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FORMULATION AND EVALUATION OF EFFERVESCENT FLOATING TABLETS OF GRISEOFULVIN

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ABSTRACT

The purpose of this research work was to develop gastroretentive drug delivery system of Griseofulvin Floating tablets were prepared by direct compression method using gas generating agents such as sodium bicarbonate and citric acid anhydrous, polymers like Carbopol 934, guar gum and HPMC K4M. Formulations tried for different ratios of drug and polymers to get desired release profile. Prepared tablets (G1-G9) were evaluated in terms of pre-compression and postcompression parameters Griseofulvin floating tablets were prepared by direct compression method were found to be good without chipping, capping and sticking. The drug content was uniform in all the tablet formulations indicating uniform distribution of drug within the matrices. All the prepared batches showed satisfactory floating lag time and total floating time found to be 12hrs. Among all formulations, G7 showed the drug release in most sustained manner and showed 99.57% of in vitro drug release at the end of 12 hrs and selected as the best formulation. The in vitro data obtained for the optimized formulation (G7) was fitted in different models viz. zero order, first order, Higuchi and Korsemeyer-Peppas equation for release kinetics and showed that the formulation follows Higuchi release mechanism Finally optimized formulation G7 complying with all properties of floating tablets and found to be satisfactory.

Keywords: Griseofulvin, Carbopol 934, guar gum and HPMC K4M.

INTRODUCTION

The main motive of any drug delivery system is to deliver a sufficient concentration of drug to the specific target (cell, organ, tissue) in the body to achieve therapeutic concentration and maintain optimum concentration. Oral drug delivery system is the most commonly used system for drug delivery because of its several advantage like easy administration, easy to formulate and high patient compliance. Oral controlled –release drug delivery system deliver the drug at a predetermined and controlled rate hence maintain optimum therapeutics concentration .oral controlled release drug delivery system have a several merit enhancement of activity of duration for short half-life drug, elimination of side effect , reducing frequency of dosing and wastage of drug and high patient compliance.[1]

Floating System (FDDS) are also known as hydro dynamically balanced system has a bulk density less than that of gastric fluid and so remains floating in the stomach without affecting gastric emptying rate for longer time . During floating period drug is slowly released at desired rate from the system. Floating system can be divided in to two types: effervescent and non –effervescent system[2].

The oral bioavailability of many drugs is limited by their unfavourable physicochemical characteristics or absorption in well-defined part of the gastrointestinal tract (GIT) referred as “absorption window” . Prolonged gastric retention improves bioavailability, reduces drug waste, and improves the solubility for drugs that are less soluble in a high pH environmen . Various approaches have been investigated to increase the retention of oral dosage form in the stomach, including floating systems, swelling and expanding systems, bioadhesive systems, modified shape systems, high density systems, and other delayed gastric emptying devices[3].

These are designed to distribute the drug's active component gradually and predictably over a 12-to 24-hour period. Through more reliable medicine delivery, diminished side effects, increased convenience, and improved rates of patient compliance, they offer greater effectiveness in the treatment of chronic illness conditions. When a polymer, natural or synthetic, is correctly coupled with a drug or other active agent so that the active medication is delivered in a predetermined manner, this is known as controlled drug delivery. Less absorption, potential toxicity, and the creation of unfavourable by products are some drawbacks of these goods, not with standing their benefits. Floating drug delivery systems and other delivery methods with extended gastric residence times were developed to solve these problems. These systems fall under the category of gastro-retentive dosage forms, which are retained in the stomach for longer periods of time, assisting in the absorption of the drug for the intended duration of time. The floating system is an extensively used technique in this. Most often, the non-effervescent approach was used to prepare floating systems. When dissolved in water, hydroxyethyl cellulose, also known as hydroxypropyl methylcellulose (HPMC), creates a colloid solution. It is a semi-synthetic, inert, and viscoelastic polymer. It functions as a binder during the granulation process and in modified release formulations as well as a thickening agent, coating polymer, bio adhesive, solubility enhancer in solid dispersions, and binder. It is frequently employed as a delivery element in oral pharmaceutical products to give the controlled release of a drug, effectively increasing the time of release to extend the therapeutic effects of a drug[4].

Floating drug delivery systems (FDDS) float in the stomach without slowing down the gastric emptying rate since their bulk density is lower than that of gastric fluids. The medicine is slowly withdrawn from the system at the desired rate while the body is floating on the contents of the stomach. The stomach's residual system is emptied following medication release [5].

Drug administration by oral delivery is recommended over other conventional routes like intravenous and intramuscular injection because it is more natural and less invasive. Numerous strategies are developed to ensure optimal bioavailability, and one of them is the use of gastro-retentive dosage forms. The system could be low-density or high-density, increasing the gastric residence time, floating, swelling, inflation, adhesion. These consist of expandable classifications, floating drug delivery systems (FDDS), expandable systems, expandable systems, High density systems and ultra porous hydrogels[6].

The real challenge in the development of a controlled drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper small intestine until all the drug is completely released in the desired period of time. The residence of a drug delivery system in the upper part of the gastrointestinal tract (GIT) can be accomplished by several drug delivery systems, such as swelling, intragastric floating systems and expandable systems, Bioadhesive systems, high density systems, modified shape systems, delayed gastric emptying systems, and low density super porous systems, FDDS, also called hydro dynamically balanced system. It is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. This technology is suitable for drugs with an absorption window in the stomach or in the upper part of the small intestine, the drugs acting locally in the stomach and for drugs that are poorly soluble or unstable in the intestinal fluid. FDDS have a bulk density lower that gastric fluid and thus remains buoyant in stomach for prolonged period of time without affecting gastric emptying time. The drug is released slowly, while the system is floating on the gastric contents. They are also known as hydro dynamically balanced systems (HBS) as they are able to maintain their low density, Based on mechanisms of floating, two different technologies. Effervescent FDDS Non-effervescent FDDS. When they reach in stomach CO2 is liberated by the acidity of gastric content and is entrapped in jellified hydro colloid (In case of effervescent systems). When the liberated gas is expelled from the dosage form it creates pores through which water can easily pass and helps in wetting of the polymers. The CO2 generated compounds like calcium carbonate, sodium bicarbonate, citric acid/tartaric acid mixtures can be used.[7]

Advantages of Floating Drug Delivery System

- The gastro retentive systems are advantageous for drugs absorbed through the stomach.¬ Examples: Ferrous salts, antacids. Acidic substances like aspirin cause irritation on the stomach wall when come in contact¬ with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
- Administration of prolongs release floating dosage forms, tablet or capsules, will result in¬ dissolution of the drug in the gastric fluid.
- They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents.
- It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
- The gastro retentive systems are advantageous for drugs meant for local action in the¬ stomach. Example: antacids.

- When there is a vigorous intestinal movement and a short transit time as might occur in¬ certain type of diarrhoea, poor absorption is expected.
- Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.[8]

Disadvantages of Floating Drug Delivery System

- Floating system is not feasible for those drugs that have solubility or stability problem in¬ G.I. tract.
- These systems require a high level of fluid in the stomach for drug delivery to float and¬ work efficiently coat, water.
- The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo¬ significant first pass metabolism, are only desirable candidate.
- Some drugs present in the floating system causes irritation to gastric mucosa.

FDDS offers fundamental advantages approximating they are a smaller amount prone to gastric emptying resulting in summary intra and inter subject variability in plasma drug levels, successful for delivery of drugs by thin absorption windows, reduced dosing and enhanced patient compliance, reduced Cmax and expanded drug levels above the smallest effective concentration and better safety profile for drugs with side effects linked with high Cmax. Itopride has anticholinesterase (Ache) action as well as dopamine D2 receptor antagonistic action, accepted that M3 receptors exist on the smooth muscle layer every through the gut and acetylcholine (ACh) free from enteric nerve endings stimulates the contraction of smooth muscle through M3 receptors.

MATERIALS AND METHODS

Griseofulvin- PraveenLaboratories Pvt Ltd, Gujarat., Provided from SURA LABS, Dilsukhnagar, Carbopol 934-Corel Pharma, Ahmedabad, India. S, HPMC K4M-Strides Arcolab, Bangalore, Guar gum-Vishal Pharma, Vadodara, India, PVP K30-M/S Seeko Biotech,Vijayawada, India, $NaHCO_3$- Merck Specialities Pvt Ltd, Mumbai, India, Citric Acid- Merck Specialities Pvt Ltd, Mumbai, India, Mg. Stearate-Trishul reagents and chemicals, Chennai, Talc-S.S chemicals, Chennai, MCC PH 102-Merck Specialities Pvt Ltd, Mumbai, India.

METHODOLOGY:

Analytical method development:

a) Determination of absorption maxima:

A solution containing the concentration 10 µg/ mL drug was prepared in 0.1N HCL UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 291nm.

b) Preparation calibration curve:

10mg Griseofulvin pure drug was dissolved in 10ml of methanol (stock solution1) from stock solution1 1ml of solution was taken and made up with10ml of 0.1N HCL (100µg/ml). From this 1ml was taken and made up with 10 ml of 0.1N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 2,4,6,8,10 µg /ml of per ml of solution. The absorbance of the above dilutions was measured at 291 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight-line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

Pre-formulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone ,   r = Radius of the cone base

Table 7.1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

Bulk Density = M / V_o

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap = M / V

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of inter particulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - \text{b}) / \text{tap}] \times 100$$

Where, b = Bulk Density

Tap = Tapped Density

Table: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable

2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of floating Tablets: For optimization of Carbopol 934 concentration, granules were prepared by direct compression method.

Procedure for direct compression method:

1) Drug and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method by using 7mm punch.

FORMULATION OF TABLETS:

Table: Formulation composition for Floating tablets

Formulation Code	**G1**	**G2**	**G3**	**G4**	**G5**	**G6**	**G7**	**G8**	**G9**
Griseofulvin	125	125	125	125	125	125	125	125	125
Carbopol 934	20	40	60	-	-	-	-	-	-
HPMC K4M	-	-	-	20	40	60	-	-	-
Guar gum	-	-	-	-	-	-	20	40	60
PVP K30	8	8	8	8	8	8	8	8	8
$NaHCO_3$	10	10	10	10	10	10	10	10	10
Citric Acid	7	7	7	7	7	7	7	7	7
Mg. Stearate	3	3	3	3	3	3	3	3	3
Talc	4	4	4	4	4	4	4	4	4
MCC PH 102	123	103	83	123	103	83	123	103	83
Total weight	300	300	300	300	300	300	300	300	300

All the quantities were in mg

RESULT AND DISCUSSION

Analytical Method

a. Determination of absorption maxima

The standard curve is based on the spectrophotometry. The maximum absorption was observed at 291 nm.

b. calibration curve

Graphs of Griseofulvin was taken in 0.1N HCL (pH 1.2)

Table: Observations for graph of Griseofulvin in 0.1N HCL

Conc [µg/mL]	Abs
0	0
2	0.139
4	0.276
6	0.434
8	0.576
10	0.712

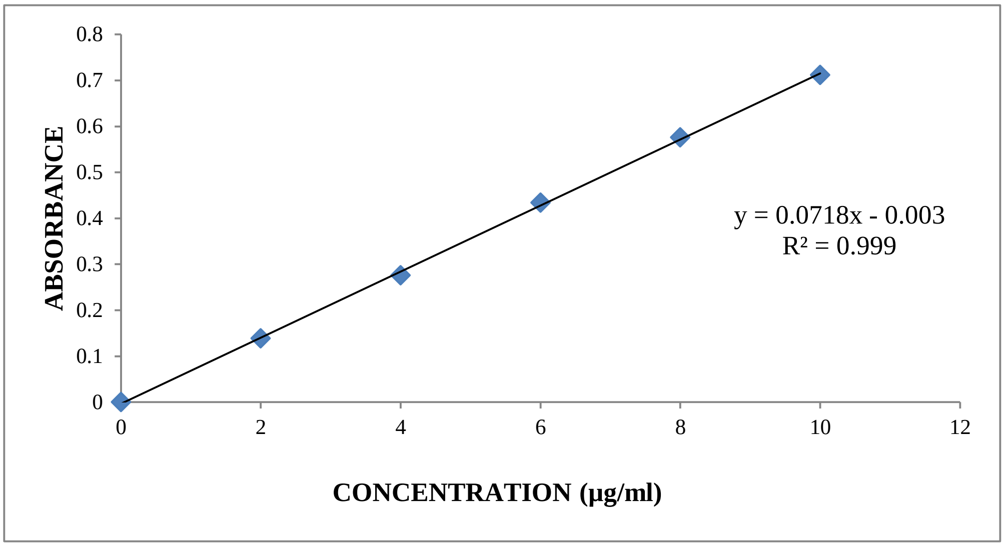

Fig : Standard graph of Griseofulvin in 0.1N HCL

Standard graph of Griseofulvin was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig. The standard graph of Griseofulvin showed good linearity with R^2 of 0.999, which indicates that it obeys "Beer- Lamberts" law.

Preformulation parameters of powder blend:

Table: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
G1	38.806	0.339	0.414	18.1	1.221
G2	37.427	0.322	0.392	17.7	1.215
G3	38.474	0.328	0.395	16.9	1.203
G4	38.719	0.315	0.390	19.3	1.239
G5	39.183	0.325	0.397	18.2	1.222
G6	39.396	0.322	0.390	17.4	1.211
G7	38.876	0.317	0.394	19.5	1.242
G8	39.611	0.333	0.409	18.5	1.227
G9	37.253	0.320	0.394	18.7	1.230

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.315 to 0.345 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.380 to 0.430 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 19.8 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 1.203 to 1.247 indicating the powder has good flow properties.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for floating tablets.

Formulation codes	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (min)	Total Floating Time(Hrs)
G1	96.42	5.3	0.57	3.3	97.12	4.2	4
G2	98.20	5.4	0.47	3.1	98.50	4.8	5
G3	97.36	5.2	0.58	3.4	97.78	5.2	10
G4	99.38	5.1	0.62	3.2	99.32	5.6	6
G5	95.54	5.5	0.59	3.5	98.65	3.8	8
G6	97.48	5.4	0.68	3.3	97.45	4.5	10
G7	98.63	5.3	0.72	3.6	99.15	4.7	7
G8	96.60	5.2	0.78	3.7	98.13	3.9	11
G9	99.52	5.4	0.80	3.3	99.35	4.3	12

All the parameters for SR layer such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

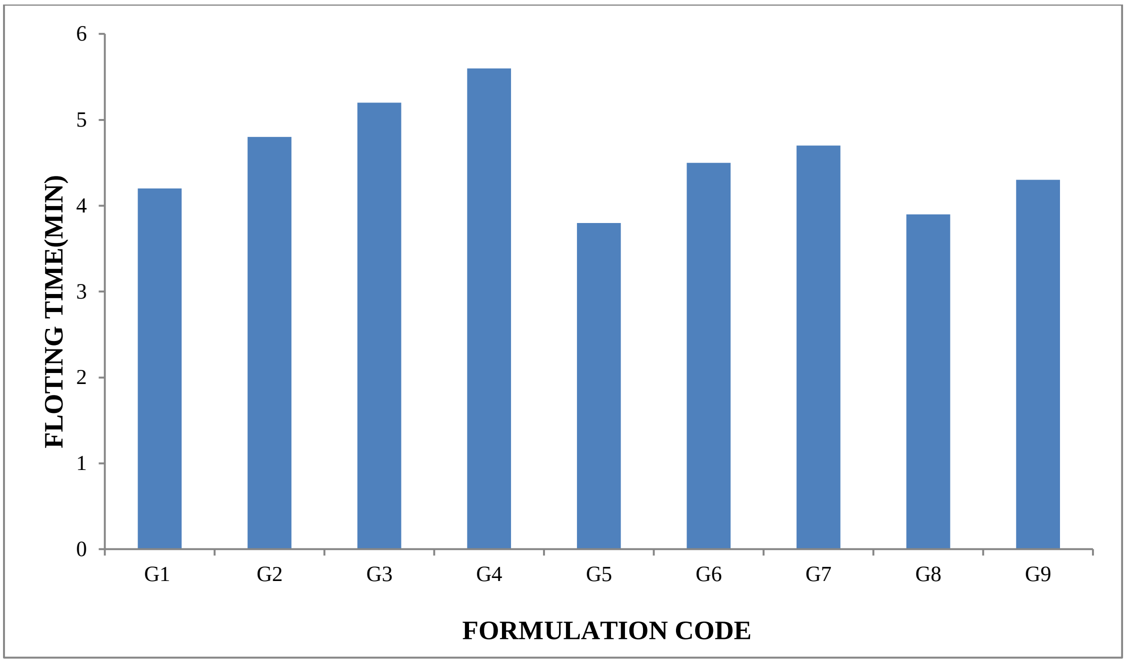

Figure : Floating lag time (min)

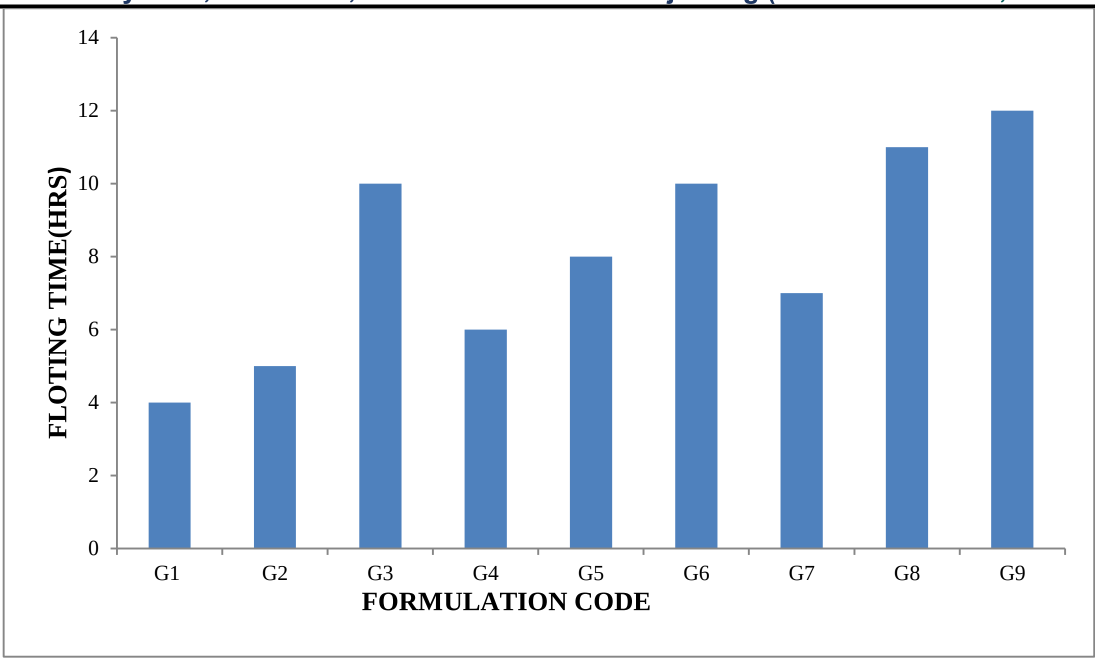

Figure: Total Floating Time (Hrs)

In Vitro Drug Release Studies

Table: Dissolution data of Floating Tablets

Time (hr)	G1	G2	G3	G4	G5	G6	G7	G8	G9
0	0	0	0	0	0	0	0	0	0
0.5	14.21	12.12	16.45	19.16	12.90	11.76	10.40	18.76	17.16
1	26.53	24.26	24.32	28.20	29.15	26.43	27.52	29.89	26.44
2	38.90	36.35	38.50	35.54	34.21	38.35	35.23	33.24	35.78
3	45.96	42.20	42.15	46.20	45.23	46.89	47.54	38.32	43.25
4	57.14	49.15	54.25	50.46	49.60	54.39	59.73	45.75	56.40
5	62.85	56.64	62.78	58.44	55.18	65.31	63.46	53.09	62.60
6	69.36	63.56	69.57	63.01	65.74	69.15	68.22	60.16	69.67
7	71.76	69.95	75.79	69.57	72.05	74.67	76.37	68.36	72.26
8	79.45	73.87	79.27	73.78	79.93	79.02	83.87	74.12	79.67
9	81.56	80.35	84.64	79.45	80.26	83.15	89.26	83.78	84.42
10	88.78	85.67	89.87	83.65	85.30	89.45	90.23	89.79	88.21

11	93.48	90.45	90.36	89.56	89.56	90.50	94.85	92.31	92.36
12	97.45	93.35	95.78	94.65	95.37	96.56	99.57	95.65	97.40

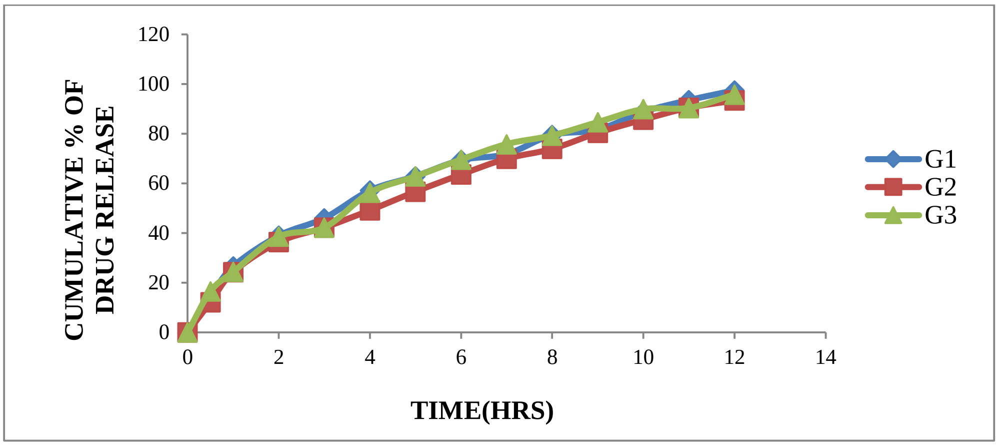

Fig: Dissolution data of Griseofulvin Floating tablets containing Carbopol 934

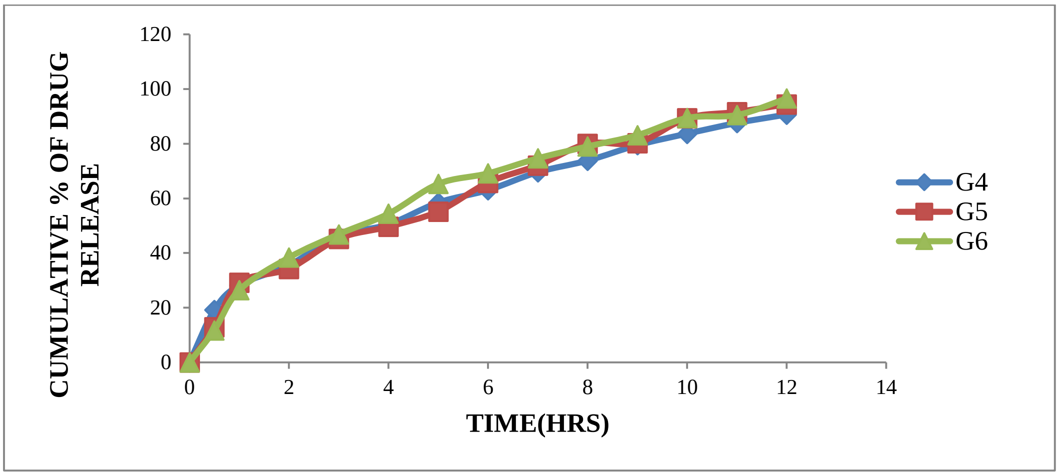

Fig: Dissolution data of Griseofulvin Floating tablets containing HPMC K4M

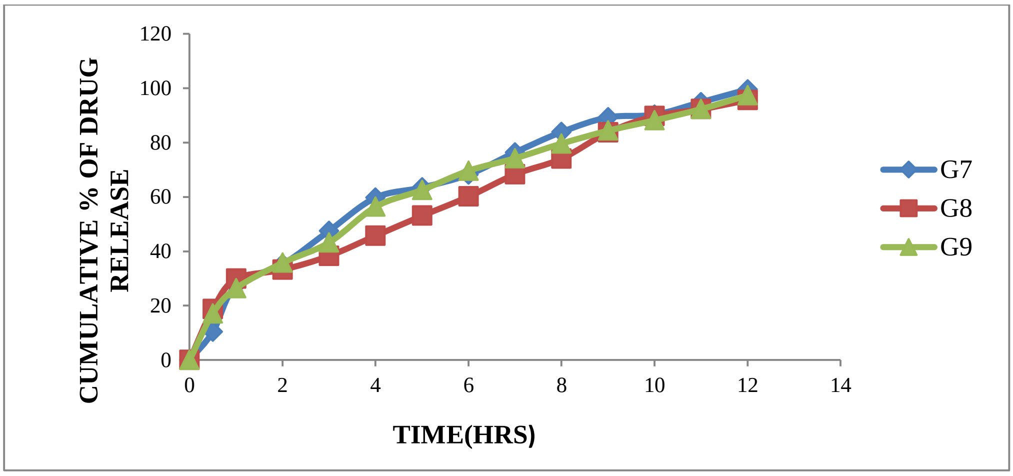

Fig: Dissolution data of Griseofulvin Floating tablets containing Guar gum

From the dissolution data it was evident that the formulations prepared with Carbopol 934 as polymer were unable to retarded the drug release 12 hours.

Whereas the formulations prepared with higher concentration of Guar gum retarded the drug release up to 12 hours . In lower concentrations the polymer was unable to retard the drug release.

The formulations prepared with HPMC K4M showed very less retardation capacity hence they were not considered.

Hence from the above dissolution data it was concluded that G7 formulation was considered as optimised formulation because good drug release (99.57%) in 12 hours.

Application of Release Rate Kinetics to Dissolution Data for optimised formulation:

Table : Application kinetics for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
10.4	**0.5**	0.707	1.017	0.301	1.952	20.800	0.0962	-0.983	89.6	4.642	4.475	0.167
27.52	**1**	1.000	1.440	0.000	1.860	27.520	0.0363	-0.560	72.48	4.642	4.169	0.472
35.23	**2**	1.414	1.547	0.301	1.811	17.615	0.0284	-0.453	64.77	4.642	4.016	0.626
47.54	**3**	1.732	1.677	0.477	1.720	15.847	0.0210	-0.323	52.46	4.642	3.743	0.898
59.73	**4**	2.000	1.776	0.602	1.605	14.933	0.0167	-0.224	40.27	4.642	3.428	1.214
63.46	**5**	2.236	1.803	0.699	1.563	12.692	0.0158	-0.197	36.54	4.642	3.318	1.323
68.22	**6**	2.449	1.834	0.778	1.502	11.370	0.0147	-0.166	31.78	4.642	3.168	1.474
76.37	**7**	2.646	1.883	0.845	1.373	10.910	0.0131	-0.117	23.63	4.642	2.870	1.772
83.87	**8**	2.828	1.924	0.903	1.208	10.484	0.0119	-0.076	16.13	4.642	2.527	2.115
89.26	**9**	3.000	1.951	0.954	1.031	9.918	0.0112	-0.049	10.74	4.642	2.206	2.435
90.23	**10**	3.162	1.955	1.000	0.990	9.023	0.0111	-0.045	9.77	4.642	2.138	2.504
94.85	**11**	3.317	1.977	1.041	0.712	8.623	0.0105	-0.023	5.15	4.642	1.727	2.915
99.57	**12**	3.464	1.998	1.079	-0.367	8.298	0.0100	-0.002	0.43	4.642	0.755	3.887

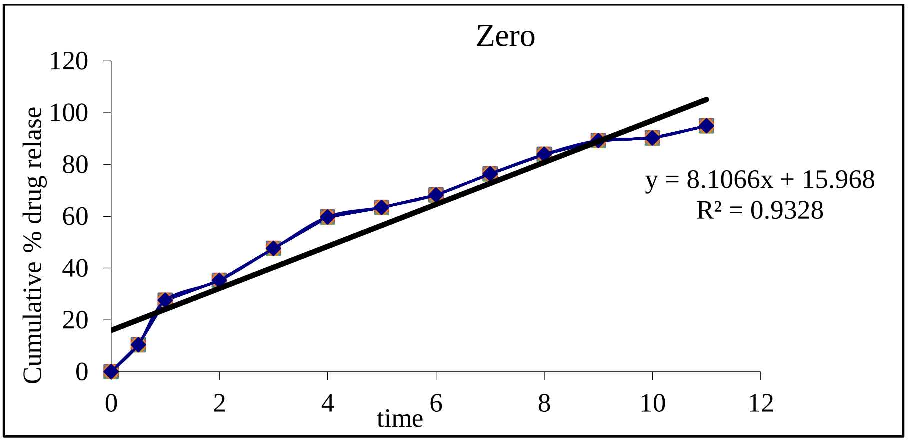

Fig : Zero order release kinetics

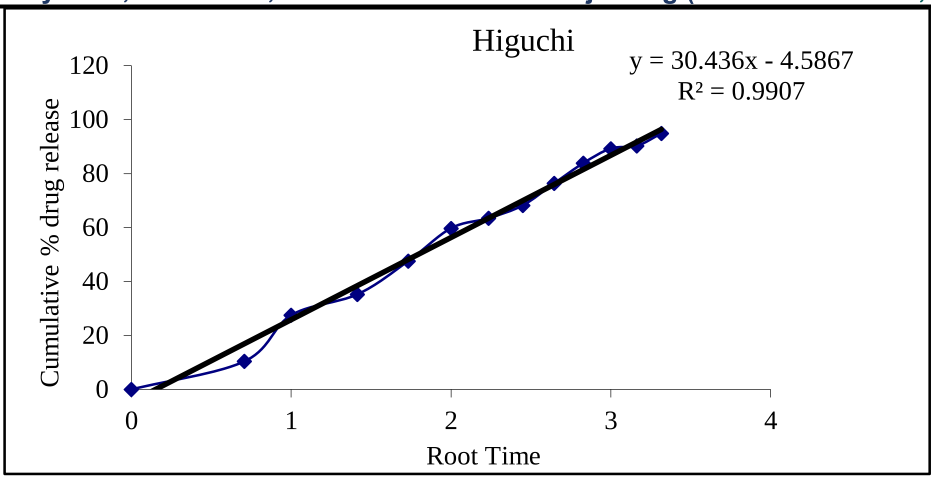

Fig : Higuchi release kinetics

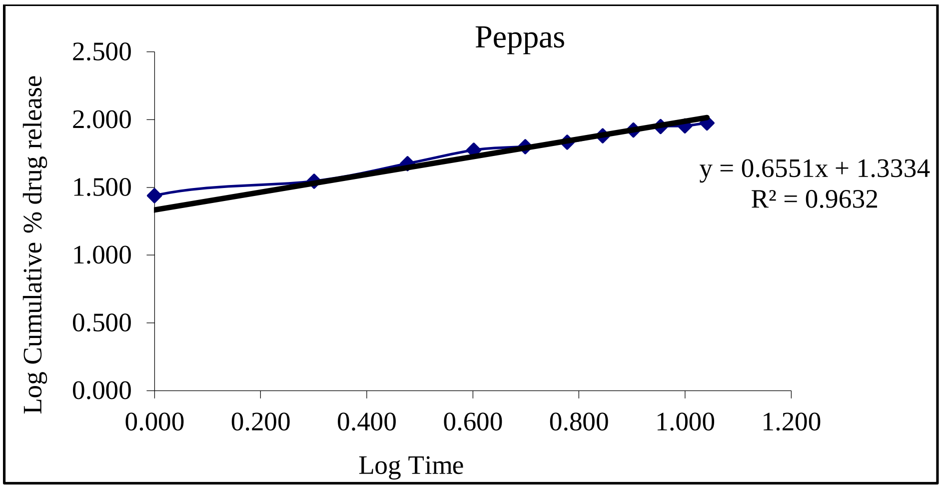

Fig : Kors mayer peppas release kinetics

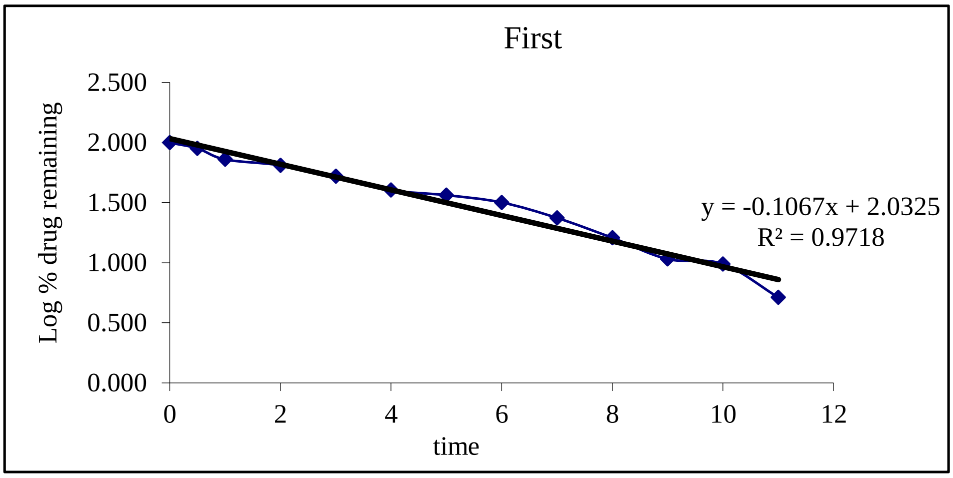

Fig: First order release kinetics

Optimised formulation G7 was kept for release kinetic studies. From the above graphs it was evident that the formulation G7 was followed Higuchi release mechanism.

8.5. Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy:

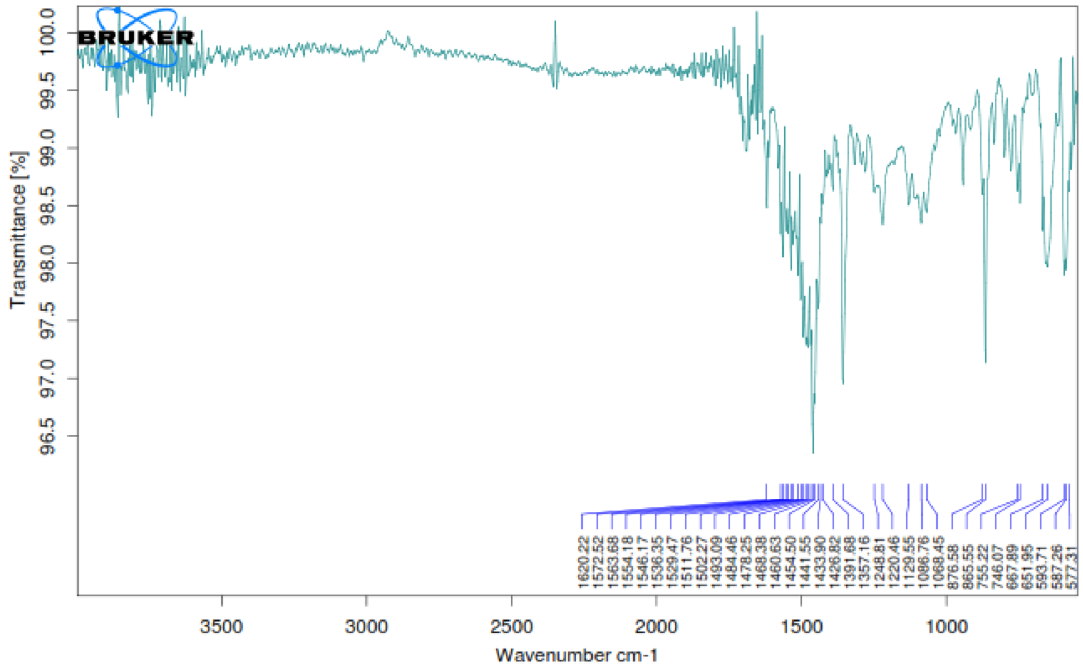

Figure : FTIR Spectrum of pure drug:

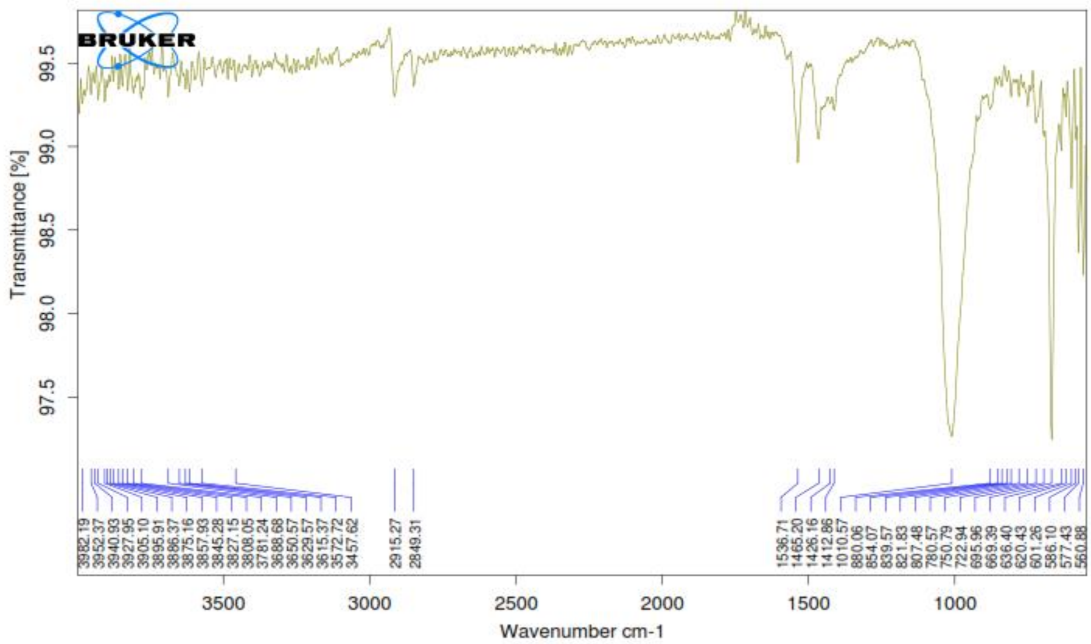

Fig : FTIR Spectrum of optimised formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Griseofulvin are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

CONCLUSION

From the above studies it is concluded that gastro retentive floating tablets of Griseofulvin be formulated using gas generating agents such as sodium bicarbonate and citric acid, polymers like Carbopol 934, HPMC K4M and Guar gum. Varying in the ratios of polymers (Carbopol 934, HPMC K4M and Guar gum) with respect to drug in formulations affected the water uptake efficiency, in vitro buoyancy and in vitro drug release rate of formulations. As concentration of polymers was increased in formulations and total floating time increased and also the drug released in more sustained way. In vitro studies have shown that this is a potential drug delivery system for Griseofulvin with a good stability and sustain release profile. The optimized formulation shows good controlled release for 12 h. It also showed good entrapment efficiency and in vitro floating efficiency. Hence, it can be concluded that the developed formulation is a potential dosage form for Griseofulvin.

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