# Effect of Effervescent Agents on the Formulation of Famotidine Loaded Sodium Alginate Floating Beads

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## Abstract

Famotidine is histamine $H_2$ receptor antagonist; it is widely used in treatment of gastric ulcer and gastroesophageal reflux disease. The low bioavailability (40-45%), short biological half life (2.5-4 hrs) of famotidine in addition to have an absorption window, this favor the development of controlled release gastroretentive dosage forms of the drug.

In this study, the floating beads of famotidine by ionotropic gelation technique were formulated in two different combinations such as sodium alginate withhydroxypropyl methyl cellulose(HPMC) and sodium alginate with guar gum. The effect of $CO_2$ gas forming agents such as $CaCO_3$ or $NaHCO_3$ on drug loading, % drug entrapment efficiency, floating properties and invitro drug release were evaluated.

It was found that as the ratio of gas forming agents increased from 0.2 to 1 , the floating property was increased for both type of gas forming agents while % entrapment efficiency of famotidine beads are decreased from 86.11 % to 68.5% for $CaCO_3$ and from 84.3% to 60.7% for $NaHCO_3$ .

Increasing the $CaCO_3$ ratio did not appreciably accelerate drug release as compared with $NaHCO_3$, indicating that $CaCO_3$ is superior to $NaHCO_3$ as gas forming agent in floating beads of famotidine.

On the other hands, beads containing guar gum produce more sustained release of famotidine than that beads containing HPMC.

Furthermore, the release mechanism were investigated and the results indicate that most of the formulations follow Higuchi modelwith non fickian anomalous drug release behavior.

## تأثير العوامل الفوارة على تصييغ الفاموتدين المحمل بالحبيبات الطافية لالجينات الصوديوم

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**مفتاح البحث :**فاموتدين، قرحة المعدة، الحبيبات الطافية.

**الخلاصه**

الفاموتيدين هومضاد مستقبلات الهستامين فإنه يوصف بنطاق واسع فيقرحة المعدةوإمراضالاسترجاعالمعدي .أناالتوافر الحيوي المنخفض(40-45٪) ،قصرالعمر البيولوجيالنصفي ( 2.5-4ساعات) للفاموتيدينبالإضافة إلى محدودية نطاق الامتصاص لذلك يفضل تطويره إلىإشكالدوائية محورة التحرر ذو قابلية البقاء في المعدة .

في هذه الدراسة تم تحضير الخرزالطافية للفاموتدين بواسطة طريقة تكوين المادةالهلامية وبتركيبتين مختلفتين مثل الجينيت الصوديوم مع هايدروكسي بروبيل مثل سيللوز والجينيت الصوديوم معصمغ الغار.تم دراسةتأثيرعوامل تشكيل الغازمثلكاربونات الكالسيوم وكاربونات الصوديوم الهايدروجينيه على خواص الطفو، التحمل الدوائي ونسبة كفاءته والتحرر الدوائي خارج الجسم .
كانت النتائج انه كلما زادت نسبة المواد ألمكونهللغاز من 0.2 إلى 1 ، قابلية الطفو ازدادت من 6 ساعات الى 22 ساعة لكلا النوعين من مكونات الغاز ،بينما نسبة كفائة التحمل الدوائي قلت من 86.11% الى 68.5% للحبيبات التي تحتوي كربونات الكالسيوم ومن 84.3% الى 60.7% لكربونات الصوديوم الهايدروجينيه.
كما ان زيادة نسبةكربونات الكالسيوم لم تسرع التحرر الدوائي بشكل ملحوظبالمقارنة مع كربونات الصوديوم الهايدروجينيه وهذا يشير إلىانكربونات الكالسيوم متفوقة على كربونات الصوديوم الهايدروجينيه كعامل مكون للغاز في الخرز الطافية للفاموتدين .
وبالمقارنة الحبيبات التي تحتوي على صمغ الغار تنتج تحرر دوائي اطول للفاموتدين من الحبيبات التي تحتوي على هايدروكسي بروبل مثيل سيللوز بالاضافه إلى ذلك فقد وجد إنآليةالتحرر الدوائيعن معظم التركيباتتتبع نموذج هيكوجي .

**Introduction**

Gastroretetive drug delivery system (GRDDS) can improve the controlled delivery of drugs that have a narrow absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability. [(1)] appropriate candidates for control release gastroretentive dosage forms (CRGRDF) include the following drugs: [(2)]

- Narrow absorption window in gastrointestinal tract (GIT) e.g., riboflavin
- Primarily absorbed from stomach and upper part of GIT e.g. cinnarazine .
- drug that act locally in the stomach e,gantiacide and misoprostol .
- Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., Amoxicillin trihydrate.

Floating multiparticulate oral sustained release drug delivery system include hollow microspheres (micro balloons), low density floating micro pellets, floating micro beads, etc. [(3,4)]

The availability of various polymeric materials enhanced the ability of microparticles to target drugs to specific body organs; this is mainly achieved by a number of approaches, among which are:

- Floating Beads and Microspheres[(5)]
- Mucoadhesive Beads and Microspheres[(6)]
- Floating-Bioadhesive Microspheres[(7)]
- Stimuli Responsive Hydrogel Beads and Microspheres**[(8)]**

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS that are effervescent System, and non- effervescent System.[(9)]

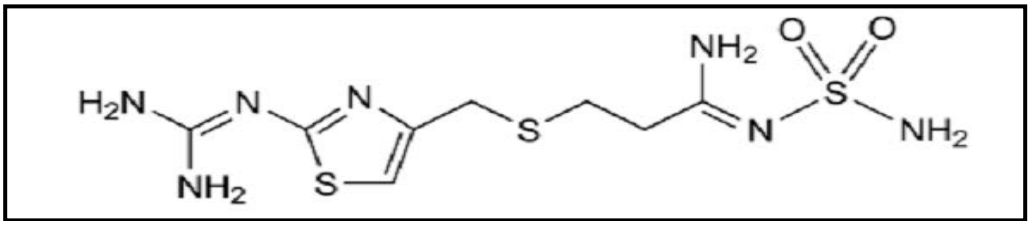
- **Effervescent Floating Dosage Forms :**

These are the matrix types of systems which are prepared by using swellable polymer like methyl cellulose and HPMC as well as various effervescent compounds like Sodium carbonate or Calcium carbonate. They are formulated in such a way that when in contact with the acidic gastric contents liberation of $CO_2$ takes place and gets entrapped in to the swollen hydrocolloids which provides buoyancy to the dosage forms .[9,10]

- **Non Effervescent Floating Dosage Form:**

These dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides and matrix forming polymers like polycarbonates and polystyrene [11]
The formulation is done by mixing the drug and the gel-forming hydrocolloid, after oral administration of this dosage form swells while in contact with gastric fluids attains bulk density of <1. [12]
There are several techniques used for preparation of floating multiparticulate system from which: Solvent Evaporation Method[13] , Emulsion Solvent Diffusion Method[14] andIonotropic Gelation Method[15]

Famotidine is chemically 3-[[[2-[(Diaminomethylene)amino]thiazol-4-yl]methyl]sulphanyl]-*N*-sulphamoylpropanimidamide **.**It is very slightly soluble in water (0.1% at 20°); practically insoluble in alcohol, in acetone, in chloroform, in ether, and in ethyl acetate. The bioavailability of oral famotidine is about 40 to 45% and is not significantly affected by the presence of food. The elimination half-life from plasma is reported to be about 3 hours and Dissociation Constant is pKa 7.06.[16]




This work is done to achieve the following aims:

- To prepare floating bead of famotidine by ionotropic gelation technique and evaluate it .
- The effects of effervescent agents such as sodium bicarbonate and calcium carbonate on drug release profile, floating properties and on the entrapment efficiency well be study.
- To study the effect of polymer sodium alginate concentration on release profile and % entrapment efficiency.
- To study effect of polymer type such as HPMC and guar gum

**Experimental**

**Materials**

Famotidine was Gift from SDI . Sodium alginate , Hydroxyl propyl methyl cellulose k100 and Guar gum were purchased from Himedia lab. Pvt.ltd. India. Calcium carbonate, Sodium

hydrogen carbonate, Calcium chloride, Acetic acide , Monobasic sodium phosphate, Dibasic sodium phosphate purchased from Merck , Germany . all other chemical and reagent used were of analytical grade.

**Preparation of Floating Beads of Famotidine by Ionotropic Gelation Technique**

Exactly 150 mg of famotidine was dissolved in 5ml of distilled water. This solution was dispersed in 10 ml of 2.5 %w/v alginate solution containing HPMC K100M or guar gum (alginate: HPMC or guar gum = 9: 1). Then Gas forming agents was added to the solution in weight ratio ranging from 0.2: 1 to 1: 1 (carbonate: alginate w/w). The resulting solution was dropped through 21 G syringe needle in to 100 ml of 4% w / v calcium chloride ($CaCl_2$) solution containing 10 % v / v acetic acid for the formation of the beads. The formed beads were stay in the solution for 5 min with stirring using magnetic stirrer to improve their mechanical structure, after that they separated, washed with D.W and dried in air for 12 hrs. [17,18]

Ten formulas were prepared by this method, the composition of which is given in table 1:

- Formulas F1 , F2 , F3 , F4 and F5 were formulated to investigate the effect of varying concentration of calcium carbonate
- Formulas F6, F7, F8, F9 and F10 were prepared to investigate the effects of varying the concentration of sodium hydrogen carbonate.
- Formulas F4, F4a and F4b were prepared to investigate the effects of varying the concentration of the polymer sodium alginate.
- Formulas F3, F3G, F8 and F8G are formulated to investigate the effect of varying the type of retarding agent HPMC and guar gum

**Evaluation**

**a) Drug Loading and Entrapment Efficiency**

The prepared beads were evaluated for percent drug loading and drug entrapment efficiency. An accurately weighed sample of beads (10 mg) was crushed in a mortar and added to 10 mL of phosphate buffer pH 7.4. This mixture was centrifuged at 4200 rpm for 30 min, filtered, through whatman filter paper and analyzed spectrophotometrically at ƛ max 266 nm against buffer as blank. The percent drug loading was calculated by dividing the amount of drug in the sampled beads by the weight of beads. Drug entrapment efficiency was determined by weighing beads contains equivalent to 25 mg of famotidine and dissolved it in 50 ml of phosphate buffer pH 7.4. The prepared solution was filtered and analyzed at 266 nm by using UV spectrophotometer and % drug entrapment efficiency was calculated by equation (1) : [18]

**%Entrapment efficiency = Dm x 100 / Dt …… (1)**

Where

Dm is the amount of famotidine in the prepared beads

Dt is the amount of famotidine used in preparation of alginate beads.

**b) Floating Properties**

Floating properties of dry beads were evaluated in dissolution vessel filled with 900 ml of 0.1N HCl .The time between introduction of the beads into the medium and its buoyancy to the upper one third of dissolution vessel (buoyancy lag time) and the time for which the

formulation constantly floated on the surface of the medium (duration of buoyancy) where measured simultaneously by visual observation as part of dissolution studies. [19]

**c) Dissolution Studies**

In vitro dissolution studies were performed for all the formulation combinations using dissolution apparatus . An accurately weighed sample of floating alginate containing (20mg) of famotidine was dropped into 900 ml of 0.1N HCl maintained at temperature of 37 ± 0.5ºC and stirred at a speed of 50 rpm. At predetermined time intervals 5 mL aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of plain dissolution medium kept at 37. ºC. The collected samples were filtered and analyzed at ƛmax 266 nm using a UV-visible spectrophotometer against 0.1N HCL taken as blank. The concentration of famotidine released at different time interval was determined using the equation obtained from the calibration curve of famotidine in 0.1N HCl. The percent of cumulative amount of drug released at each interval was plotted against time to obtaine dissolution profile. [20]

**d) Release kinetics**

To analyze the mechanism of release and release rate kinetics of the dosage form , the dose obtained were fitted in to zero order , first order , higuchi matrix and peppas and based on the $R^2$ value the best fit model was selected .[21]

**Results and discussion**

**Floating Property**

The floating ability of the prepared beads was evaluated as shown in table2. The beads containing 0.2: 1 $CaCO_3$ / $NaHCO_3$: alginate (F1 and F6) sank in few hrs in 0.1 N HCl, while the beads containing $CaCO_3$/ $NaHCO_3$: alginate 0.4:1 and more demonstrated instantaneous and excellent floating ability . This finding due to the fact that beads upon contact with acidic medium, $NaHCO_3$ or $CaCO_3$ effervesces, releasing $CO_2$. In this case the released $CO_2$ was most likely entrapped in the beads gel net work produced by the reaction of calcium ion present in the gellation medium with alginate. [22]

**Drug Loading and Entrapment Efficiency**

The % entrapment efficiency for various famotidine floating bead formulations was found to vary between 60.79% and 92.02 % as shown in table 3. [20]

It was observed that an increase in the ratio of gas forming agent: alginate from 0.2:1 to 1:1 resulted in a decrease in the entrapment efficiency of famotidine in floating beads from 86.11% to 68.5% for beads containing $CaCO_3$ and from 84.3% to 60.79% for that beads containing $NaHCO_3$.

The beads with small amount of gas forming agent, because of the highly dense internal structure of the alginate matrix, were able to retain famotidine more effectively while the porous beads, with a less dense internal structure, result in decreased entrapment efficiency of the drug. [19]

The % entrapment efficiency was increased from 17.7% to 21.1 % as concentration of polymer mixture used was increased from 2% to 3.5% w/v (formula F4a and F4b) as shown in table 5.This can be explained by the greater availability of active calcium binding site in polymeric chain and consequently a greater degree of cross linking which creates a stronger immobilization matrix that hinders drug migration to words the external phase of calcium

chloride and washing solution , and hence produces higher drug entrapment efficiency and drug loading .( 23,24)

In F3G and F8G in which guar gum is used instead of HPMC in their corresponding formulas F3 and F8 there are slightly increase in drug loading and % entrapment efficiency , this due to that highly viscous polymer ( guar gum ) which induce the formation of strong gel layer that hinder drug and increase % entrapment efficiency .(25)

**In Vitro Drug Release**

Figures 1and 2 demonstrate the release rates of famotidine from dried alginate beads with different amount of $CaCO_3$ or $NaHCO_3$ respectively while table 4 represent the percent of cumulative amount of drug release after 12 hrs.

We found that in the presence of small amount of gas forming agents as in F1 and F6, the release rate of the drug from the beads was slow for both type of gas forming agents, this due to the fact that the highly dense internal structure of the alginate beads prepared with small amount of gas forming agents was expected to retain the drug more effectively. The rate of drug release was found to increase with increasing weight ratios of $NaHCO_3$ as shown in figure 2. This is a direct results due increasing the porosity of sodium hydrogen carbonate containing beads. (19)

Conversely, increasing the $CaCO_3$ weight ratio also accelerate the release rate of famotidine from the alginate matrix as in F1 to F5 in which the % accumulative drug release at the end of 12 hours range from 71 % to 86.2% , but the rate is less than that of corresponding weight of $NaHCO_3$ This result may be due to the internal ion tropic gelation effect of $CaCO_3$.

The effect of sodium alginate concentration on the release profile for F4a, F4 and F4b is shown in figure 3 .These results indicate that the drug release rate decrease as the concentration of sodium alginate was increased .Such an effect may be due to the fact that at higher concentration, alginate gel might have provide a better barrier to the penetration of the dissolution medium, there by suppressing the diffusion of the drug through the alginate matrix. (26)

The % accumulative amount of famotidine from beads in formula F3G and F8G which have guar gum instead of HPMC as shown in figure 4 were found to be 78 % and 85% respectively. This result is due to that viscous polymer (guar gum) induce the formation of strong viscous gel layer that slowed down the rate of water diffusion in to the beads matrix , which may result in retarding or decreasing the drug release. (27)

**Kinetics of Drug Release**

The obtained results are given in table 4. The release pattern of famotidine from alginate beads in 0.1N HCl showed higher correlation coefficients when they were fitted to Higuchi kinetic model, $R^2$ value above 0.95. This indicates that a diffusion process is responsible for the release of the drug.

On the other hand , korsmeyer – peppas model for the formulas show non fickian anomalous diffusion since n values range from 0.45 to 0.59 which is an indication of both diffusion/polymer relaxation controlled drug release . (28)

**Conclusions**

On the basis of the results obtained from this study the followings are concluded :

- $CaCO_3$ is a better and effective gas-forming agent than $NaHCO_3$ by producing superior famotidine floating beads with more control of drug release rates.
- Drug release and floatation patterns can effectively be adjusted by varying simple formulation parameter such as sodium alginate and calcium carbonate or sodium hydrogen carbonate concentration.
- Drug entrapment efficiency and loading of famotidine beads can be increased by increasing alginate concentration and decrease by increasing carbonate ratio.
- Type of retarding agents (HPMC or Guar Gum) can affect significantly on drug release and % entrapment efficiency.

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Table 1: Different Formulations of Famotidine Loaded Floating Beads.

| Formula code | Famotidine ( mg ) | Calcium carbonate (mg) | Sodium hydrogen carbonate ( mg ) | Alginate concentration w/v % | Sodium alginate :HPMC = 9 :1 (mg) | Sodium alginate :guar gum =9:1 (mg) | Carbonate : alginate ratio | Total Wt (mg) |
|---|---|---|---|---|---|---|---|---|
| F1 | 150 | 50 | - | 2.5 | 250 | - | 0.2 : 1 | 450 |
| F2 | 150 | 100 | - | 2.5 | 250 | - | 0.4 : 1 | 500 |
| F3 | 150 | 150 | - | 2.5 | 250 | - | 0.6 : 1 | 550 |
| F3G | 150 | 150 | - | 2.5 | - | 250 | 0.6 : 1 | 550 |
| F4 | 150 | 200 | - | 2.5 | 250 | - | 0.8 : 1 | 600 |
| F4a | 150 | 160 | - | 2 | 200 | - | 0.8 :1 | 510 |
| F4b | 150 | 280 | - | 3.5 | 350 | - | 0.8 : 1 | 780 |
| F5 | 150 | 250 | - | 2.5 | 250 | - | 1 : 1 | 650 |
| F6 | 150 | - | 50 | 2.5 | 250 | - | 0.2 : 1 | 450 |
| F7 | 150 | - | 100 | 2.5 | 250 | - | 0.4 : 1 | 500 |
| F8 | 150 | - | 150 | 2.5 | 250 | - | 0.6 : 1 | 550 |
| F8G | 150 | - | 150 | 2.5 | - | 250 | 0.6 : 1 | 550 |
| F9 | 150 | - | 200 | 2.5 | 250 | - | 0.8 : 1 | 600 |
| F10 | 150 | - | 250 | 2.5 | 250 | - | 1 : 1 | 650 |

Table 2: Formulation Variables and Evaluation Parameters of Various Famotidine Floating Bead Formulation

| Formulation Cod | $CaCO_3$ or $NaHCO_3$ : NaAlginate (%w/w) | Duration OfFloating (hrs) | % cumulative DrugRelease at the end 12 hrs |
|---|---|---|---|
| F1 | 0.2 : 1 | 7 | 71 |
| F2 | 0.4 : 1 | 11 | 76 |
| F3 | 0.6 : 1 | 20 | 80.2 |
| F3G | 0.6 : 1 | 22 | 78 |
| F4 | 0.8 : 1 | 22 | 86 |
| F4a | 0.8 : 1 | 22 | 100 |

| | | | |
|---|---|---|---|
| F4b | 0.8 : 1 | 22 | 66 |
| F5 | 1 : 1 | 22 | 86.2 |
| F6 | 0.2 : 1 | 6 | 76.7 |
| F7 | 0.4 : 1 | 11 | 86 |
| F8 | 0.6 : 1 | 19 | 91 |
| F8G | 0.6 : 1 | 21 | 85 |
| F9 | 0.8 : 1 | 21 | 95.3 |
| F10 | 1 : 1 | 22 | 98.2 |

Table 3: % Drug Loading Efficiency and% Drug Entrapment Efficiency of Famotidine Beads

| Formula no. | % Drug loading efficiency | % Drug Entrapment efficiency |
|---|---|---|
| F1 | 28.7 | 86.11 |
| F2 | 25 | 83.33 |
| F3 | 20.6 | 75.54 |
| F3G | 20.8 | 76.3 |
| F4 | 18 | 72 |
| F4a | 21.1 | 71.74 |
| F4b | 17.7 | 92.04 |
| F5 | 15.8 | 68.5 |
| F6 | 28.1 | 84.3 |
| F7 | 24 | 80 |
| F8 | 19.2 | 70.4 |
| F8G | 19.4 | 71.14 |
| F9 | 16.4 | 65.6 |
| F10 | 14 | 60.79 |

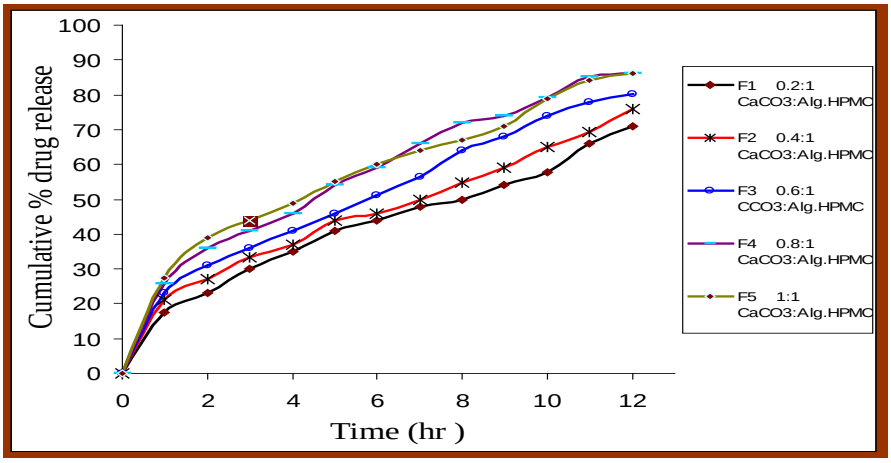


Figure 1: Release profile show the effect of $CaCO_3$ in 0.1N HCl at 37C

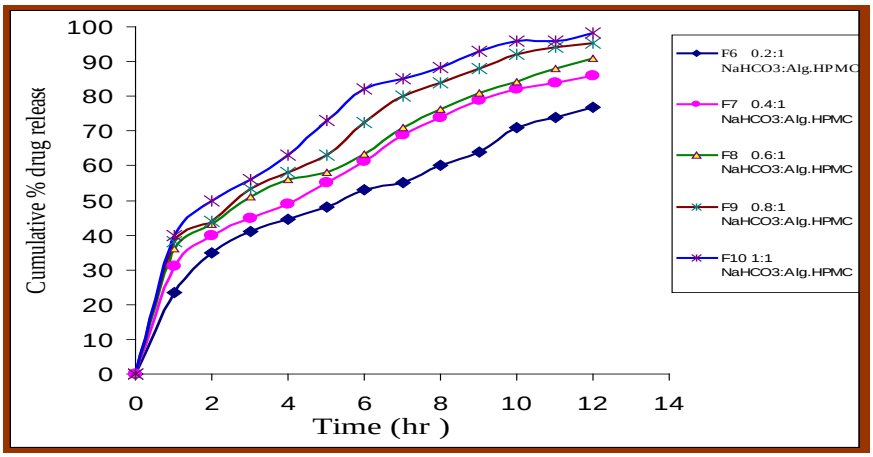


Figure 2: Release profile show the effect of $NaHCO_3$ in 0.1N HCl at 37C

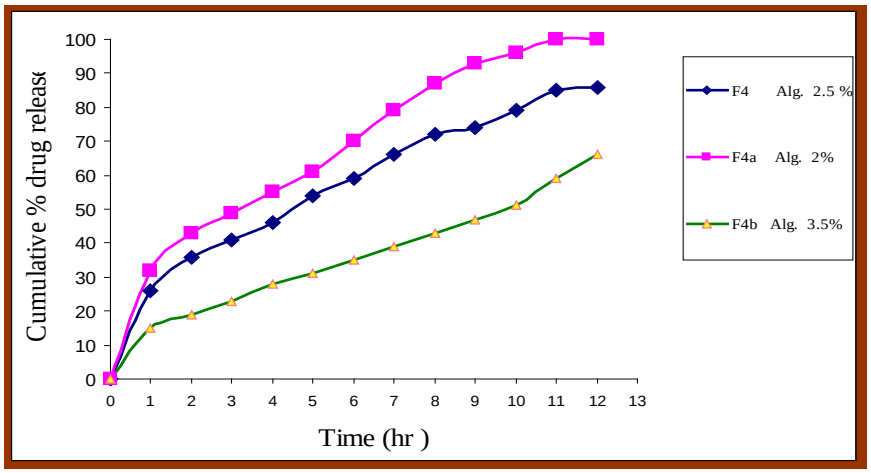


Figure 3: Effect of polymer sodium alginate concentration on release profile in 0.1N HCl at 37C

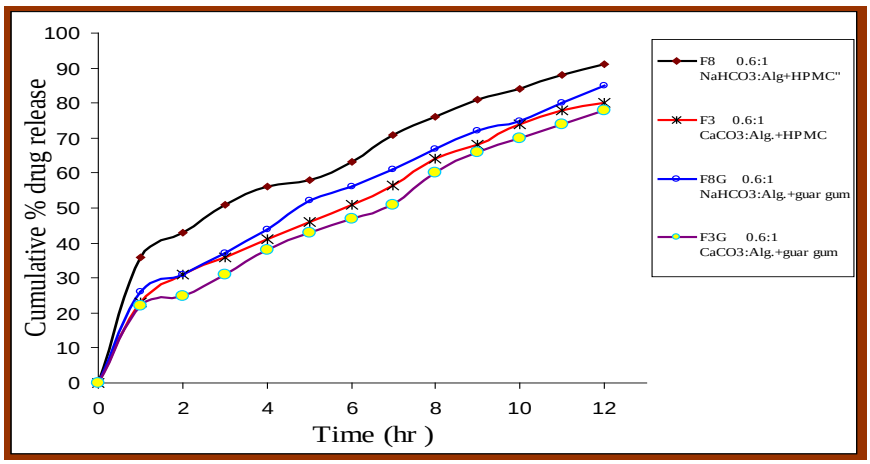


Figure 4: Effect of polymer type on release profile of famotidine beads in 0.1 N HCl at 37C

Table 4: The Release Mechanism of Famotidine from Beads in 0.1 N HCl at 37 $C^0$

| Formula no | $R^2$ value | | | | |
|---|---|---|---|---|---|
| | Zero order | First order | Higuchi | Peppas | N |
| F1 | 0.956 | 0.972 | 0.983 | 0.989 | 0.55 |
| F2 | 0.954 | .9650 | 0.9847 | 0.979 | 0.51 |
| F3 | 0955 | 0.975 | 0.9879 | 0.982 | 0.51 |
| F3G | 0.968 | 0.97 | 0.976 | 0.964 | 0.55 |
| F4 | 0.934 | 0.981 | 0.995 | **0.991** | 0.5 |
| F5 | 0.914 | 0.961 | **0.99** | 0.99 | 0.45 |
| F4a | 0.92 | 0.9 | **0.99** | 0.98 | 0.489 |
| F4b | 0.97 | 0.94 | .950 | 0.968 | 0.59 |
| F6 | 0.91 | 0.978 | **0.9919** | 0.988 | 0.468 |
| F7 | 0.90 | 0.987 | 0.991 | 0.983 | 0.45 |
| F8 | 0.885 | 0.966 | 0.987 | 0.981 | 0.39 |
| F8G | 0.94 | 0.975 | **0.9929** | 0.97 | 0.5 |
| F9 | 0.878 | 0.974 | 0.988 | 0.975 | 0.4 |
| F10 | 0.8416 | 0.967 | 0.979 | 0.986 | 0.39 |