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# Formulation and *In-Vitro* Evaluation of Floating Beads of Propranolol Hydrochloride Using Foam Technology

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## Abstract

An attempt was made to formulate the floating alginate beads containing Propranolol hydrochloride, using foam solution. Propranolol hydrochloride is a sympatholytic non-selective beta blocker with its absorption site at stomach. propranolol hydrochloride is more soluble in acidic pH and slightly soluble in neutral or alkaline pH conditions. Therefore development of a sustained release formulation of propranolol hydrochloride is advantageous, if the system can remain in stomach for prolonged period of time. Three polymers sodium alginate, poloxamer188, poloxamer407 were used for the present study. Poloxamer were used to impart buoyancy to the beads. Total 14 formulations were prepared with different polymer concentrations. Formulated beads were evaluated for production yield, particle size, swelling index, buoyancy, drug entrapment efficiency, morphology, *in vitro* release characteristics. Formulated beads showed satisfactory floating characteristics and subjected for *in vitro* release study using 0.1N HCl (pH 1.2) in USP apparatus II (paddle type). The results indicated that sodium alginate with poloxamer 188 sustain the drug release better up to 12 hr. To analyze the mechanism of drug release from the beads, the *in vitro* release data was fitted into various release models.

**Keywords:** Floating Beads, Propranolol hydrochloride, HPMC, Buoyancy Test, Poloxamer.

## Contents



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## 1. Introduction

The oral route represents nowadays the predominant and most preferable route for drug delivery. Oral drug delivery systems (DDS) are divided into immediate release and modified release systems. Immediate release DDS are intended to disintegrate rapidly, and exhibit instant drug release. Modified release systems, on the other hand, have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance, as well as reducing side effects (1). Extended, sustained or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery devices, with predictability and reproducibility in the drug release kinetics. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance. Therefore, extended release DDS possessing gastric retention properties may be potentially useful (2). The concept of floating drug delivery was reported in the literature as early as 1968, where Davis discovered a method for overcoming the difficult experienced by some persons of gagging or choking while swallowing medicinal pills. Some other suggested that such difficulty could be overcome by proving pills having a density of less than 1.004gm/cm$^3$ so they float on water surface. The various buoyant preparation include hollow microsphere (microballoons), granules powder, capsule, tablet (pills) laminated films (3).

**Advantages of Floating Drug Delivery Systems** (4)**:**

- **Controlled Drug Delivery:** These systems can remain in the stomach for longer period of time and hence can release the drug over an extended period. The problem of short gastric residence time, encountered with an oral CR formulation can hence be overcome with these systems. These systems have a bulk density of less than 1, as a result of which they can float on the gastric contents.
- **Site-Specific Drug Delivery:** These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine. Eg. Riboflavin, Furosemide, Ciprofloxacin, etc.
- **Absorption Enhancement:** Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.
- **Reduction of dose:** By formulating FDDS of a drug, the dose of the drug can be reduced along with the frequency of administration.

## 2. Materials and Methods

Propanalol HCl was gifted from Oniosome Healthcare Pvt. Ltd., Mohali. Sodium alginate and calcium chloride was purchased from Thomas Baker Pvt. Ltd. Poloxamer 188 was obtained from Signet chemical corporation Pvt. Ltd. Poloxamer 407 was purchased from Ludwigshfen/BASF Company. All the ingredients used were of analytical grade.

**Preparation of Floating Beads:**

Sodium alginate and poloxamer (Alg) was dissolved in distilled water and then poloxamer was then added into the sodium alginate solution and agitated vigorously by using mechanical stirrer for 20 min. Then drug was added into the foam solution under vigorous stirring condition continuously. The foam solution was introduced using a 21 gauge syringe into the $CaCl_2$ solution under gentle stirring condition. The distance between the edge of the needle and the surface of the $CaCl_2$ medium was about 10 cm. The beads formed were left in the solution with gentle stirring for 10 min at room temperature to be cured. The beads were collected, washed with distilled water twice and oven-dried subsequently (40 ˚C) (5).

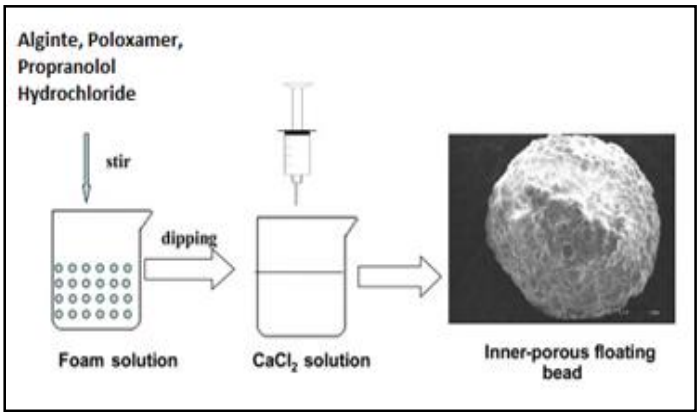


**Figure 1. Method of preparation of floating beads using foam solution**

**Formula design:** 14 batches of floating beads of Propranolol hydrochloride were formulated. Firstly, we optimize the concentration of Poloxamer for preparation of floating beads by formability and foam stability study.

**Foamability and foam stability:** Foamability refers to the "ability" of the system to form foam. Foam stability is a parameter describing variations of the foam properties (mostly as changes of height or volume) with time, immediately after the foam was generated. Foams were prepared using magnetic stirring. Different amount of Alginate, poloxamer and Propranolol hydrochloride was added into water and agitated for 20 min at 2600 rpm; foams were immediately transferred into a graduated cylinder for continued observation. The initial foam volume after preparation is used to evaluate the foamability. Foamability (FD) was characterized as the physical density of the foam (ratio of volume of foam/volume of liquid used).

**FD = V (foam)/ V (liquid)**

Foam stability is characterized as the time interval after which 10 percent of the original amount of liquid has drained from the foam.

**Table 1. Fomability and foam stability**

| S. No. | Poloxamer 188, 407 % | Poloxamer 188 | | Poloxamer 407 | |
|---|---|---|---|---|---|
| | | Foamability (Density) | Foam Stability (Min) | Foamability (Density) | Foam Stability (Min) |
| 1. | 0.0125 | 1.22 | 5 | 1.6 | 16 |
| 2. | 0.025 | 1.6 | 10 | 2.2 | 17 |
| 3. | 0.05 | 1.7 | 18 | 2.1 | 22 |
| 4. | 0.075 | 2.4 | 30 | 1.22 | 24 |
| 5. | 0.1 | 2.5 | 40 | 1.8 | 42 |
| 6. | 0.2 | 1.96 | 10 | 2.2 | 13 |
| 7. | 0.4 | 2.2 | 11 | 2.22 | 18 |
| 8. | 0.5 | 1.92 | 21 | 2.2 | 15 |

So it was found that as the concentration of poloxamer was increased, foamability and foam stability also got increased up to 0.1% and then decreased on further increasing the concentration of poloxamer, therefore the optimize conc. of poloxamer was taken as 0.1% which has highest foam stability for preparation of floating beads.

**Table 2. Formula development**

| Formulation code | Drug (mg) | Sodium Alginate | Poloxamer 188 (mg) | Poloxamer 407 (mg) | Calcium Chloride |
|---|---|---|---|---|---|
| F-1 | 80 | 1% | 200 | - | 1% |
| F-2 | 80 | 1% | - | 200 | 1% |
| F-3 | 80 | 1.5% | 200 | - | 1% |
| F-4 | 80 | 1.5% | - | 200 | 1% |
| F-5 | 80 | 2% | 200 | - | 1% |
| F-6 | 80 | 2% | - | 200 | 1% |
| F-7 | 80 | 3% | 200 | - | 1% |
| F-8 | 80 | 3% | - | 200 | 1% |
| F-9 | 80 | 4% | 200 | - | 1% |
| F-10 | 80 | 4% | - | 200 | 1% |
| F-11 | 80 | 4% | - | 200 | 2% |
| F-12 | 80 | 4% | - | 200 | 3% |
| F-13 | 80 | 4% | - | 200 | 4% |
| F-14 | 80 | 4% | - | 200 | 5% |

**Evaluation parameters for floating beads:**

1. **Surface Morphology and Particle Size:** The surface morphology and particle size of prepared floating beads determined by scanning electron microscopy. (5)
2. **Percentage Yield:** The obtained Beads of each formulation were collected and weighed to determine production yield (PY) using following equation (6).
   Practical yield/Theoritical yield X100
3. **Buoyancy study:** Floating properties of beads were evaluated using USP dissolution apparatus containing SGF (pH 1.2). Beads (one hundred) of each batch were placed in 100 ml of 0.1 N HCl agitated at 100 rpm,

temperature was maintained at 37±0.5$^0$c. The number of sinking beads was observed visually. The percentage of floating beads was calculated according to the following equation:

**F (%) = NF/NT X 100**

F: floating percent; NF: number of floating beads; NT: total number of the beads. (7).

4. **Drug entrapment and entrapment efficiency:** Accurately weighed quantities of approximately 50 mg beads were dissolved in 5 ml 0.1 N HCL (simulated gastric fluid, pH 1.2) and then boil for 20 minute. The solution was centrifuged at 5000 rpm for 30 min and drug concentration was assayed at 289 nm using a spectrophotometer. The drug concentration in the sample was used to calculate the percentage drug loading by dividing the weight of beads initially dissolved and the encapsulation efficiency was calculated as

   **DL (%) = WD/WT ×100**

   DL: drug loading; WD: the weight of the drug loaded in the beads; WT: the total weight of the beads.

   **EE (%) = WA/WT × 100**

   EE: encapsulation efficiency; WA: actual drug content; WT: theoretical drug content (5).

5. **Swelling study:** Swelling studies of the beads were carried out by taking Known weight of the Beads and immersed in excess of 0.1NHCL for definite time interval and then beads were removed and weighed immediately at regular time interval. The percentage swelling (*P*s) of the beads was calculated as:

   **$Ps = [W_s - W_d] / W_d X 100$**

   Where $W_s$ is the weight of swollen beads and $W_d$ is the weight of dried beads. (8)

6. ***In vitro* drug release study:** *In vitro* dissolution studies were performed for all the formulations using USP apparatus II (paddle type). An accurately weighed floating alginate beads were taken into 900 ml 0.1N HCL (pH 1.2). The temperature was maintained at 37±0.5$^0$c and stirred at a speed of 50 rpm. At definite time intervals, a 5-ml aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of plain dissolution medium kept at 37±0.5$^0$c. The collected samples were filtered and analyzed at 289 nm using UV- visible spectrophotometer against 0.1N HCl (pH 1.2) taken as blank (9).

7. **Drug release kinetics:** The release kinetic was studied by various kinetic models as zero order plot, first order plot, higuchi plot and korsmeyer-peppas. In order to identify a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model. It is therefore clear that only a combination of accurate and precise data with models accurately depicting the physical situation will provide an insight into the actual mechanism of release. To analyse the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted into Zero order, First order, Higuchi matrix, Korsemeyer-Peppas. By comparing the $R^2$-values obtained from the above equations, the best-fit model was selected (10).

## 3. Results and Discussion

**FT-IR Spectra of drug:** The samples were scanned in 400-4000 wave number range, using KBr pellet technique.

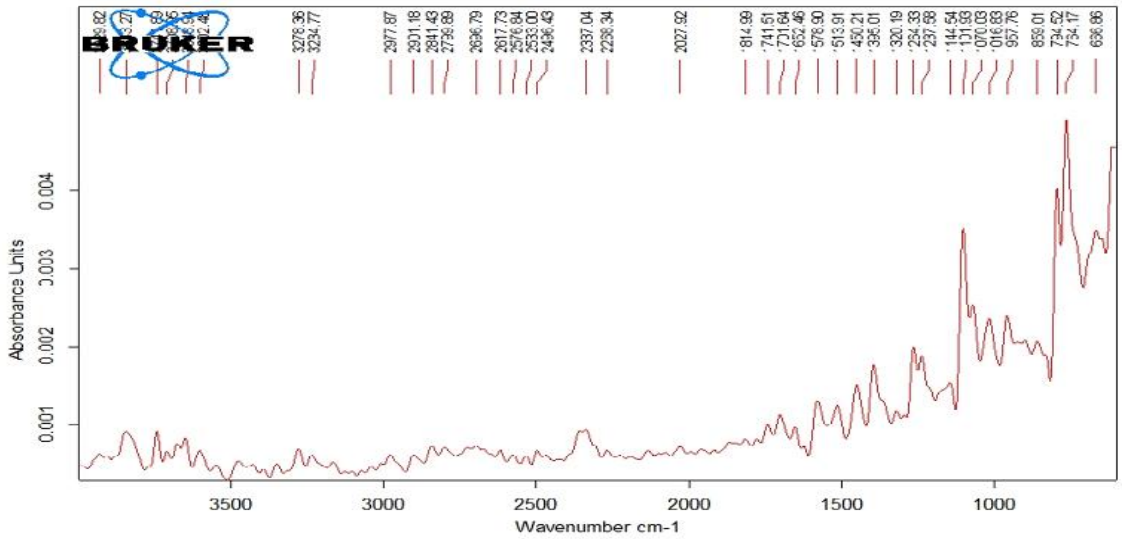


**Figure 2. FT-IR Spectra of Propranolol hydrochloride**

**Drug-Excipient Interaction Study:** This study was carried out by using FT-IR spectrophotometer to find out if there is any possible chemical interaction of Propranolol hydrochloride with sodium alginate, poloxamer188, poloxamer 407 and Calcium chloride. No significant interaction is found owing to IR range of drug.

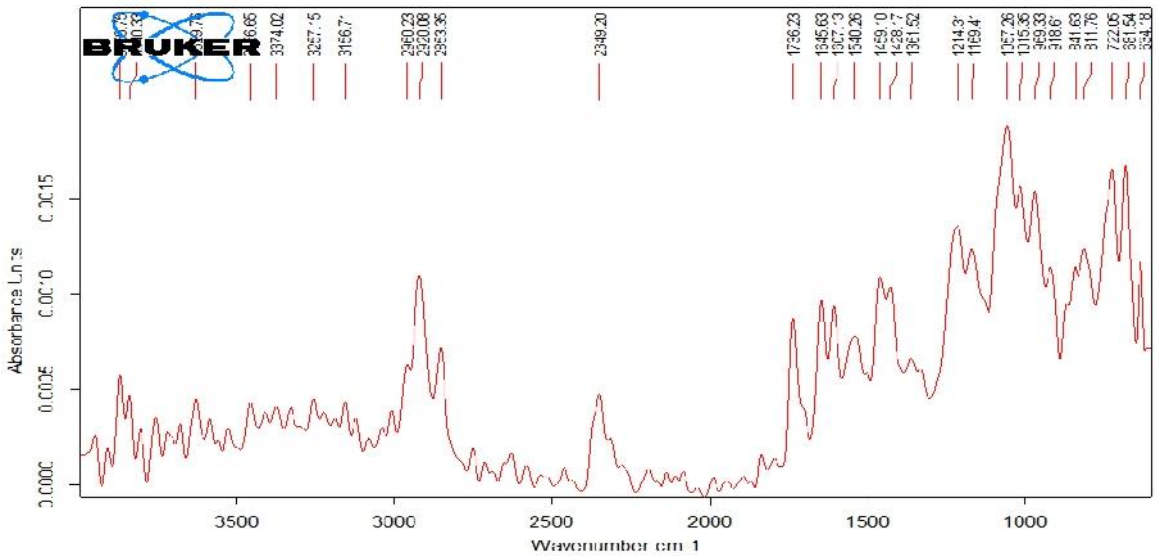


**Figure 3. Drug-excipients compatibility study**

**Evaluation parameters for floating beads:**

**Production yield of floating beads:** The Production yield of all formulation is tabulated below

**Table 3. Production yield of floating beads**

| Formulation | Percentage yield (%) |
|---|---|
| F3 | 60.67 |
| F4 | 60.97 |
| F5 | 68.64 |
| F6 | 69.87 |
| F7 | 81.25 |
| F8 | 82.81 |
| F9 | 79.68 |
| F10 | 88 |
| F11 | 85 |
| F12 | 90 |
| F13 | 82 |
| F14 | 87 |

**Micromeritic Properties of floating beads of propranolol hydrochloride:**

**Table 4. Micromeritic Properties of floating beads**

| Formulation code | Angle of repose | Bulk density | Tap density | Carrs index | Hausners ratio |
|---|---|---|---|---|---|
| F3 | 18.85 | 0.695 | 0.805 | 13.65 | 1.15 |
| F4 | 19.10 | 0.712 | 0.810 | 12.10 | 1.13 |
| F5 | 19.85 | 0.745 | 0.855 | 12.86 | 1.14 |
| F6 | 20.55 | 0.695 | 0.807 | 13.87 | 1.16 |
| F7 | 23.15 | 0.625 | 0.758 | 17.62 | 1.20 |
| F8 | 28.16 | 0.566 | 0.675 | 16.14 | 1.19 |
| F9 | 22.65 | 0.665 | 0.782 | 14.96 | 1.17 |
| F10 | 25.15 | 0.595 | 0.735 | 19.05 | 1.23 |
| F11 | 27.75 | 0.565 | 0.697 | 18.95 | 1.22 |
| F12 | 24.66 | 0.588 | 0.724 | 18.80 | 1.24 |
| F13 | 30.65 | 0.515 | 0.665 | 22.55 | 1.29 |
| F14 | 26.25 | 0.635 | 0.753 | 17.64 | 1.21 |

**Surface morphology and Particle size distribution analysis:** The morphology of the floating beads was examined by SEM the view of the microspheres showed a spherical shape with a smooth surface morphology.

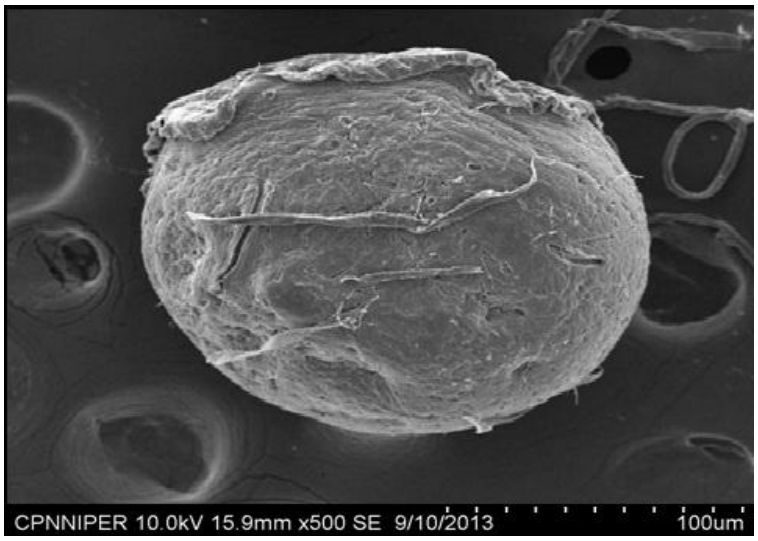


**Figure 4. SEM of optimized batch (F-14)**

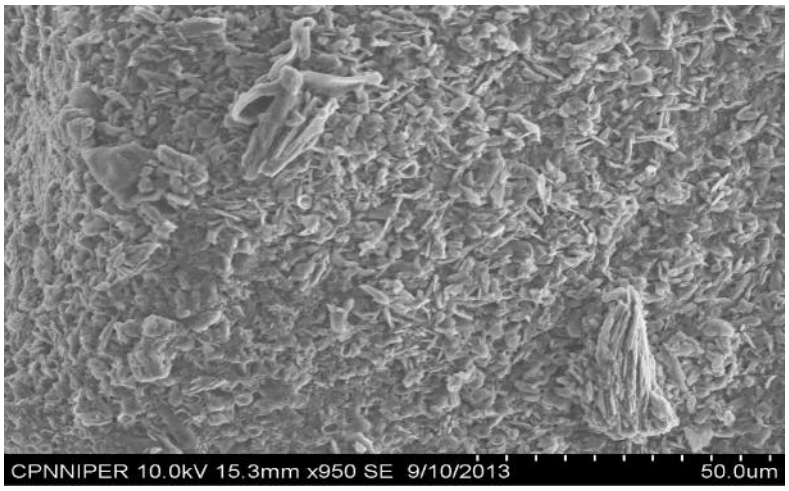


**Figure 5. SEM of optimized batch (F-14)**

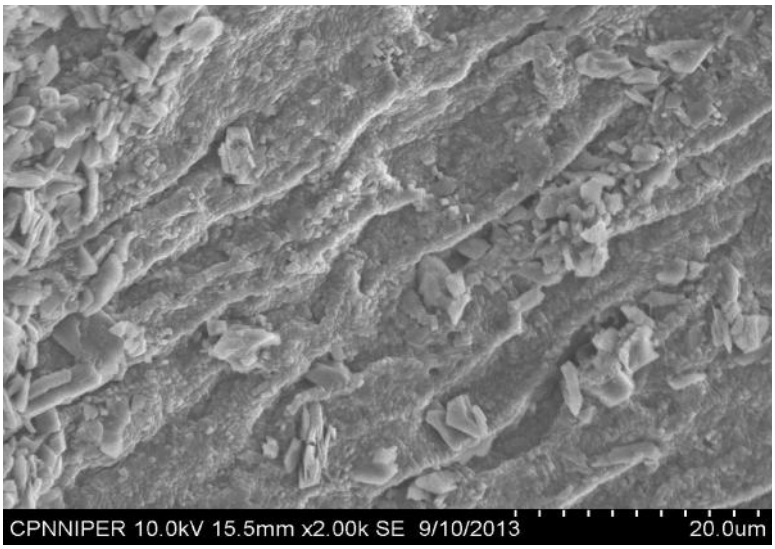


**Figure 6. SEM of optimized batch (F-14)**

**Particle size:** It's determined by an optical microscope fitted with an ocular and stage micrometer and particle size distribution was calculated. The instrument was calibrated at 1unit of eyepiece micrometer was equal to 1/30mm (33.33µm).

**Table 5. Particle Size**

| Formulation code | Mean Particle Size (µm) |
|---|---|
| F3 | 334.78 |
| F4 | 335.12 |
| F5 | 321.11 |
| F6 | 326.25 |
| F7 | 422.16 |
| F8 | 456.36 |
| F9 | 482.22 |
| F10 | 512.34 |
| F11 | 516.14 |
| F12 | 515.12 |
| F13 | 525.17 |
| F14 | 544.22 |

Floating beads of Propranolol hydrochloride prepared in this study were well rounded spheres with the size range from 321.11 to 544.22 µm.

**Drug entrapment efficiency:**

The entrapment efficiency varied from 18.06% to 87.15%. The formulation F14 is having high encapsulation efficiency of 87.15% and F3 is having low encapsulation efficiency of 18.06%. The results of drug loading and drug entrapment efficiency of all formulation are given below.

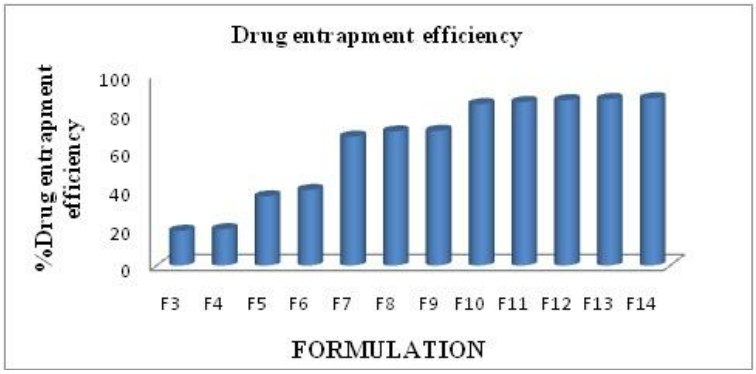


**Figure 7. % Drug entrapment efficiency**

**Buoyancy of floating beads:** The results indicate that poloxamer is good floating agent which is an important parameter for floating drug delivery system. Total floating time was found to be greater than 12 hrs and % floating found in range 80-100%.

**Table 6. Buoyancy study of floating beads**

| Formulation | Total floating time (hrs.) | % Floating (F (%) = NF/NTX100) |
|---|---|---|
| F3 | 24 | 90 |
| F4 | 24 | 80 |
| F5 | 24 | 95 |
| F6 | 24 | 92 |
| F7 | 24 | 100 |
| F8 | 24 | 100 |
| F9 | 24 | 100 |
| F10 | 24 | 100 |
| F11 | 24 | 100 |
| F12 | 24 | 100 |
| F13 | 24 | 100 |
| F14 | 24 | 100 |

**Swelling study of floating beads:**
All formulation show good swelling index, on increasing concentration of sodium alginate swelling index increases while conc. of calcium chloride have no significant effect on swelling index. Swelling index is directly proportional to concentration of sodium alginate. The results of swelling studies are given below.

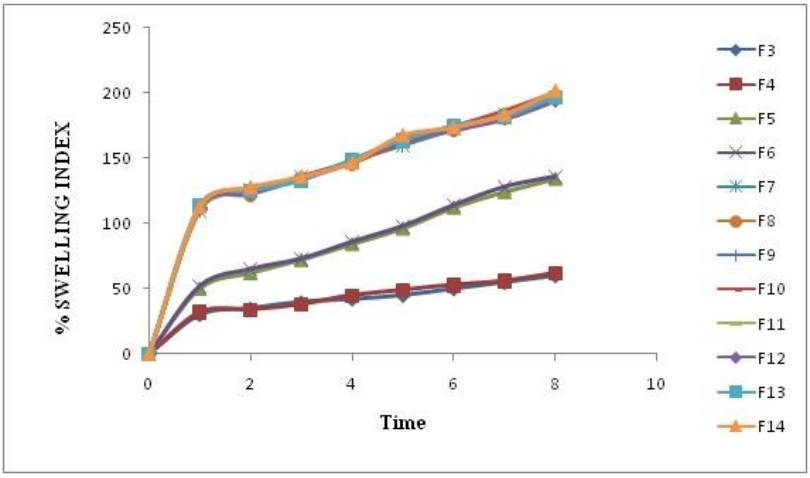


**Figure 8. % swelling index of floating beads formulation (F-3 to F-13)**

All formulation show good swelling index, on increasing concentration of sodium alginate swelling index increases while conc. of calcium chloride have no significant effect on swelling index. Swellling index is directly proportional to concentration of sodium alginate.

***In-vitro* drug release study:** The results of in vitro drug release are given below of optimized formulation F-14.

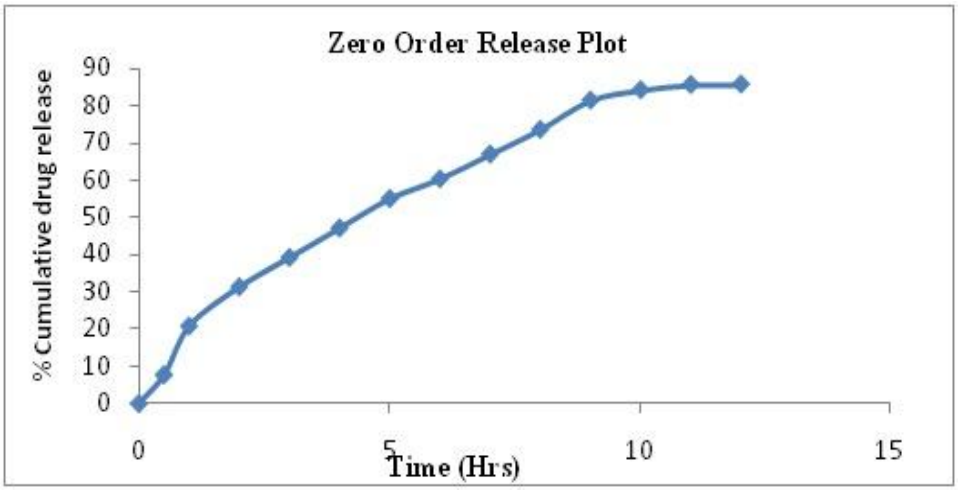


**Figure 9. Drug release pattern of optimized batch F-14**

## 4. Conclusion

The aim of the study was to develop and physically characterize the floating alginate beads of propranolol hydrochloride using foam solution. Propranolol hydrochloride is a sympatholytic non-selective beta blocker with its absorption site at stomach. propranolol hydrochloride is more soluble in acidic pH and slightly soluble in neutral or alkaline pH conditions. Therefore development of a sustained release formulation of propranolol hydrochloride is advantageous, if the system can remain in stomach for prolonged period of time. Three polymers sodium alginate, poloxamer188, poloxamer 407 were used for the present study. Poloxamer were used to impart buoyancy to the beads. Total fourteen formulations were prepared with different polymer concentrations. In the present work, it was concluded that formulation F14 shows the best release that follows zero order kinetics with anomalous diffusion method. Therefore, it can be concluded that the Propranolol hydrochloride Floatin Beads have an advantages of lowering the dose frequency and improve the patient compliance by providing the better management of hypertension.

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