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Effect of HPMC K4M, HPMC K15M, sodium alginate and carbopol 934 in the formulation of carbonyl iron capsule

[1]Ketan Gulabrao Albhar*, [2]Vaibhav Sudhakar Wagh , [1]Bhagwat Babasaheb Chavan

[1]JSPMS Jayawantrao Sawant College of Pharmacy & Research, Hadapsar, Pune
[2]Padamshri Dr Vithalrao Vikhe Patil Foundations College of Pharmacy (PDVVP), Ahmednagar

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ABSTRACT

The need of iron therapy prompted present study to develop a formulation of floating drug delivery system of carbonyl irons. Out of the chosen polymers as HPMC K15M, Sodium alginate, Carbopol 934 & HPMC K4M the positive and encouraging results in accordance to the aim have been obtained with HPMC K4M and HPMC K15M.Sodium bicarbonate has been used as the gas generating agent to assist to formulation. The formula has been optimized using factorial design. The optimized formulation shows maximum drug release with good floating behavior in vitro. The in vitro floating behavior has been further confirmed with in vitro floating behavior of the same formulation.

Key Words: Carbonyl irons, HPMC K15M, Sodium alginate, Carbopol 934 & HPMC K4M Floating drug delivery system, Factorial design, Drug release.

INTRODUCTION

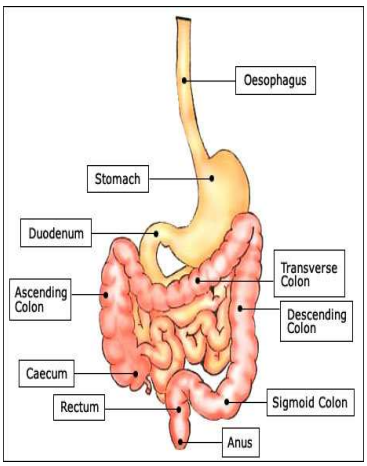
I. Introduction to sustained release and controlled release [Y.W. Chein et.al. ,L .Lachman et.al.]
For many decades, conventional drug delivery systems have been commonly used for drug administration. They have been known to provide a prompt release of drug. Therefore to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. This results in a significant fluctuation in drug levels.

Sustained release dosage forms are designed to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed, and the duration of its therapeutic effect is sustained. Thus the rate of appearance of drug in the body is controlled by the dosage form.Controlled release dosage forms are those systems from which therapeutic

agents may be automatically delivered at predefined rates over a long period of time. This implies that the release of drug ingredients is reproducible from one unit to another.
Controlled release drug delivery systems enjoy a number of advantages over immediate release systems. They bring about reduction in drug plasma level fluctuations, thus maintaining a steady plasma level of the drug over prolonged time period. The decrease in dosing frequency results in enhanced patient compliance. A decreased incidence or intensity of side effects is seen. In addition, these systems are extremely cost-effective resulting in reduction of total cost of therapy.

II. Anatomy and physiology of the gastrointestinal tract. [G.J. Tortora et.al. ,N.K. Jain et.al.] Due to its convenience, the oral route is the most preferred route for drug administration.The gastrointestinal tract is essentially a tube about 9 m long that runs from the mouth to the anus and includes throat (pharynx), esophagus, stomach, small intestine and large intestine.

Figure No. 01:-Gastrointestinal tract.



The gastrointestinal tract is always in a state of continuous motility called as peristaltic movement. There are two modes of motility pattern: the digestive mode and the interdigestive mode involved in the digestion of food. The interdigestive gastrointestinal motility is characterized by a cyclic pattern that originates in the foregut and propagates to the terminal ileum and consists of four distinct phase:

Phase I Period of no contraction
Phase II Period of intermittent contractions.
Phase III Period of regular contractions at the maximal frequency that migrate Distally
Phase IV Period of transition between Phase III and Phase I

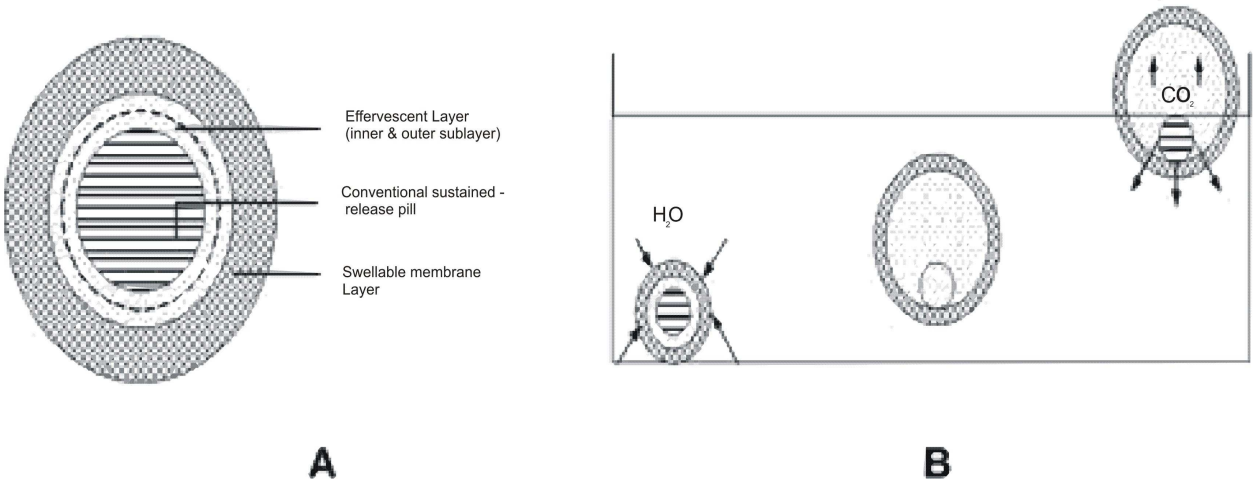
Table No.01:- pH and transit time of organs of GIT.

Sr. No.	Organs in the GIT	pH	Transit time (hours)
1.	Oral cavity	5.2-6.8	Short
2.	Esophagus	5.0-6.0	Very short
3.	Stomach	1.2-3.5	0.25-3.0
4.	Duodenum	4.6-6.0	1.0-2.0
5.	Jejunum	6.3-7.3	-
6.	Ileum	7.6	1.0-10.0
7.	Cecum	7.5-8.0	Short
8.	Colon	7.9-8.0	4.0-20.0
9.	Rectum	7.5-8.0	Variable

III. Targeting the gastrointestinal tract as a site of sustained release.[M. Chavanpatil et.al.,AO Nur et.al.,V . Iannuccelli et.al. ,A. Patel et.al., J. Varshosaz et.al. , Y. Sato et.al. ,EA Klausner,AK Srivastava et.al., Y. Machida et.al.,AH El-Kamel et.al., W. Sawicki et.al., JK Patel et.al.,A. E-Kamel et.al., I.El-Gibaly et.al., AK Srivastava et.al., L. Whitehead et.al., C. Narendra et.al., L. Yang et.al.,K. Takagi et.al.]

Except esophagus, all organs in gastrointestinal tract can be targeted to develop a sustained release dosage form. The stomach is a good target for drugs which are absorbed in stomach and duodenum.The drugs which are mainly absorbed in the stomach and small intestine are ofloxacin, captopril, furosemide, metformin, ciprofloxacin, repaglinide, riboflavin, levodopa, atenolol, cinnarizine, ketoprofen, verapamil, glipizide, metronidazole, melatonin, cimetidine, amoxicillin, metoprolol tartrate, tetracycline, theophylline etc.

Figure No.02:- (A) Multiple-unit oral floating drug delivery (B) Working principle of effervescent Floating drug delivery system.



IV Gastroretentive drug delivery systems.

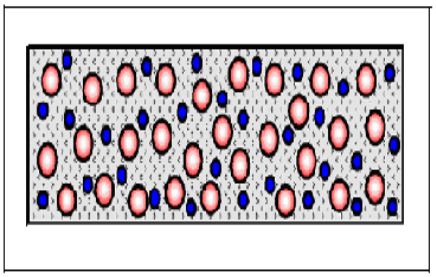
The following are different gastroretentive drug delivery systems:

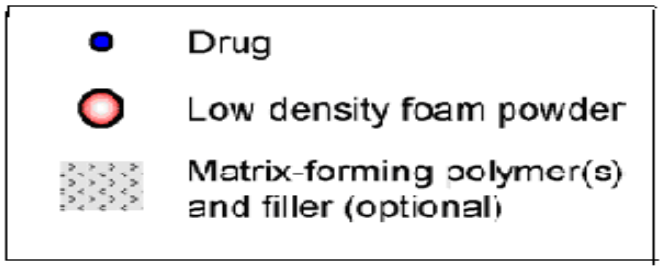
A) **Floating systems** [S. Stithit et.al, S. Arora et.al., P. Mathur et.al., H.Dutt et.al.]:

Many approaches are used in the designing of intragastric floating systems. They are discussed below.

1) Low density systems [A.A. Deshpande et.al., N.J. Joseph et.al., A. Streubel et.al.,R. Talukder et.al.]:

Figure No. 03:- Schematic representation of the low density, floating matrix tablets.



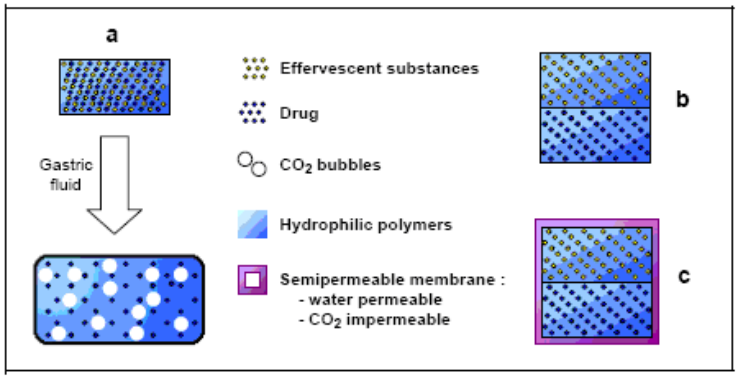


Due to a bulk density of less than1 g/cm^3, low density systems show immediate buoyancy. They are made of low density materials, entrapping oil or air. In this approach, globular shells apparently having lower density than that of gastric fluid can be used as carrier for drug for its sustained release. Fluid-filled chamber type of dosage forms are also an example of low density systems. They are mostly multiple unit systems and are also called 'microballoons' due to their characteristic internal hollow structure.

2) Gas generating systems [Y. Machida et.al., Chen GL et.al., Wei Z et.al., M. Chavanpatil et.al.,A.A. Deshpande et.al., Choi BY et.al., F. Stops et.al.,Y. Sato et.al.,X. Xiaoqiang et.al., PM De la Torre et.al.,W. Sawicki et.al., T. Nakagawa et.al., AH El-Kamel et.al., GL Chen et.al., S. Baumgartner et.al.,M. Ichikawa et.al., F. Atyabi et.al.]:

These systems are prepared with the help of polymers like Hydroxypropyl cellulose' , Hydroxypropylmethyl cellulose, Sodium alginate, Sodium carboxymethyl cellulose, Polymetacrylic acid, various grades of Carbopol such as Carbopol 971P, Carbopol 974P**,** Chitosan various grades of Eudragit such as Eudragit NE 30D, Eudragit L30D55 **,** Eudragit RL, Eudragit S100 etc.

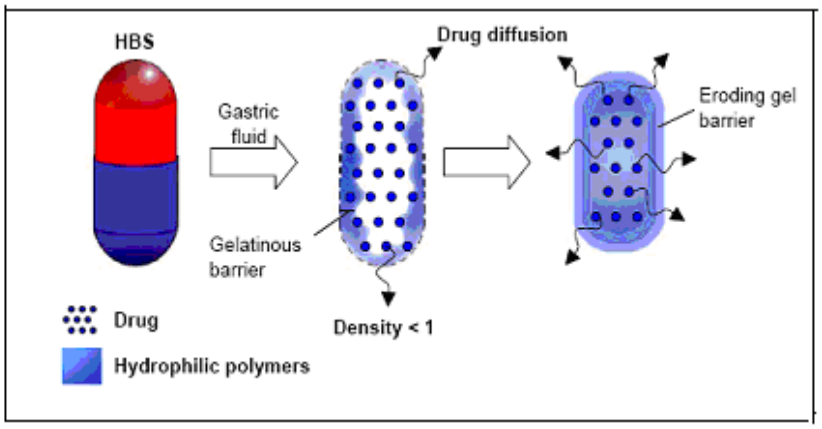
Figure No.04:- Gas generating systems. Schematic monolayer drug delivery systems. (a)Bilayer gas generating system with (c) or without (b) semipermeable membranes.



2) Hydrodynamically balanced systems [L.H. Reddy et.al.,SJ. Hwang et.al.,W. Erni et.al.,M. Oth et.al.]:

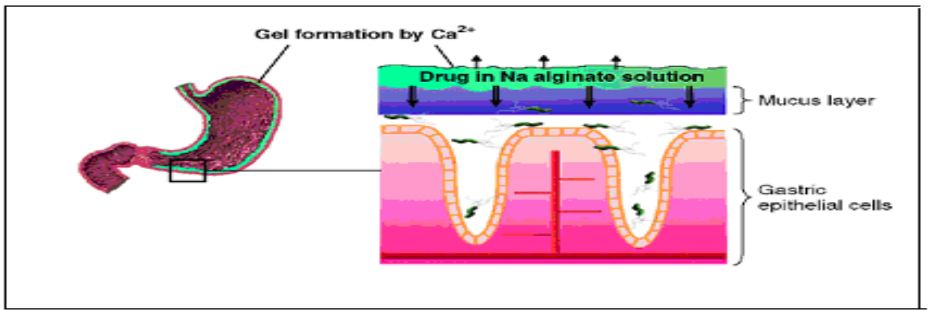
These are single unit dosage forms, containing one or more gel forming hydrophilic polymers. Hydroxypropylmethyl cellulose is the most commonly used excipient, although Hydroxyethyl cellulose, Hydroxypropyl cellulose, Sodium carboxymethyl Cellulose, Agar, Carageenans or Alginic acid are also used.

Figure No.05:- Hydrodynamically balanced systems



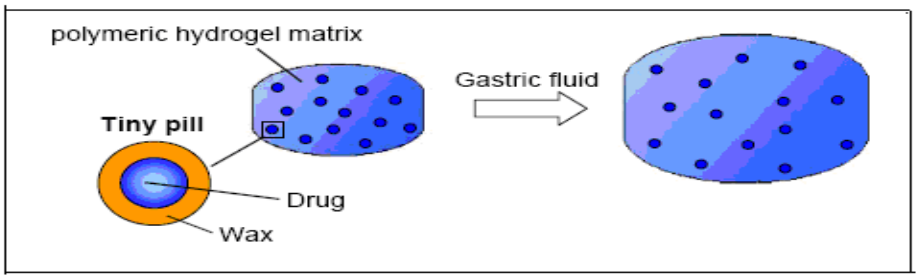
3) Raft forming systems [J. Foldager et.al.]:
Here, a gel forming solution (eg. Sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped carbon dioxide bubbles. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. As raft forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment.

Figure No.06:- In vitro functioning of sodium alginate raft



A) Expandable systems [E.A.Klausner et.al., J. Urquhart et.al.]:
A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. The concept is to make a carrier, such as a capsule, incorporating a compressed system which extends to in the stomach.
Swellable systems are also retained because of their mechanical properties

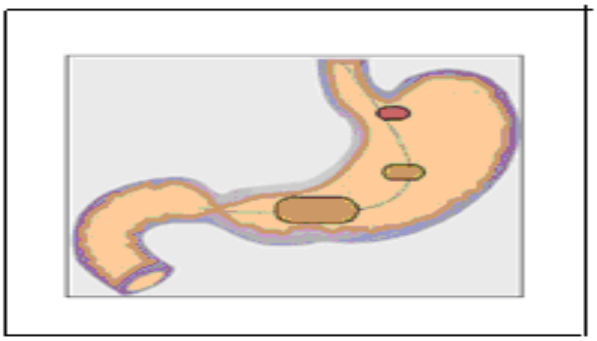
Figure No. 07:- Swellable systems.



Expandable systems should not interfere with gastric motility, must be easily biodegradable, and must not have sharp edges or cause local damage on prolonged retention.

B)Superporous hydrogels[S.J. Hwang et.al.,J. Chen et.al. J. Chen et.al.]:
With pore size ranging between 10 nm and 10 µm, absorption of water by conventional hydrogel is a very slow process and several hours may be needed to reach an equilibrium state, during which premature evacuation of the dosage form may occur. Superporous hydrogels, average pore size >100 µm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores.

Figure No.08:- Superporous hydrogels.



C) Mucoadhesive systems [Y. Huang et.al.]:
The basis of mucoadhesion is that a dosage form can stick to the mucosal surface by different mechanisms. Different theories are invoked to explain these mechanisms.
Firstly, the electronic theory proposes attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material. Secondly, the adsorption theory suggests that bioadhesion is due to secondary forces such as Van der Waals forces and hydrogen bonding.

D) Magnetic systems [R. Groning et.al.]:
These systems are based on a simple idea: the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

MATERIALS AND METHODS

I. Materials:

i) The drug Carbonyl iron was generously supplied as a gift sample by ISP Technologies
ii) The polymers Hydroxypropylmethyl cellulose K4M and Hydroxypropylmethyl cellulose K15M were kindly gifted by Colorcon Asia Pvt. Ltd., Goa , India.
iii) Sodium alginate was kindly supplied by ISP Technologies.
iv)Carbopol 934, talc, magnesium stearate and concentrated hydrochloric acid were obtained from Loba Chemie Pvt. Ltd., Mumbai, India.
v)Sodium bicarbonate, aerosil, citric acid, and strong ammonia solution were purchased from Research Lab, Mumbai, India.

II. Instruments:

i) Double beam UV Spectrophotometer,Model No. V-530, Make: Jasco Corporation, Tokyo, Japan.

ii) Fourier Transform Infrared Spectrophotometer,Model No. FT/IR-4100, Make: Jasco Corporation, Tokyo, Japan.
iii) Brookfield Viscometer,Model No.CAP-2000,Make: Brookfield Engineering Lab Inc, Middleboro, MA-02346, USA.
iv) Electronic weighing balance,Model No. CB-330,Make: Contech Instruments Ltd., Navi Mumbai, India.
v) Electrolab Dissolution apparatus,Model No. TDT-08L
vi) Vernier calipers,Absolute Digimatic No. 107
vii) Bulk density apparatus.
viii) X-ray machine
a)Siemens 300 MA Klinoscope, Pleophos D X-ray machine.
b) Computerized X-ray Plate,Kodak CR 500, Computed Radiography system.
c) X-ray Printer,Kodak Dry View 8200 Laser Images.

III. PREFORMULATION

A] Characterization of carbonyal Iron:

i) Bulk density [A.W. Newman et.al.]**:**
For the determination of bulk density, a weighed amount of powder was poured into the graduated cylinder via a large funnel and the resulting volume was measured.
ii) Tap density[A.W. Newman et.al.]***:***
This was determined by tapping the graduated cylinder by keeping the cylinder, containing a known quantity of powder, in a bulk density apparatus and volume after tapping was measured.
iii) Solubility Profile[A.Martin et.al.]:
The solubility of the drug was checked in various solvents. This was done by dissolving a known quantity of carbonyl iron in different solvents like distilled water, boiling distilled water, chloroform, diethyl ether and 0.1N HCl.

iv) Assay of iron content in carbonyl iron [Indian Pharmacopoeia 1996 Vol. I]**:**
The drug content of each formulation was determined by the assay method for iron. 0.5 g of powder was dissolved in a mixture of 15 ml distilled water and 1 ml concentrated sulfuric acid and was warmed until the dark brown colour changed to yellow. After cooling the solution to 15^0C, 0.02M potassium permanganate was added dropwise till pink colour persisting for 5 seconds was obtained. To above solution, 15 ml of concentrated hydrochloric acid and 2 g potassium iodide was added and the solution was allowed to stand for 3 minutes. Then 60 ml of distilled water was added to this solution. It was then titrated with 0.1 M sodium thiosulphate using starch solution as indicator.
The factor is,Each ml of 0.1M sodium thiosulphate is equivalent to 0.005585 g of iron

v) Calibration curve for carbonyl iron:
50 mg of carbonyl iron was accurately weighed. It was dissolved in 100 ml of 0.1N HCl, to get a stock solution of 500 µg/ml. From this stock solution 10ml of solution was pipetted and diluted to 50ml with 0.1N HCl, to get a final stock solution of 100 µg/ml. From this stock solution working aliquots were prepared by diluting specific volume of stock solution with 1ml ammonium thiocyanate, 1ml ammonium citrate and 3ml dilute ammonia solution and distilled water. The maximum absorbance was measured at 530 nm. by Jasco V-530 Spectrophotometer, Jasco Corporation, Tokyo, Japan.

B] Characterization of polymers:

i) Viscosity of polymers:

a) Determination of the viscosity of Hydroxypropylmethyl cellulose K4M [R.C. Rowe et.al., A. K. Joshi et.al.]:

The viscosity of 2% w/v solution of Hydroxypropylmethyl cellulose K4M was determined by dispersing and thoroughly hydrating the polymer in about 20-30% of the required amount of water. The water was vigorously stirred and heated to 80-90^{0}C, followed by the addition of the remaining polymer. Cold water was then added to produce the required volume.

b) Determination of the viscosity of Hydroxypropylmethyl cellulose K15M[R.C.Rowe et.al.]:

The viscosity of 2% w/v solution of Hydroxypropylmethyl cellulose K15M was determined by dispersing and thoroughly hydrating the polymer in about 20-30% of the required amount of water. The water was vigorously stirred and heated to 80-90^{0}C, followed by the addition of the remaining polymer. Cold water was then added to produce the required volume.

c) Determination of the viscosity of Sodium alginate[R.C.Rowe et.al.]:

The viscosity of a 2% w/v solution of sodium alginate was determined by dispersing the required amount of polymer in water. The viscosity was calculated with the help of Brookfield viscometer.

d) Determination of the viscosity of Carbopol 934 [R.C. Rowe et.al.]:

The viscosity of a 0.5% solution of Carbopol 934 was determined. The required amount of polymer was first dispersed into vigorously stirred water taking care to avoid the formation of indispersible lumps. It was then neutralized by the addition of sodium hydroxide. During preparation of the gel, the solution was agitated slowly to avoid introducing air bubbles.

iii)Infrared spectra of polymers:

The infra red spectrum of each polymer was determined by mixing a small quantity of previously dried potassium bromide with the respective polymer.

Table No.02:- Formulation of batches P1 to P8 for carrying out preliminary trials in 0.1N HCl.

Sr. No	Ingredients (mg)	Formulation No.							
		P1	P2	P3	P4	P5	P6	P7	P8
1.	Carbonyl iron	44.5	44.5	44.5	44.5	44.5	44.5	44.5	44.5
2.	HPMC K4M	20.0	20.0	20.0	13.5	13.5	20.0	20.0	15.0
3.	HPMC K15M	20.0	20.0	20.0	7.5	-	25.0	25.0	30.0
4.	Carbopol 934	-	-	-	-	7.5	-	-	-
5.	Polyplasdone	-	-	4.0	-	-	5.0	-	-
6.	Sodium alginate	-	-	-	-	-	-	-	-
7.	Citric acid	-	-	-	-	-	-	-	-
8.	Sodium bicarbonate	2.0	4.0	-	2.0	2.0	-	5.0	5.0
9.	Calcium carbonate	-	-	-	-	-	-	-	-
10.	Talc	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
11.	Aerosil	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
12.	Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Total weight (mg)	89.5	91.5	91.5	70.5	70.5	97.5	97.5	97.5

IV. Formulations:

Method of preparation of formulations:

All the formulations were prepared by using dry mixing method. All the ingredients used in the formulation were initially passed through sieve #40 separately before mixing. The required quantity of carbonyl iron and various polymers were weighed according to the formulation and transferred to a mortar and triturated for thorough mixing. To the above mixture was added talc and aerosil and was further mixed for 2 minutes. Finally to this mixture, magnesium stearate was

added and mixed further for 2 minutes. The required calculated weight of the drug and polymer mixture was weighed and was filled in hard gelatin capsule of size 2.

A] Formulations for preliminary trials:

The capsules for the preliminary trials consisted of the following ingredients. Please refer Table 2 & 3.

Table No. 03:- Formulation of batches P9 to P16 for carrying out preliminary trials in 0.1N HCl.

Sr. No	Ingredients (mg)	Formulation No.							
		P9	P10	P11	P12	P13	P14	P15	P16
1.	Carbonyl iron	44.5	44.5	44.5	44.5	44.5	44.5	44.5	44.5
2.	HPMC K4M	20.0	20.0	15.0	15.0	15.0	20.0	40.0	-
3.	HPMC K15M	-	25.0	30.0	30.0	-	35.0	-	30.0
4.	Carbopol 934	-	-	-	-	-	-	-	15.0
5.	Polyplasdone	-	2.0	-	-	-	-	-	-
6.	Sodium alginate	25.0	-	-	-	30.0	30.0	50	-
7.	Citric acid	-	-	5.0	-	-	-	-	-
8.	Sodium bicarbonate	5.0	-	-	10.0	10.0	10.0	-	25.0
9.	Calcium carbonate	-	-	-	-	-	-	15	-
10.	Talc	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
11.	Aerosil	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
12.	Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Total weight (mg)	97.5	94.5	97.5	102.5	102.5	142.5	152.5	117.5

B] Optimization of polymer quantity:

The capsules containing Hydroxypropylmethyl cellulose K4M and Hydroxypropylmethyl cellulose K15M did not burst and also showed good floating properties. Hence, it was decided to optimize the quantity of the above two polymers. Please refer Table 4.

This was done by varying the quantity of the drug while keeping the amount of polymers constant. The swelling properties of each capsule were noted in 0.1N HCl at 37 ± 0.5^{0}C.

Table No.04:- Formulation of batches H17 to H20 for carrying out trials for optimization of polymer quantity in 0.1N HCl.

Sr. No.	Ingredients (mg)	Formulation No.			
		H17	H18	H19	H20
1.	Carbonyl iron	10.0	20.0	30.0	44.5
2.	HPMC K4M	20.0	20.0	20.0	20.0
3.	HPMC K15M	35.0	35.0	35.0	35.0
4.	Sodium bicarbonate	10.0	10.0	10.0	10.0
5.	Talc	1.0	1.0	1.0	1.0
6.	Aerosil	1.0	1.0	1.0	1.0
7.	Magnesium stearate	1.0	1.0	1.0	1.0
	Total weight (mg)	78.0	88.0	98.0	112.5

C] Formulation of capsules after optimization of polymers:

After optimizing the quantity of Hydroxypropylmethyl cellulose K4M and Hydroxypropylmethyl cellulose K15M, trials were again carried out. Formulations containing Sodium alginate and Carbopol 934 were also prepared. Please refer Table 05.

Table No.05:- Formulation of batches O21 to O26 for carrying out trials after optimization of polymer quantity in 0.1N HCl.

Sr No	Ingredients (mg)	Formulation No.					
		O21	O22	O23	O24	O25	O26
1	Carbonyl Iron	44.5	44.5	44.5	44.5	44.5	44.5
2	HPMC K4M	44.5	44.5	44.5	--	--	40.0
3	HPMC K15M	77.9	77.9	77.9	77.9	--	--
4	Carbopol 934	--	--	--	--	--	--
5	Polyplasdone	10.0	20.0	--	--	--	--
6	Sodium alginate	--	--	--	44.5	77.9	77.9
7	Citric acid	--	--	16.0	--	--	--
8	Sodium bicarbonate	10.0	10.0	22.3	--	--	--
9	Calcium carbonate	--	--	--	22.3	15.0	15.0
10	Talc	1.0	1.0	1.0	1.0	1.0	1.0
11	Aerosil	1.0	1.0	1.0	1.0	1.0	1.0
12	Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0
	Total Weight (mg.)	189.9	145.4	189.9	192.2	140.4	180.4
	Duration of Floating (Hrs.)	B	B	B	B	2	2
	Percent cumulative drug released.	NS	NS	NS	NS	66.09	40.02

Where
B : Capsule Bursted
NS: Dissolution not seen

D] Optimization of quantity of sodium bicarbonate:

The results of above trials showed that only the formulations containing sodium bicarbonate displayed promising results. Hence, it was decided to fix the quantity of sodium bicarbonate by optimizing it. The following formulations were prepared for optimization trials. Please refer Table no.06.

Table No. 06:- Formulation of batches N1 to N4 for carrying out trials for optimization of sodium bicarbonate quantity in 0.1N HCl.

Sr.No	Ingredients (mg)	Formulation No.			
		N1	N2	N3	N4
1.	Carbonyl iron	44.5	44.5	44.5	44.5
2.	HPMC K4M	44.5	44.5	44.5	44.5
3.	HPMC K15M	77.9	77.9	77.9	77.9
4.	Sodium bicarbonate	20.0	22.3	25.0	27.5
5.	Talc	1.0	1.0	1.0	1.0
6.	Aerosil	1.0	1.0	1.0	1.0
7.	Magnesium stearate	1.0	1.0	1.0	1.0
	Total weight (mg)	189.9	192.2	194.9	197.4

E] Optimization of formulations by factorial design [S.V. Shirolkar et.al]:

Factorial designs are used in experiments where the effects of different factors, or conditions, on experimental results are to be elucidated. They are the designs of choice for simultaneous determination of the effects of several factors and their interactions.

In the absence of interactions, factorial designs have maximum efficiency in estimating main effects. If interactions exist, factorial designs are necessary to reveal and identify the interactions. Since factor effects are measured over varying level effects of other factors, conclusions apply to a wide range of conditions. Maximum use is made of the data since all main effects and interactions are calculated from all of the data. Finally, factorial designs are orthogonal; all

estimated effects and interactions are independent of effects of other factors.In the present study, after fixing the quantity of Hydroxypropylmethyl cellulose K4M, Hydroxypropylmethyl cellulose K15M and sodium bicarbonate, these values were put in a 3^2 factorial design to see which formulation showed the most favourable results.

In this factorial design 2 factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations The amounts of Hydroxypropylmethyl cellulose K4M (X_1) and Hydroxypropylmethyl cellulose K15M (X_2) were selected as independent variables while all the other quantities remained constant. Percent cumulative drug release and duration of floating were selected as dependent variables.

Table No. 07:- Variable levels used in factorial design

Batch Code	Variable Level in Coded Form	
	X_1	X_2
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

Table No.08:- Coded values and actual values used in factorial design

Coded Values	Actual Values	
	X_1	X_2
-1	15	30
0	20	35
1	44.5	77.9

The following formulations were prepared for factorial design. Please refer Table 09.

Table No.9:- Formulation of batches F1 to F4 for carrying out trials for factorial design in 0.1N HCl.

Sr.No	Ingredients (mg)	Formulation No.								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Carbonyl iron	44.5	44.5	44.5	44.5	44.5	44.5	44.5	44.5	44.5
2.	HPMC K4M	15.0	15.0	15.0	20.0	20.0	20.0	44.5	44.5	44.5
3.	HPMC K15M	30.0	35.0	77.9	30.0	35.0	77.9	30.0	35.0	77.9
4.	Sodium bicarbonate	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
5.	Talc	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
6.	Aerosil	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
7.	Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Total weights (mg)	**117.5**	**122.5**	**165.4**	**122.5**	**127.5**	**170.4**	**147.0**	**152.0**	**194.9**

V. Evaluation of formulations prepared by factorial design:

The formulations prepared by factorial design were evaluated using the following parameters

A] Bulk density [W.A.Newman et.al., A.Sayeed et.al.]:

The bulk density of the powder was determined by pouring the powder into a graduated cylinder via a large funnel and measuring the resultant volume.

B] Tap density [W.A.Newman et.al.]:

The tap density of the powder was determined by tapping the graduated cylinder, after keeping it in a bulk density apparatus. The resultant volume after tapping was then measured.

C] Angle of repose [W.A.Newman et.al.]:
Angle of repose has been used as an indirect method of quantifying powder flowability, because of its relationship with inter particular cohesion. Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and the horizontal plane. The angle of repose for the powder of each formulation was determined by funnel method. The powder mass was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This formed the pile of powder on the paper.

D] Determination of floating lag time [A.K.Srivastava et.al.]**:**
The floating lag time is defined as the time taken by the capsule to reach the top from the bottom of the dissolution flask. The floating lag time of capsules was determined by using a USP (type II) dissolution apparatus containing 900 ml of 0.1N HCl at 37 ± 0.5^0.

E] Determination of duration of floating[A.K.Srivastava et.al]:
The time for which the formulation floats constantly on the surface of the medium is known as the duration of floating.The duration of floating of capsules was determined by using a USP (type II) dissolution apparatus containing 900 ml of 0.1N HCl at 50 rpm and 37 ± 0.5^0.

F] Determination of swelling index [A. El-Kamel et.al., M. Chandira et.al.]:
The swelling index of capsules was determined in 0.1N HCl at room temperature. The initial weight of capsule was noted. It was then introduced in 5 ml of 0.1N HCl. The swollen weight of capsule was determined after every hour.

G] Determination of drug content [Indian Pharmacopoeia 1996 Vol. I]:
The drug content of each formulation was determined by the assay method for iron. 0.5 g of powder was dissolved in a mixture of 15 ml distilled water and 1 ml concentrated sulfuric acid and was warmed until the dark brown colour changed to yellow. After cooling the solution to 15^0C, 0.02M potassium permanganate was added dropwise till pink colour persisting for 5 seconds was obtained. To above solution, 15 ml of concentrated hydrochloric acid and 2 g potassium iodide was added and the solution was allowed to stand for 3 minutes. Then 60 ml of distilled water was added to this solution. It was then titrated with 0.1 M sodium thiosulphate using starch solution as indicator.

The factor is,Each ml of 0.1M sodium thiosulphate is equivalent to 0.005585 g of iron.

H] In vitro dissolution [GL Chen et.al., B.V.Basavaraj et.al.]:
The drug release studies were performed in USP (type II) dissolution apparatus at 50 rpm in 900 ml 0.1N HCl at 37 ± 0.5^0. 10 ml aliquots were withdrawn after each hour and the volume of the dissolution medium was maintained by adding the same volume of fresh dissolution medium. Each sample was filtered through Whatman no. 1 filter paper. Ammonium thiocyanate, ammonium citrate and dilute ammonia solution was added to 1 ml of sample in a 10 ml volumetric flask. The volume was made up to the mark by distilled water. The absorbance of this solution was measured at 530 nm using Jasco V-530 spectrophotometer. Drug concentrations in the sample were determined using the standard curve.

I] In vivo evaluation for floating behavior [Y.Machida et.al.]:
In vivo evaluation for floating behaviour of optimized formulation was done in a healthy volunteer under fasted condition. Barium sulphate was added to the optimized formulation [F9] (instead of drug) and the density was matched to the density of the formulation with drug. The capsule was administered along with 200 ml of water. Roentgenograms were obtained from zero

till six hours using Siemens 300 MA Klinoscope, Pleophos D X-ray machine. The images were recorded on the computerized plate, Kodak CR 500, Computed Radiography system. They were printed by using the printer, Kodak Dry View 8200 Laser Images.

RESULTS AND DISCUSSION

I.Results of preformulation studies:

A] Results of characterization of carbonyl iron:

i) Bulk density and tap density *:*

The bulk density of carbonyl iron was found to be 2.5 g/ml. The tap density of carbonyl iron was found to be 5 g/ml. The high value of bulk density and tap density indicates that the pure drug was a denser material and to make the drug buoyant in stomach the density had to be considerably reduced

ii)Solubility Profile:

10 mg of carbonyl iron was taken and solubility profile was done.

Table No. 10:- Solubility profile of carbonyl iron.

Sr. No.	Solvent	ml of solvent required	Remarks
1.	Distilled water	10.0	Soluble.
2.	Boiling distilled water	30.0	Sparingly soluble.
3.	Chloroform	30.0	Sparingly soluble.
4.	Diethyl ether	100.0	Slightly soluble.
5.	0.1N HCl.	10.0	Soluble.

The results of solubility profile confirmed that the drug had considerable solubility in acidic conditions : the condition in which drug formulation is developed.

iii) Assay of iron content in carbonyl iron :

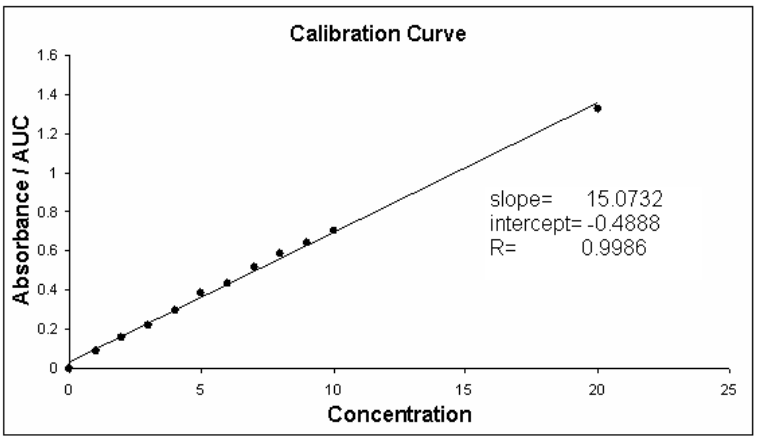
The content of iron in carbonyl iron was determined using titrimetric method and was found to be 97.73 % .The result is in accordance to the claim made by the manufacturer that the carbonyl iron powder contains 98% of elemental iron.

iv) Calibration curve for carbonyl iron:

Table No. 11:- Absorbance for standard curve in 0.1 N HCl.

Sr. No.	Concentration of drug (µg/ml)	Absorbance
1.	0	0.0000
2.	1	0.0923
3.	2	0.1565
4.	3	0.2231
5.	4	0.2993
6.	5	0.3850
7.	6	0.4337
8.	7	0.5156
9.	8	0.5880
10.	9	0.6405
11.	10	0.7042
12.	20	1.3267

Figure No. 09:- Calibration curve of Carbonyl iron in 0.1N HCl



The various working aliquots of carbonyl iron prepared from stock solution of 100µg/ml.showed the following absorbances (Table No.11).and the plot of the calibration curve showed linearity which indicates that the solution in concentration range of 1 to 20 µg/ml. obeys Beer-Lambert's law. The calibration curve was further used to calculate the release of drug from various formulations.

B] Results of characterization of polymers:

i)Viscosity of polymers:

For characterization of polymers used in the present study the viscosities were determined and compared with the reported value and spectra by FTIR of the polymer were taken. The evaluating parameters agreed with reported parameters.

a)Viscosities of various polymers

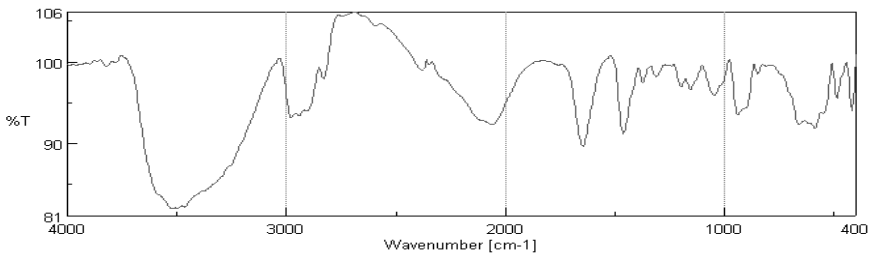
Table No.12:- Viscosities of polymers used.

Sr. No	Polymer	Viscosity obtained(mPa.s)	Viscosity reported(mPa.s)
1	HPMC K4M	3000 – 4000	2308 – 3755
2	HPMC K15M	13500- 15000	12000-21000
3	Sodium alginate	250 – 300	100 – 300
4	Carbopol 934	35500- 39000	30500 – 39400

ii) Infrared spectra of polymers:

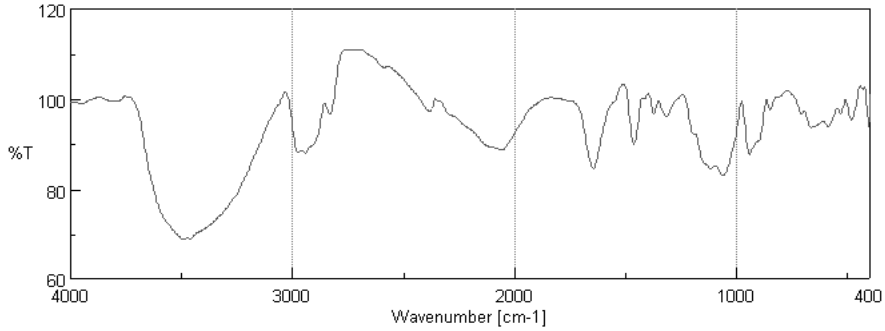
a) Infrared spectrum of Hydroxypropylmethyl cellulose K4M

Figure No.10:- IR spectrum of HPMC K4M



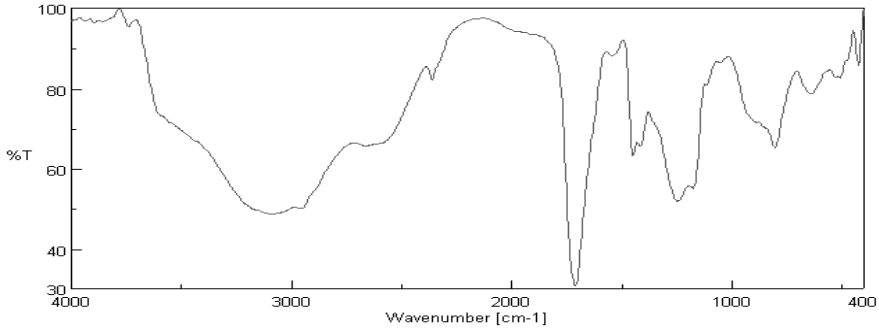
b) Infrared spectrum of Hydroxypropylmethyl cellulose K15M

Figure No. 11:- IR spectrum of HPMC K15M



c)Infrared spectrum of Carbopol 934

Figure No.12:- IR spectrum of Carbopol 934



II. Formulations:

A] Formulations for preliminary trials**:**

The following are the results for formulations prepared for preliminary trials. Please refer Table 13 & 14.

Table No. 13:- Floating properties and percent cumulative drug released of P1 – P8 in 0.1N HCl.

Sr. No	Ingredients (mg)	Formulation No.							
		P1	P2	P3	P4	P5	P6	P7	P8
1.	Carbonyl iron	44.5	44.5	44.5	44.5	44.5	44.5	44.5	44.5
2.	HPMC K4M	20.0	20.0	20.0	13.5	13.5	20.0	20.0	15.0
3.	HPMC K15M	20.0	20.0	20.0	7.5	-	25.0	25.0	30.0
4.	Carbopol 934	-	-	-	-	7.5	-	-	-
5.	Polyplasdone	-	-	4.0	-	-	5.0	-	-
6.	Sodium alginate	-	-	-	-	-	-	-	-
7.	Citric acid	-	-	-	-	-	-	-	-
8.	Sodium bicarbonate	2.0	4.0	-	2.0	2.0	-	5.0	5.0
9.	Calcium carbonate	-	-	-	-	-	-	-	-
10.	Talc	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
11.	Aerosil	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
12.	Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Total weight (mg)	89.5	91.5	91.5	70.5	70.5	97.5	97.5	97.5
	Duration of floating(hrs.)	2	2	3	4	3	4	-	5
	Drug release seen as long as the capsule floated (%)	40.26	45.01	55.19	75.25	68.12	69.57	-	80.92

Table No. 14:- Floating properties and percent cumulative drug release of P9 to P15 in 0.1 N HCl.

Sr. No	Ingredients (mg)	Formulation No.						
		P9	P10	P11	P12	P13	P14	P15
1.	Carbonyl iron	44.5	44.5	44.5	44.5	44.5	44.5	44.5
2.	HPMC K4M	20.0	15.0	15.0	15.0	20.0	40.0	-
3.	HPMC K15M	25.0	30.0	30.0	-	35.0	-	30.0
4.	Carbopol 934	-	-	-	-	-	-	15.0
5.	Polyplasdone	2.0	-	-	-	-	-	-
6.	Sodium alginate	-	-	-	30.0	30.0	50	-
7.	Citric acid	-	5.0	-	-	-	-	-
8.	Sodium bicarbonate	-	-	10.0	10.0	10.0	-	25.0
9.	Calcium carbonate	-	-	-	-	-	15	-
10.	Talc	1.0	1.0	1.0	1.0	1.0	1.0	1.0
11.	Aerosil	1.0	1.0	1.0	1.0	1.0	1.0	1.0
12.	Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Total weight (mg)	94.5	97.5	102.5	102.5	142.5	152.5	117.5
	Duration of floating (hrs.)	B	5	5	B	4	3	1
	Drug release seen as long as the capsule floated (%)	NS	83.92	80.96	NS	70.08	50.29	16.2

Where
B: Capsule bursted
NS : Dissolution not seen

In the preliminary trial formulations, various polymers like HPMC K4M, HPMC K15M, Sodium alginate and Carbopol 934 were tried, along with various channelizing agents and gas generating agents. In formulations P1 and P2, HPMC K4M and HPMC K15M were used in the same quantity and only the concentration of sodium bicarbonate was changed. The capsules floated for about two hours indicating the polymers used were not sufficient to make the capsule buoyant. In trial P3 the concentration of HPMC K4M and HPMC K15M was similar to P1 and P2 but instead of sodium bicarbonate, Polyplasdone was added, as Polyplasdone has got the property to imbibe water and swell so it was thought that floating behaviour showed enhance swelling behaviour. The result indicated that capsule floated for 3 hours and bursted after 3 hours. Hence in the next trial formulation it was decided to reduce the concentration of HPMC K4M and HPMC K15M while keeping the concentration of sodium bicarbonate as 2 mg. The capsule floated for 4 hours but the release of drug from the capsule was high, as 75% of drug got released within 4 hours which was not desirable.

To control the fast release of drug it was decided to use Carbopol 934 as it forms a strong matrix. But with Carbopol 934 the capsules were able to float only for 3 hours.

Thus the concentration of HPMC K4M and HPMC K15M was increased and also the quantity of Polyplasdone and sodium bicarbonate was increased but still the capsules were not able to float for 8 hours.

Trial formulations were prepared by changing the quantity of HPMC K4M and HPMC K15M and by using the channelizing agents as sodium bicarbonate, Polyplasdone, citric acid in formulations from P9 to P11. P9 formulation was not able to float, but formulations P10 and P11 showed floating for 5 hours with almost 80% of drug release in 5 hours.

Trial formulations were then prepared using various combinations of HPMC K4M and Sodium alginate. By varying the ratio of HPMC K4M, HPMC K15M and Sodium alginate, capsules P12 & P13 were prepared using sodium bicarbonate as gas generating agents.

P12 was not able to float at all and sank immediately with bursting. Literature review suggested that Sodium alginate has gelling properties in presence of calcium ions, hence formulation P14 it was decided to add calcium carbonate which showed a positive result with capsule floating for 3 hours and percent release of 50.29%.

B] Optimization of polymer quantity:

Table No. 15:- Swelling properties of formulations prepared for optimization of polymer quantity in 0.1 N HCl.

Sr. No.	Ingredients (mg)	Formulation No.			
		H17	H18	H19	H20
1.	Carbonyl iron	10.0	20.0	30.0	44.5
2.	HPMC K4M	20.0	20.0	20.0	20.0
3.	HPMC K15M	35.0	35.0	35.0	35.0
4.	Sodium bicarbonate	10.0	10.0	10.0	10.0
5.	Talc	1.0	1.0	1.0	1.0
6.	Aerosil	1.0	1.0	1.0	1.0
7.	Magnesium stearate	1.0	1.0	1.0	1.0
	Total weight (mg)	**78.0**	**88.0**	**98.0**	**112.5**
	Observation based on capsule swelling	Less swelling	Maximum swelling	Less swelling	Less swelling

Hence it was decided to optimize the concentration of the polymers HPMC K4M and HPMC K15M by varying the concentration of carbonyl iron and keeping the concentration of effervescent agent constant. The results showed that in formulations from H17 – H20, the maximum swellability and floating was seen in formulation H18 where the concentration of carbonyl iron and HPMC K4M was 1:1.and concentration of carbonyl iron and HPMC K15 M was 1:1.75 .Thus for further formulations it was decided to calculate the quantity of polymer as per H18 formulation, keeping the ratio of polymer similar to H18.

C] Formulation of capsules after optimization of polymers:

Table No.16:- Floating properties and percent cumulative drug release of O21 - O26 in 0.1 N HCl.

Sr. No	Ingredients (mg)	Formulation No.					
		O21	O22	O23	O24	O25	O26
1	Carbonyl Iron	44.5	44.5	44.5	44.5	44.5	44.5
2	HPMC K4M	44.5	44.5	44.5	--	--	40.0
3	HPMC K15M	77.9	77.9	77.9	77.9	--	--
4	Carbopol 934	--	--	--	--	--	--
5	Polyplasdone	10.0	20.0	--	--	--	--
6	Sodium alginate	--	--	--	44.5	77.9	77.9
7	Citric acid	--	--	16.0	--	--	--
8	Sodium bicarbonate	10.0	10.0	22.3	--	--	--
9	Calcium carbonate	--	--	--	22.3	15.0	15.0
10	Talc	1.0	1.0	1.0	1.0	1.0	1.0
11	Aerosil	1.0	1.0	1.0	1.0	1.0	1.0
12	Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0
	Total Weight (mg.)	189.9	145.4	189.9	192.2	140.4	180.4
	Duration of Floating (hrs)	B	B	B	B	2	2
	Percent cumulative drug released.	NS	NS	NS	NS	66.09	40.02

Where

B : Capsule bursted; NS: Dissolution not seen

Thus after optimization of polymer ratio, it was thought to use Polyplasdone & sodium bicarbonate together so as to get the maximum swelling and floating. But formulation O21 was not able to float and bursted immediately. As the concentration of Polyplasadone used in O21 may have helped in disintegration of capsule, since in lower concentration Polyplasdone acts as superdisintegrant.In the next formulation O22, it was decided to increase the quantity of Polyplasdone and observe the effect of Polyplasdone on swelling and floating of capsule. But still the capsules were not able to float and bursted immediately. After this trial it was decided to exclude Polyplasdone from further studies.Formulation using the gas generating system citric acid & sodium bicarbonate in trial O23 but the capsules were did not float and they bursted. Hence citric acid was also excluded from study as it was not showing any positive contribution.

Formulations were tried using Sodium alginate and its combination either with HPMC K4M and HPMC K15M in trial O24 & O25 but both the trials did not show any positive result. Trials were also carried out using only Sodium alginate in formulation O26 but again the results were not promising. Hence it was decided to carry out further studies using HPMC K4M, HPMC K15M and sodium bicarbonate.

D] Optimization of quantity of sodium bicarbonate:

Table No.17:- Floating properties of N1 – N4 in 0.1 N HCl.

Sr.No	Ingredients (mg)	Formulation No.			
		N1	N2	N3	N4
1.	Carbonyl iron	44.5	44.5	44.5	44.5
2.	HPMC K4M	44.5	44.5	44.5	44.5
3.	HPMC K15M	77.9	77.9	77.9	77.9
4.	Sodium bicarbonate	20.0	22.3	25.0	27.5
5.	Talc	1.0	1.0	1.0	1.0
6.	Aerosil	1.0	1.0	1.0	1.0
7.	Magnesium stearate	1.0	1.0	1.0	1.0
	Total weight (mg)	189.9	192.2	194.9	197.4
	Duration of floating	5 hours	5 hours	8 hours	4 hours

The gas generating agent which helps in buoyancy of the formulation has to be optimized, because the excessive use of sodium bicarbonate may hamper absorption of formulation by imparting alkaline character to the medium.The optimization is also needed since less concentration of sodium bicarbonate may not be able to aid & assist the polymers in swelling & floating.So it was inevitable to optimize the concentration of sodium bicarbonate.

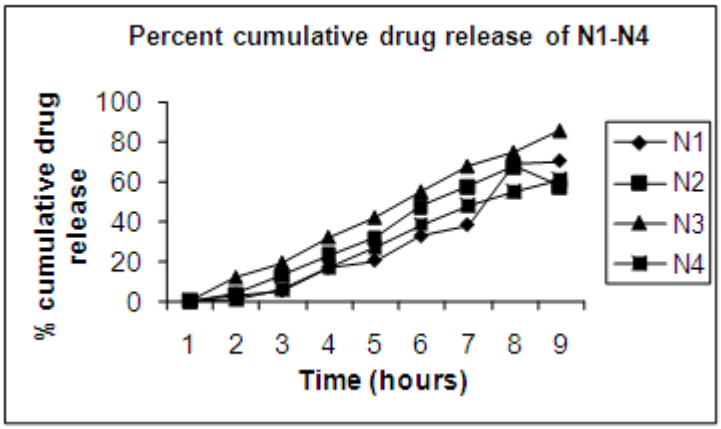
Table No. 18:-Percent cumulative drug released in N1 – N4 in 0.1 N HCl.

Sr.No	Time (hours)	Formulation No. (% cumulative release)			
		N1	N2	N3	N4
1.	0	0	0	0	0
2.	1	3.48	3.80	11.99	1.25
3.	2	5.23	12.81	19.38	6.26
4.	3	16.76	23.06	32.35	16.99
5.	4	20.49	31.54	42.27	26.83
6.	5	32.77	47.80	55.34	38.55
7.	6	38.33	57.56	68.27	47.85
8.	7	69.01	67.89	75.35	55.40
9.	8	70.51	57.88	86.28	61.34

Formulations from N1 to N4 were prepared and their floating behaviour and dissolution was seen for 8 hours. Formulation N3 containing 25mg of sodium bicarbonate showed good floating of capsule for 8 hours along with maximum release (86.28%) of drug.

Hence it was decided to use 25 mg of sodium bicarbonate for further factorial design experiment to study the optimum quantity of HPMC K4M and HPMC K15M.

Figure No.13:- Dissolution profile of N1 -N4 in 0.1 N HCl.



III. Evaluation of formulations prepared by factorial design:

A] Bulk density and tapped density:

The bulk density and tapped density of formulations prepared by factorial design is as follows:

Table No.19:- Bulk density and tapped density of formulations prepared by factorial design

Sr. No.	Formulation	Bulk density (g/cm^3)	Tap density (g/cm^3)
1.	F1	0.7142	0.9090
2.	F2	0.5411	0.8956
3.	F3	0.5555	0.7142
4.	F4	0.5567	0.7089
5.	F5	0.5419	0.7177
6.	F6	0.5498	0.7256
7.	F7	0.5478	0.7045
8..	F8	0.5345	0.7172
9.	F9	0.5263	0.6666

The results indicate that out of the formulations F1 to F9, F9 has the minimum bulk density and tapped density in comparison to other formulations.

B] Angle of repose of formulations prepared by factorial design:

Table No. 20:- Angle of repose values for formulations prepared by factorial design

Sr. No.	Formulation	Angle of repose
1.	F1	21.8
2.	F2	23.58
3.	F3	22.61
4.	F4	21.57
5.	F5	22.57
6.	F6	23.04
7.	F7	21.78
8..	F8	23.94
9.	F9	20.09

The result of angle of repose of all formulations from F1 to F9 is within the range of 20° - 23° indicating that powder posse's good flowability.

C] Determination of floating lag time:

The capsules of all formulations from F1 to F9 started to float immediately after introduction in the dissolution fluid. Thus floating lag time was found to be zero.

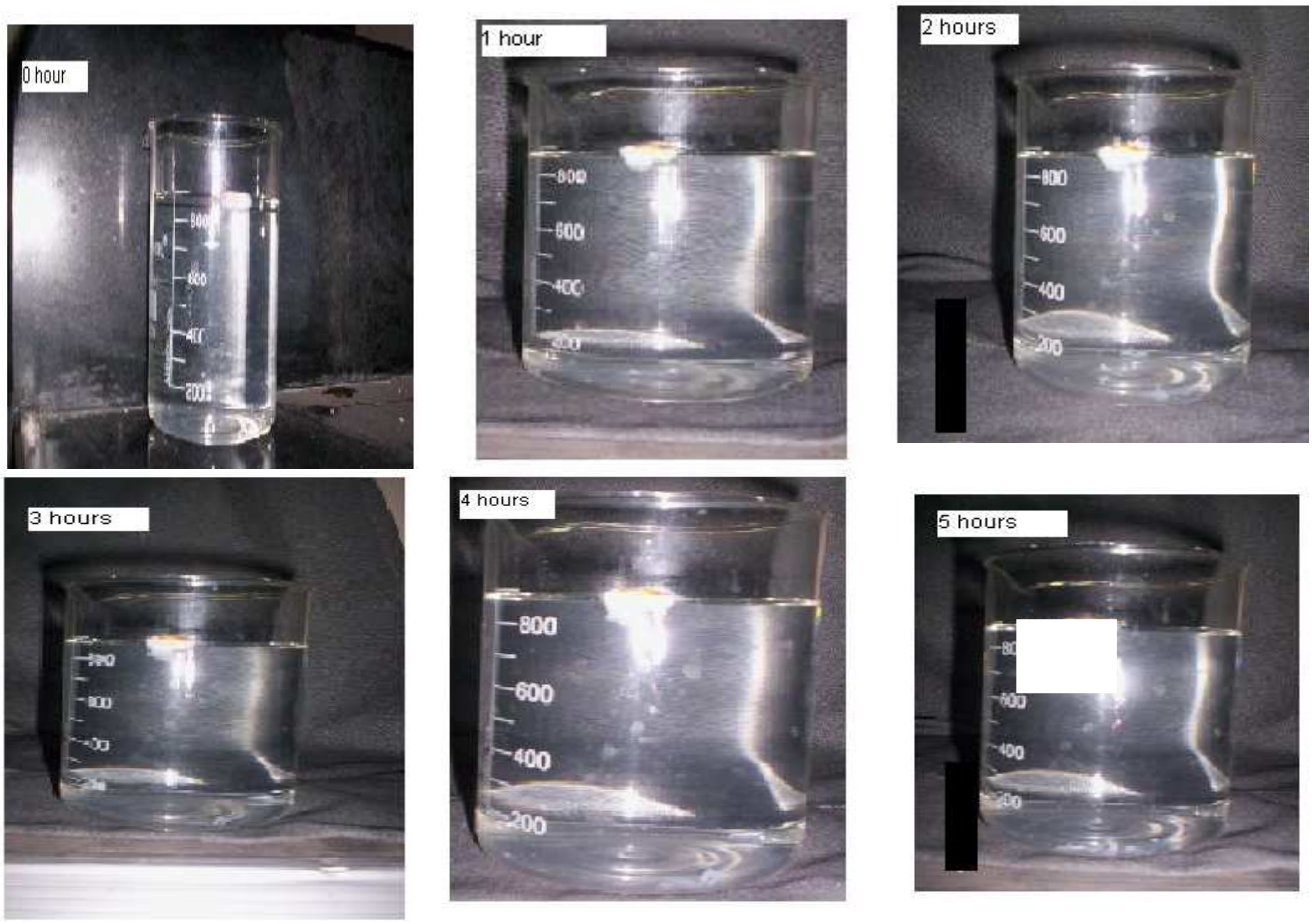
D] Determination of duration of floating:

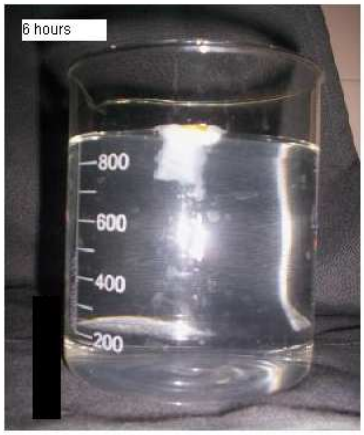
Table No. 21:- Duration of floating of formulations prepared by factorial design.

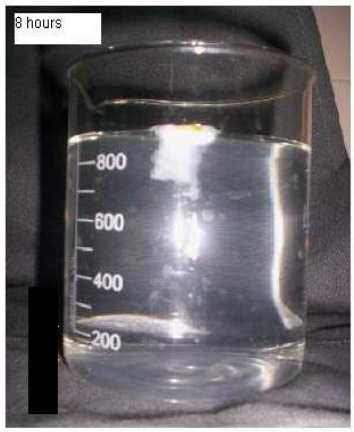
Sr. No.	Formulation	Duration of floating (h)
1.	F1	5.0
2.	F2	5.0
3.	F3	6.0
4.	F4	6.0
5.	F5	7.0
6.	F6	7.0
7.	F7	6.0
8..	F8	7.0
9.	F9	8.0

All formulations from F1 to F9 were studied for their duration of floating in 0.1N HCl maintained at $37.5^{o}C$ at 50 RPM. Formulation F9 floated for almost 8 hours as shown in Figure No.14.

Figure No.14:- Swelling studies of F9







E] Determination of swelling

Swelling index:

The swelling index was determined with the following formula:

$$\text{Swelling index} = \frac{W_t - W_0}{W_0}$$

Where,

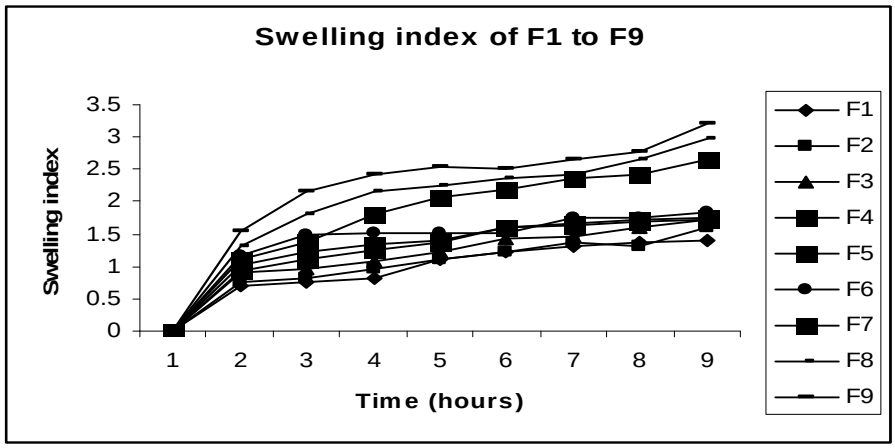
W_0 = initial weight of tablet.

W_t = weight of tablet at time‘t’

Table No. 22:- Swelling index of F1 – F3 in 0.1 N HCl.

Sr. No.	Time (h)	Swelling Index								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	0	0	0	0	0	0	0	0	0	0
2.	1	0.7122±0.25	0.7661±0.15	0.8966±0.11	0.9459±0.12	1.0121±0.11	1.1548±0.14	1.1211±0.23	1.3216±0.44	1.5315±0.23
3.	2	0.7546±0.12	0.8173±0.14	0.9681±0.10	1.1162±0.19	1.2312±0.15	1.4986±0.27	1.3577±0.31	1.7978±0.36	2.1496±0.22
4.	3	0.8121±0.14	0.9737±0.15	1.0893±0.12	1.2568±0.16	1.3519±0.14	1.5060±0.43	1.8122±0.22	2.1619±0.22	2.4261±0.11
5.	4	1.1191±0.26	1.1145±0.16	1.2311±0.14	1.3830±0.15	1.3922±0.12	1.5106±0.39	2.0691±0.24	2.2419±0.21	2.5471±0.12
6.	5	1.2143±0.30	1.2353±0.17	1.4253±0.14	1.6000±0.32	1.6161±0.22	1.5240±0.41	2.1865±0.23	2.3656±0.23	2.5191±0.14
7.	6	1.3146±0.22	1.3569±0.18	1.4596±0.16	1.6463±0.30	1.6543±0.21	1.7413±0.51	2.3663±0.41	2.4132±0.17	2.6510±0.13
8.	7	1.3742±0.11	1.3011±0.17	1.5928±0.18	1.7027±0.35	1.7222±0.15	1.7595±0.44	2.4117±0.12	2.6618±0.15	2.7578±0.21
9.	8	1.4029±0.13	1.5977±0.15	1.7137±0.19	1.7095±0.39	1.7486±0.16	1.8519±0.43	2.6417±0.15	2.9817±0.16	3.2143±0.15

Figure No. 15:- Swelling index of F1 to F9 in 0.1 N HCl.



As per the result obtained after swelling index, it was found that formulation F9 possessed highest swelling index among all the formulation. It swelled approximately three times to its size on the stipulated 8 hours study. High swelling results in formation of a good polymer network which in turn may cause retention of capsule in stomach for longer period of time along with uniform diffusion of drug.

F] Drug content in formulations prepared by factorial design:

Table No. 23:- Drug content values for formulations prepared by factorial design.

Sr. No.	Formulation	Drug content (%)
1.	F1	97.17
2.	F2	97.25
3.	F3	97.64
4.	F4	96.23
5.	F5	96.78
6.	F6	97.56
7.	F7	97.45
8..	F8	97.42
9.	F9	97.66

The average drug content is 97.24%. The results of drug content complies with normally acceptable limits. (95-105%)

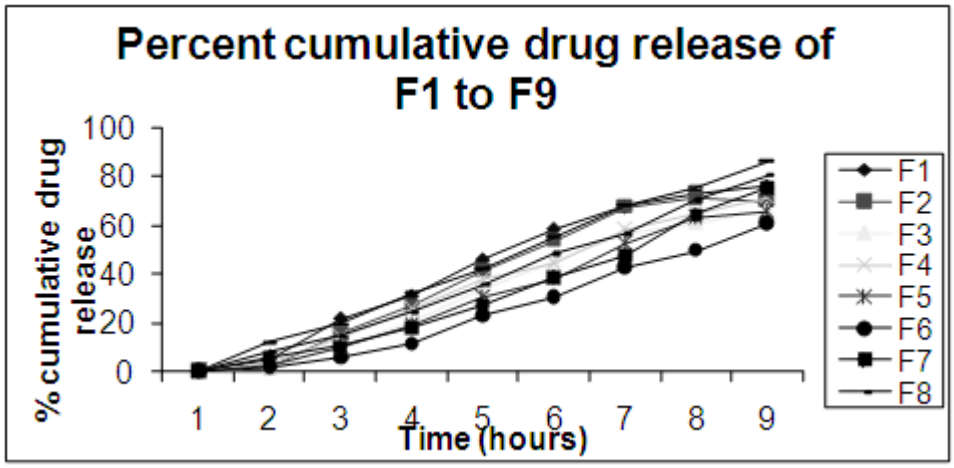
G] In vitro dissolution:

Table No. 24:- Percent cumulative drug released from F1 TO F9 as seen in 0.1 N HCl

Sr. No.	Time (h)	Percent cumulative drug released								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	0	0	0	0	0	0	0	0	0	0
2.	1	4.86 ± 0.81	2.03 ± 0.40	1.73 ± 0.29	3.24 ± 0.27	2.23 ± 0.46	1.69 ± 0.52	5.78 ± 0.67	8.19 ± 0.41	11.99 ± 0.13
3.	2	21.59 ± 0.59	15.24 ± 0.69	10.13 ± 0.41	14.20 ± 0.36	9.62 ± 0.56	5.54 ± 0.54	10.25 ± 0.42	14.38 ± 0.35	19.38 ± 0.35
4.	3	30.87 ± 0.40	26.84 ± 0.52	20.92 ± 0.16	25.63 ± 0.75	19.08 ± 0.67	11.29 ± 0.53	17.97 ± 0.46	24.33 ± 0.52	32.35 ± 0.47
5.	4	45.84 ± 0.33	41.45 ± 0.26	34.08 ± 0.78	37.83 ± 0.13	30.80 ± 0.15	22.76 ± 0.34	27.31 ± 0.13	35.40 ± 0.62	42.27 ± 0.46
6.	5	58.47 ± 0.53	53.78 ± 0.67	45.24 ± 0.28	44.37 ± 0.19	38.12 ± 0.23	30.53 ± 0.77	38.78 ± 0.72	48.21 ± 0.05	55.34 ± 0.55
7.	6	67.79 ± 0.43	67.94 ± 0.37	56.99 ± 0.39	58.41 ± 0.64	52.82 ± 0.36	42.92 ± 0.43	47.63 ± 0.13	56.37 ± 0.15	68.27 ± 0.87
8.	7	73.08 ± 0.26	71.65 ± 0.82	61.05 ± 0.73	65.15 ± 0.18	63.02 ± 0.20	49.57 ± 0.61	64.37 ± 0.50	70.28 ± 0.24	75.35 ± 0.47
9.	8	76.12 ± 0.18	70.29 ± 0.18	66.68 ± 0.47	71.49 ± 0.33	65.81 ± 0.49	60.82 ± 0.60	75.41 ± 0.17	80.27 ± 0.16	86.28 ± 0.12

For all formulations the dissolution studies were carried out in two set of 6 capsules ezach in 0.1N HCl for 8 hours at 50 rpm in apparatus II. The dissolution behaviour and release data indicated F9 as optimised formulation with desired floating behaviour & release of 86.28% at the end of 8 hours.

Figure No.16:- Comparative drug release of F1 to F9



H) In vivo evaluation for floating behavior:

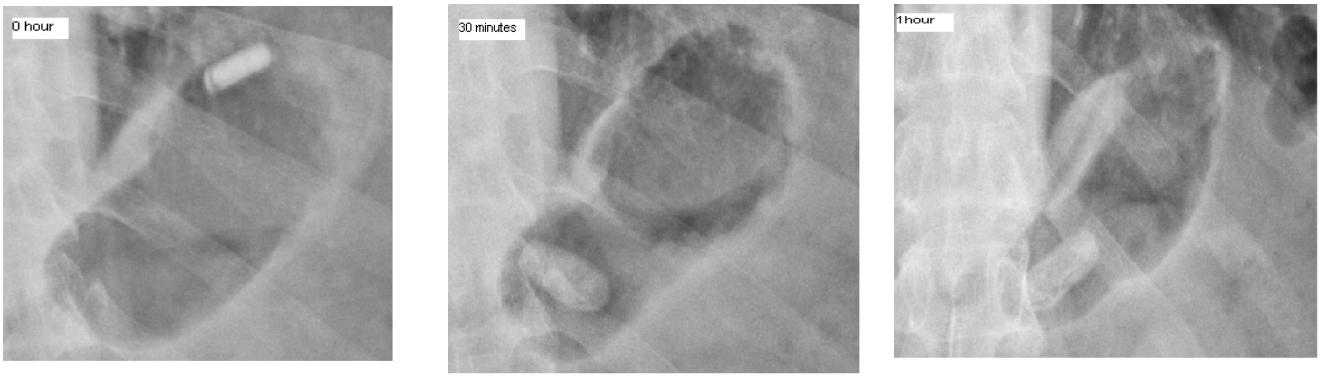
For In vivo evaluation of floating behaviour, a capsule of selected formulation containing barium sulphate was prepared. The density and floating behaviour of this formulation was compared with that of F9.

Table No.25 :-Comparison of F9 formulation and barium sulphate capsule

Sr. No.	Parameters	F9 Formulation with carbonyl iron	F9 formulation with Barium Sulphate
1	Bulk Density (gm/ml)	0.5263	0.5472
2	Floating behaviour (in vitro)	8 hours	8 hours

Density and floating behaviour of barium sulphate formulation was similar to F9 formulation. Capsules of formulation containing barium sulphate floated in healthy volunteer under fasted condition for 6 hours without showing any fragmentation.The capsule of plain barium sulphate of the same density was studied by X-ray in the same conditions. The capsule had sunk and was retained for 1 1/2 hours of ingestion.Hence, it can be inferred that floating behaviour of capsule with formulation was because of developed formulation with the formula.Picture of in vivo floating behaviour as shown in Figure No.17.

Figure No.17:- In vivo Xray studies of F9 formulation containing barium sulphate.



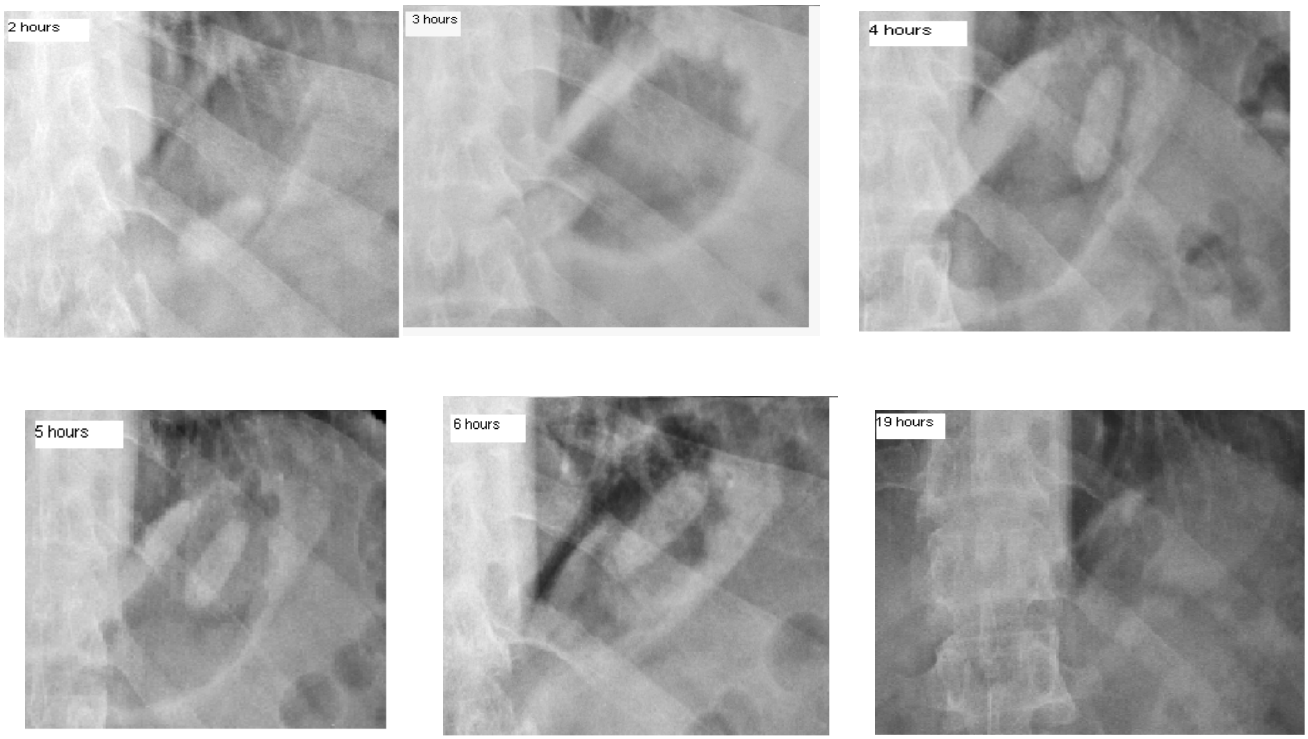
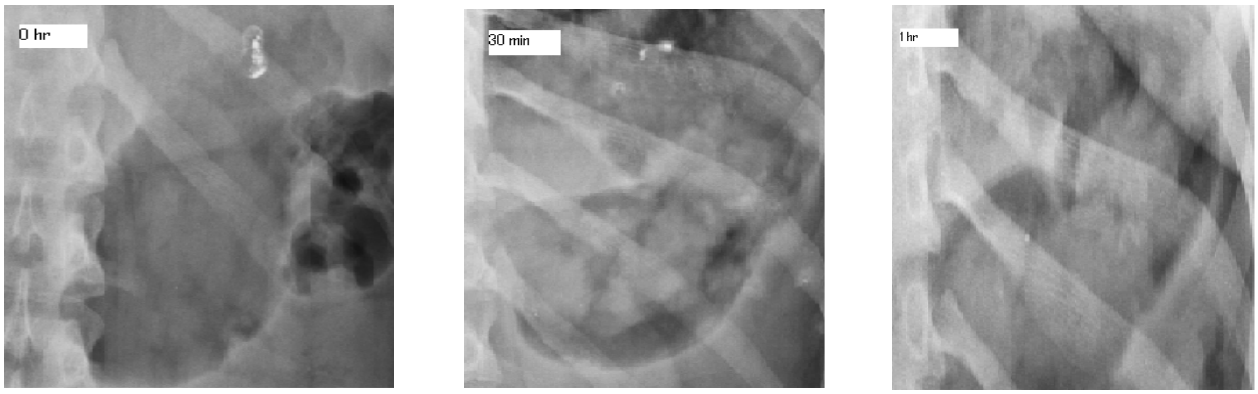


Figure No.18: In vivo Xray studies of capsules containing only b



CONCLUSION

The difficulties in and need of iron therapy prompted present study to develop a formulation of floating drug delivery system of carbonyl iron. Out of the choosen polymers as HPMC K4M, HPMC K15M, Sodium alginate and Carbopol 934, the positive and encouraging results in accordance to the aim have been obtained with HPMC K4M and HPMC K15M. Sodium bicarbonate has been used as the gas generating agent to assist the formulation.

The formula has been optimized using factorial design. The optimized formulation F9 shows maximum drug release with good floating behaviour in vitro. The in vitro floating behaviour has been further confirmed with in vivo floating behaviour of the same formulation.

Future study

The in vitro and in vivo floating behaviour studies need to be confirmed by exhaustive in vivo studies. The in vivo studies in anaemic patients with respect to iron absorbed as compared to conventional iron formulation should be taken up to prove advantages of the developed formulation.

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