of factorial formulations (table-29), it is evident that except formulation F2, all the remaining eight formulations have shown drug release by first order kinetics. Formulation F2 releases drug by nearly zero order kinetics (r=0.9515). The values of 'r' for Higuchi's equation of factorial formulations range from 0.91 to 0.99 and those of 'n' values of Peppas equation range from 0.59 to 0.74 (except for F3, n=8.29). This data reveals that drug release follows non-Fickian diffusion mechanism. Because of the higher gas generating agent, F3 formulation got burst within 30 minutes and shows very high value (8.29) for diffusion exponent.

Development of Polynomial Equations:

From the data of dissolution parameters shown in table-27, for factorial formulations F1 to F9, polynomial equations for three dependent variables ($t_{50\%}$, $t_{70\%}$ and $t_{90\%}$) have been derived using "PCP Disso 2000 V3 software'. Polynomial equation for 3^2 full factorial design is[83]:

$$Y = b_0+b_1 X_1+b_2 X_2+b_{12} X_1X_2+b_{11} X_1^2+b_{22} X_2^2$$

where Y is dependent variable, b_0 arithmetic mean response of nine batches, and b_1 estimated coefficient for factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 & X_2^2) are included to investigate non-linearity.

The equation derived for $t_{50\%}$ is:

$$Y_1 = 3.2100 + 1.1683X_1 – 0.7683 X_2$$

The negative sign for coefficient of X_2 indicates that as the concentration of gas generating agent ($NaHCO_3$) increases, $t_{50\%}$ value decreases.

The equation derived for $t_{70\%}$ is:

$$Y_2 = 6.2778 + 2.0667 X_1 – 1.2583 X_2$$

The equation derived for $t_{90\%}$ is:

$$Y_3 = 12.2667 + 3.0667 X_1 – 1.7167 X_2 – 1.4 X_1 X_2$$

In equations (3) and (4) also negative sign for coefficient of X_2 indicates that as the concentration of $NaHCO_3$ increases $t_{70\%}$ and $t_{90\%}$ values decrease. Validity of the above equations was verified by designing two check point formulations (C_1 and C_2) and studying the drug release profiles. The dissolution parameters predicted from the equations derived and those observed from experimental results are summarized in the table: 35

Formulation	Predicted values (hours)			Observed values (hours)		
	$t_{50\%}$	$T_{70\%}$	$t_{90\%}$	$t_{50\%}$	$t_{70\%}$	$t_{90\%}$
C_1	3.01	5.87	11.24	2.9	5.8	9.9
C_2	3.4	6.68	12.58	3.65	6.9	11.3

The closeness of predicted and observed values for $t_{50\%}$, $t_{70\%}$ and only slight variation in $t_{90\%}$ values indicates validity of derived equations for the dependent variables. The computer generated response surfaces plots for the dependent variables are shown in figures-26 to 28.

Stability Studies:

Short-term stability study was performed on the promising formulation F2 by storing the samples at 45±1ºC for 3 weeks (21 days). The samples were tested for any changes in physical appearance and drug content at weekly intervals. In vitro floating ability and *in vitro* drug release studies were performed at the end of 3 weeks storage. Statistical analysis was performed on the drug content data and drug release parameters by using 't' test. The 't' value for the drug content was found to be 3.97 against the table value of 4.3. For $t_{50\%}$ and $t_{70\%}$ the 't' values were found to be 0.95 and 0.83 respectively ($p<0.05$). These results indicate that there were no significant changes in drug content and dissolution profile of the formulation F2 during storage at 45ºC for 3 weeks.

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