IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND DEVELOPMENT OF MUCOADHESIVE FLOATING DRUG DELIVARY SYSTEM OF SITAGLIPTINE PHOSPHATE

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Abstract :-

In the present study, Mucoadhesive floating drug delivery systems of sitagliptin Phosphate, is an anti diabetic Agent , have been designed to increase the buyoncy, gastric residence time and to reduce frequency of administration. In an attempt to developed floating beads of Sitagliptine, drug loaded alginate beads were prepared by simultaneous external and internal gelation. The effect of blending of Sodium alginate with Calcium carbonate and chitosan on the bead properties were evaluated. Beads were spherical with Entrapment efficiency in the range of 52.81±2.64 to 78.95±1.92%. Beads exhibited buoyancy over a period of 7–24 hr based on the formulation variables. In vitro release of Sitagliptine from the alginate beads in simulated gastric fluid (SGF) (0.1 N HCl, pH 1.2), was influenced significantly ($p < 0.001$) by the properties and concentration of additives. Among the polymers incorporated into alginate beads. The Sodium Alginate provided an extended release over 12 hr.

Keywords- Sitagliptine , Alginate Beads, Sodium Alginate

INTRODUCTION

The newer drug delivery systems have been developed from time to time with a goal of providing the therapeutic amount of drug to the proper site in the body and to increase the bioavailability of the drug. An appropriately designed controlled-release drug delivery system can be major advance towards solving the major issues like delivering drug to the site, controlling the rate of drug delivery. This can be achieved by better control of plasma drug levels and less frequent dosing.

Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.

The improved bioavailability is expected for drugs that are absorbed readily upon release in the GI tract. These drugs can be delivered ideally by slow release from the stomach. Many drugs categorized as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the release time.

This can be overcome by developing the drug in to controlled release formulations which will release the drug slowly into the gastrointestinal tract (GIT). This approach will maintain an effective drug concentration in the systemic circulation for a longer durations. Thus the orally administered controlled drug will retained in the stomach and release the drug in a controlled manner supply the drug continuously to its absorption sites of the gastrointestinal tract (GIT).

1.1 GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs.

1.1.1 Advantages

- Improvement of bioavailability and therapeutic efficacy of the drugs and possible dose reduction e.g. Furosemide
- Enable constant therapeutic levelsover a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. E.g. b-lactam antibiotics (penicillin and cephalosporins)
- For drugs with relatively short half-life, sustained release may result in a flip- flop pharmacokinetics and also enable

reduced frequency of dosing with improved patient Compliance.

- They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because of their bulk density is lower than that of the gastric fluids.
- Gastro retentive drug delivery can produce prolongs and sustains release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.
- The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs.
- Gastro retentive drug delivery can minimize the counter activity of the body leading

- to higher drug efficiency.
- Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.
- The sustained mode of drug release from Gastro retentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

1.1.2 Factors Affecting Gastric Retention 0:

- **Density:** GRT is a function of dosage form buoyancy that is dependent on the density.
- **Size:** Dosage form units with a diameter of more than 7.5mm are reported to have and increased GRT compared with those with a diameter of 9.9mm.
- **Shape of dosage form:** Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT≈ 90% to 100% retention at 24 hours compared with other shapes.
- **Single or multiple unit formulation:** Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co- administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- **Fed or unfed state: under fasting conditions:** GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- **Nature of meal:** feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

- **Caloric content:** GRT can be increased by 4 to 10 hours with a meal that is high in
- proteins and fats.
- **Frequency of feed:** the GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender:** Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
- **Age: Elderly people, especially those over 70, have a significantly longer GRT.**
- **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration:** Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.
- **Biological factors:** Diabetes and Crohn's disease.

1.1.3 Approaches for gastro retention-

To improve the retention of an oral dosage form in the stomach various approaches have been developed, it includes floating systems and non-floating systems. Floating systems includes effervescent systems and non-effervescent systems, these systems have the bulk density lower than the gastric fluid and remain floating and releases the drug slowly in a desired rate. Non floating systems include bioadhesive systems, swelling systems, high density systems, expandable systems, raft forming systems, magnetic systems which utilize different mechanisms to prevent the exit of drugs through pyloric sphincters.

1.2 TYPES OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

The various types of gastro retentive drug delivery systems are basically classified in to two major classes based on the floating efficiency.

I. Floating systems

A. Effervescent systems

1. Volatile liquid containing systems

a. Intra gastric floating gastrointestinal drug delivery system b.Inflatable gastrointestinal drug delivery systems

c. Intra gastric osmotically controlled drug delivery system

Gas generating systems

a. floating capsules

b. floating pills

c. Floating system with ion exchange resins

B. I. Non – effervescent systems

1. Hydro dynamically balanced systems
2. Microballons/ microspheres
3. Alginate beads
4. Matrix layered tablets
5. Raft forming systems

II. Non floating systems

A. Swelling systems
B. Magnetic systems
C. Expandable systems
D. High density systems

1.2.1. FLOATING DRUG DELIVERY SYSTEMS :

These are the low density systems having the bulk density less than the gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. When the drug delivery system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. This results in increased gastro retention time and a better control of fluctuations in the plasma drug concentration.

Based on the buoyancy mechanism, floating systems are classified as follows

A. Effervescent systems

B.Non effervescent systems

A. Effervescent systems

These dosage forms are developed in such a way that, when they come in contact with gastric juices in the stomach , carbon dioxide gas is released due the reaction between sodium bicarbonate, citric acid and tartaric acid and is trapped in the swollen hydrocolloids. This provides buoyancy to the dosage form there by making it to float on the gastric fluids.

These systems may also contain liquids which gasify and evaporates at body temperature by which the specific gravity decreases and causes the dosage form to float.

B. Non effervescent systems: Non effervescent drug delivery systems are those which upon swallowing swells via imbibition of gastric fluids to an extent that it prevents their exit from the stomach. These systems may also be referred to as 'plug-type systems' since they have the tendency to remain lodged near the pyloric sphincter. Different types of non effervescent systems area. Hydrodynamic ally balanced systems (HBS): HBS are also called as 'colloidal barrier systems' these systems contains drug along with thegel forming hydrocolloids. When thecapsules containing the drughydrocolloid mixture comes in contact with the gastric fluids, the capsule shell dissolves and the mixture swells to form a gelatinous barrier, which imparts buoyancy in gastric fluids for a prolonged period of time due to the continuous erosion of the surface. This allows water penetration in to the inner layers maintaining surface hydration and buoyancy to the dosage form. This gel barrier controls the rate of fluid penetration into the device and consequent release of drug from the system.

1.3. MUCOADHESIVE APPROACH FOR GASTRO RETENTION

Mucoadhesion can be defined as a state in which two components, of which one is of biological origin are held together for extended periods of time by the help of interfacial forces. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains.

ADVANTAGES

i. Improved patient compliance,
ii. Improved Drug compliance,
iii. Better control of disease condition,
iv. Better control of plasma levels,
v. Decreasing in total amount of dose administered,
vi. Short time require for disease treatment,
vii. Reducing in health care costs.

Several research groups have been reported different gastro intestinal mucoadhesive dosage forms such as microspheres, matrix tablets, discs etc.

1.4. TYPESOF BIO ADHESION

The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bioadhesive drug delivery, the term bioadhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In cases where the bond

is formed with the mucus the term mucoadhesion may be used synonymously with bioadhesion.

- **Type I:** Type I Bioadhesion is characterized by adhesion occurring between biological objects without involvement of artificial materials.

  Example: Cell fusion and cell aggregation

- **Type II:**Type II Bioadhesion can be represented by cell adhesion onto culture dishes or adhesion to a variety of substances including metals, woods, and other synthetic materials.
- **Type III:**Type III Bioadhesion can be described as adhesion of artificial substances to biological substrates such as adhesion of polymers to skin or other soft tissues.

1.5. MECHANISM OF MUCOADHESION

Mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Mucoadhesion has the following mechanism.

1. Intimate contact between a bioadhesive and a membrane (wetting or swelling Phenomenon)
2. Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration)

Materials:

Table No.1: List of chemicals with grade and Role

Drug:

Sr no	Drug	Grade	Role
1	Sitagliptin Phosphate	AR	Antidiabetics Agent

Polymers:

Sr no	Polymers	Grade	Role
1	Sodium alginate	LR	Emulsifier , Viscosity enhancer
2	Chitosan	LR	Mucoadhesive agent

Other excipients:

Sr no	Materials	Grade	Role
1	Calcium Carbonate	LR	Gas forming agent
2	Calcium chloride	LR	Cross-linking Agent

Experimental work-

1. Determination of λ max:

Preparation of calibration curve in 0.1N HCl:

Standard solution:

Accurately weighed 10 mg of Sitagliptin was dissolved in 100 mL of 0.1N NaOH and the final volume was made up to 100 mL with 0.1 N NaOH, to get a solution containing 1000 µg/ml

Stock solution:

- From the standard solution, a stock solution was prepared to give a Aliquots of 2, 4, 6, 8 and 10 mL of stock solution were pipette out into 10 mL volumetric flasks. The volume was made up to the mark with 0.1N NaOH. These dilutions give 2,4,6, 8, and 10µg/ml. The absorbance was measured at 268nm using UV spectrophotometer.

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}	optimize
Na-Alginate (%)	2	2	3	4	2	3	3	2	3	3	4	3	4	3	4
$CaCo_3$(%)	2	2	3	2	1	2	1	3	1	2	1	3	3	2	1.847
$CaCl_2$(%) 10%(v/v) Acetic Acid	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Chitosan(%)	0	1	0	1	0.5	0.5	0	0.5	1	0.5	0.5	1	0.5	0	0.978

Table No-2 : formulation of floating mucoadhesive alginate beads of Sitagliptin Phosphate by using Design Expert.

Table No-2

Procedure For Preparation of Alginate Beads:

Phase I- Pure Drug was added into Alginate solution (w/v,%) Containing $CaCo_3$ as a gas forming agent.

Phase II- Alginate Solution was Added dropwise into the (4%) $CaCl_2$ acetic acid

Solution (10 v/v),(0.5%) Chitosan. Then use fine six gauge stainless steel needle, the solution was then magnetic stirrer for 20 min. After beads were collected wash with distilled water

Dried at 40^0C at 1 hr.

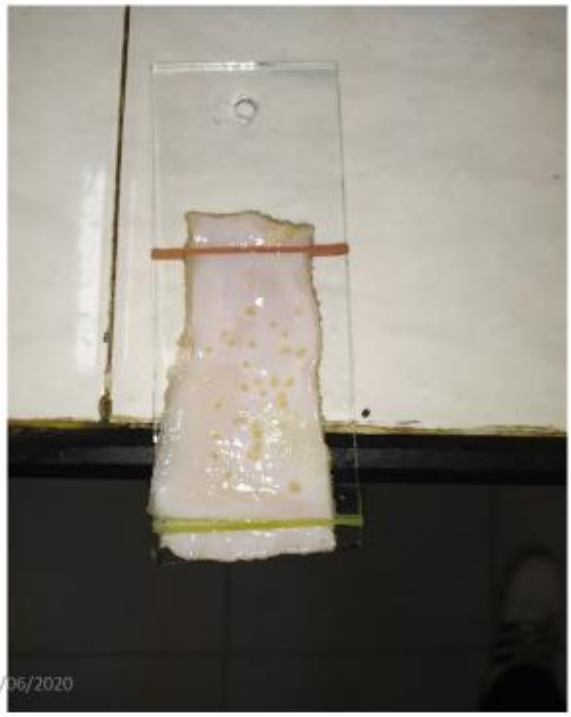
Images No.1 Preparation Of Alginate Beads

Evaluation parameters:

1. In Vitro Mucoadhesive strength:

Mucoadhesion strength of the Beads was measured by using sheep stomach mucosa as model mucosal membrane. Fresh sheep stomach mucosa was obtained from a local slaughter house and was used within 2-3 h of slaughtering. The mucosal membrane was washed with distilled water and then with pH 1.2. The mucoadhesive strength measurement apparatus was fabricated locally as shown in to the Image no.2 The mucoadhesive strength of the beads was determined using this locally fabricated apparatus. In vitro evaluation of the mucoadhesiveness of the beads, The beads were tested for their mucoadhesiveness according to the rinsing method designed by Ranga and Buri (1989). Briefly, pig stomachs were cut into 10×15 cm pieces and rinsed with 50 mL of physiological saline. 30 beads of each formulation were scattered uniformly on the surface of the gastric mucosa and then placed in a chamber maintained at 37^0C and 93% relative humidity. After 20 min, the mucosa was taken out and fixed on a polyacrylic support at an angle of 45^0. The stomach was then rinsed with SGF for five minutes at a rate of 300 mL/min. The number of beads still remaining on the surface of gastric mucosa was counted and the percentage of the remaining beads calculated.

$$\% \text{ Mucoadhesion} = \frac{\text{Number of adhered microbeads}}{\text{Total number of applied microbeads}} \times 100$$



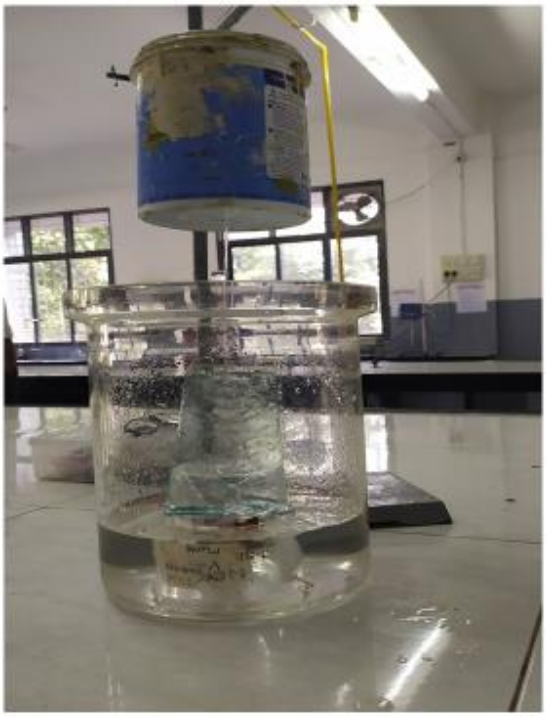


Fig no: 2 Images of Mucoadhesiveness

2) Entrapment Efficiency :

Beads (100 mg) were ground to a fine powder and transferred into a 100 ml volumetric flask with 90 mL distilled water. The suspension was sonicated in an ultrasonic bath for 60 min and the volume adjusted with distilled water to 100 mL. The suspension was filtered through a 0.45 µm nylon membrane filter, and 20 µL of filtrate was withdrawn and used to determine the entrapment efficiency by using Uv spectrometer, The EE was calculated according to the following equation.

$$EE(\%) = \frac{\text{Accual drug content}}{\text{Theoritical drug content}} \times 100\%$$

3) In vitro dissolution studies:

Dissolution tests were performed in USP dissolution eight dissolution apparatus II (paddles) at 37±0.5°C. The paddles were rotated at a speed of 100 rpm. The test was performed in 37±0.5°C with a rotation speed of 100 rpm using 900 mL of 0.1 N HCl, pH 1.2, as a dissolution medium. According to the sampling plan, samples of 5 mL were withdrawn till 12 hrs and immediately replaced with an equal volume of the respective dissolution medium maintained at 37±0.5°C. Test samples were filtered through Whatman filter paper for Sitagliptin Phosphate at 267 nm using a blank solution as reference with a UV-VIS double-beam spectrophotometer.

4) Floating properties:

The floating properties of the beads were evaluated in a flask filled with 250 mL of pepsin-free simulated gastric fluid (SGF) (0.1 N HCl, pH 1.2). For each formulation, 100 beads were placed in the flask and were then shaken in a horizontal shaking water bath at 50 rounds per minute and 37±1oC. The number (percentage) of floating beads was measured by visual observation.

Results and Discussion

I. Evaluation of Alginate Beads-

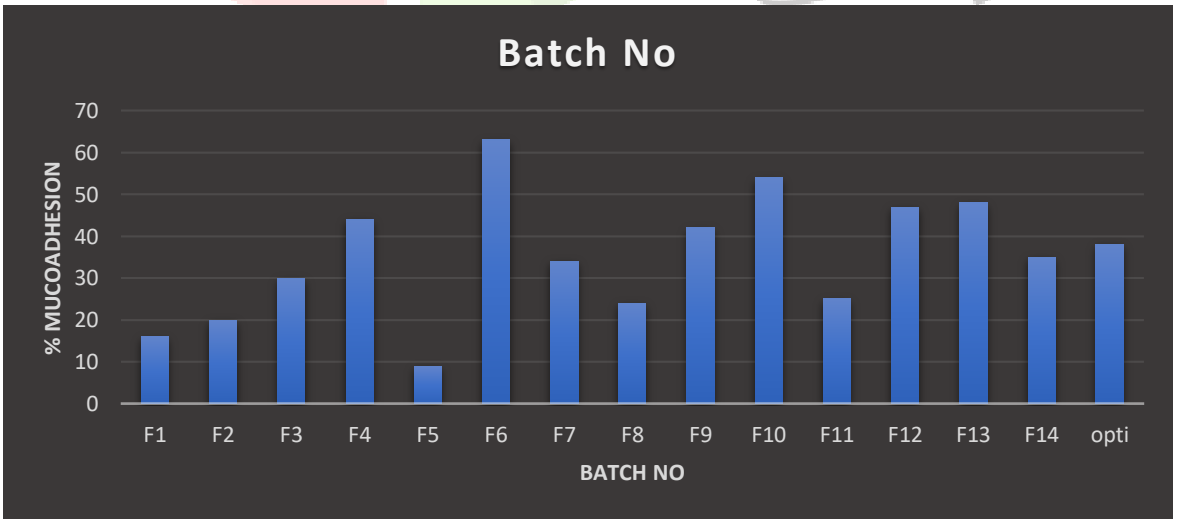
1. In vitro mucoadhesive strength:

In vitro mucoadhesive strength was carried out by using self-fabricated instrument.
Results for in vitro mucoadhesive strength and force of adhesion were shown in Table no.3

Table no 3: mucoadhesive strength of formulations(F1-F14 & optimised Batch)

Batch No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	opti
Total No of Applied Beads	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
No of Adhere Beads	5	6	9	13	9	19	10	7	12	16	7	6	14	10	11
% Mucoadhesion	16	20	30	44	9	63	34	24	42	54	25	47	48	35	37

Table No-3



Graph no:1 Percentage of Mucoadhesiveness

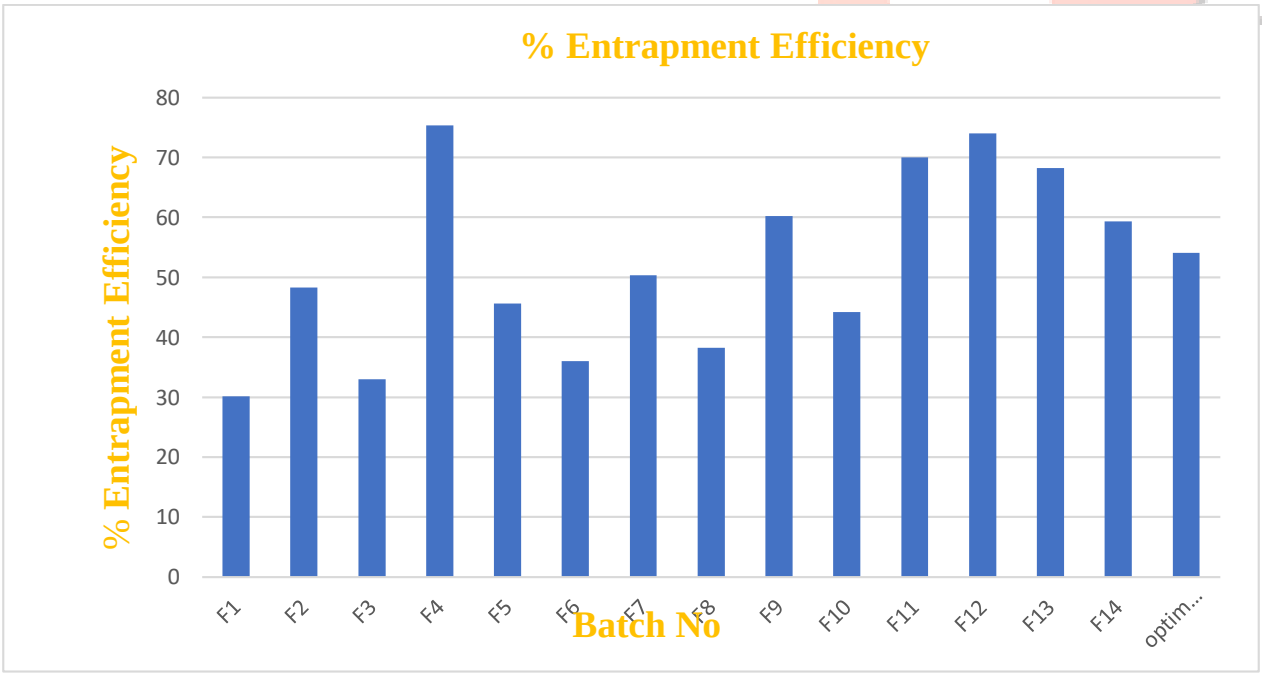
2. Entrapment Efficiency :

vitro Entrapment Efficiency was carried out . Results for in vitro entrapment efficiency and Percentage of entrapment were shown in Table no.4

Batch No	F1	F2	F3	F4	F5	F6	F7	F8	F9
(%) Entrapment Efficiency	30.14	48.33	33.00	75.31	45.66	3600	50.36	38.22	60.22

F10	F11	F12	F13	F14	opti
44.22	70.02	74.00	68.25	59.36	54.05

Table No 4



Graph No- 2 % Entrapment Efficiency

3. In vitro dissolution

Dissolution tests were performed in USP di., ssolution eight dissolution apparatus II (paddles) at 37±0.5°C. The paddles were rotated at a speed of 100 rpm. The test was performed in 37±0.5°C with a rotation speed of 100 rpm using 900 mL of 0.1 N HCl, pH 1.2, as a dissolution medium. According to the sampling plan, samples of 5 mL were withdrawn till 12 hrs and immediately replaced with an equal volume of the respective dissolution medium maintained at 37±0.5°C. Test samples were filtered through Whatman filter paper for Sitagliptin Phosphate at 267 nm using a blank solution as reference with a UV-VIS double-beam spectrophotometer.

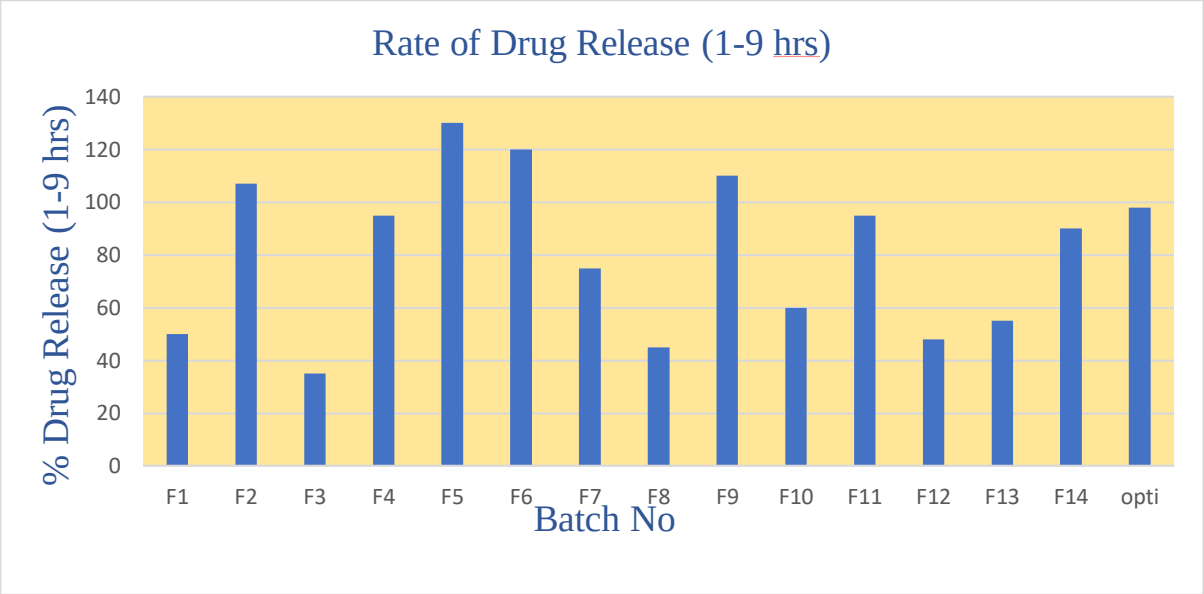
3.1 In vitro dissolution studies of formulations in (1- 9) Hrs

The in vitro drug release profiles for the formulations were tabulated in Table no.7 The plot of cumulative percentage drug release V/s time (Hr) were plotted and depicted in table no- 5.

Table no:5 % Cumulative drug release of Formulations (F_1-F_{14} & Optimised Batch)

Time (Hrs) / Sr.No	% DR – (1-9)Hr
1	72
2	67
3	63
4	59
5	67
6	60
7	54
8	69
9	64
10	60
11	57
12	51
13	48
14	52
Optimized	58

Table No-5



Graph No- 3

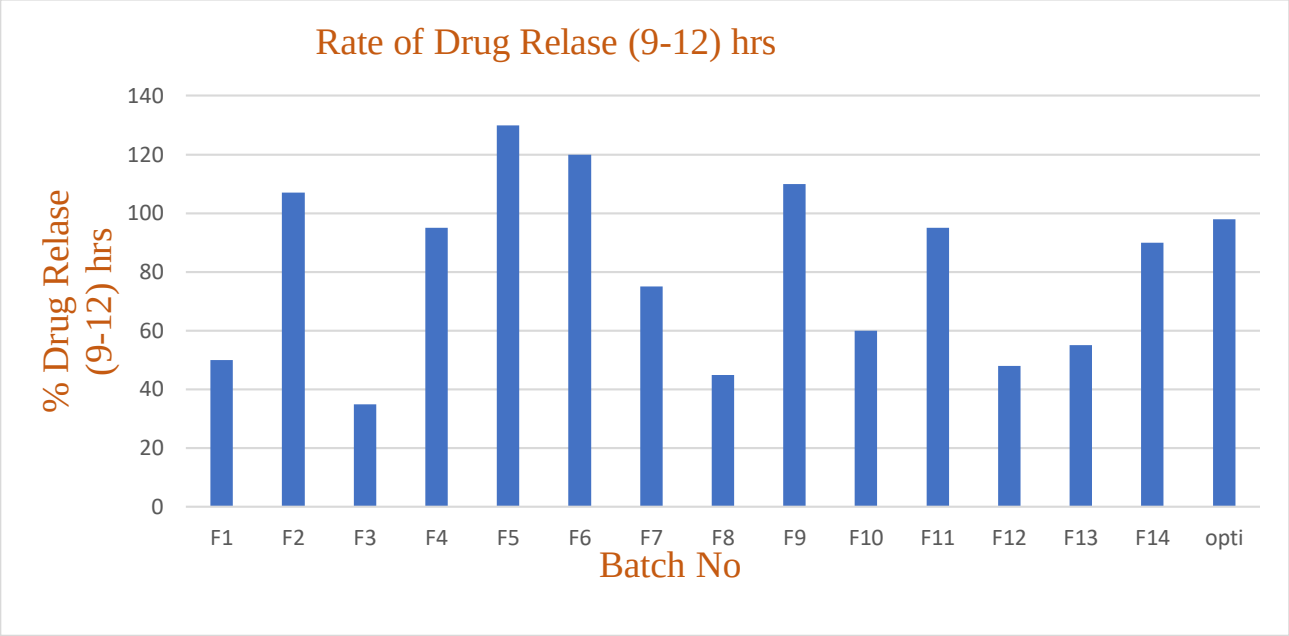
3.2 In vitro dissolution studies of formulations in (9-12) Hrs

The in vitro drug release profiles for the formulations were tabulated in Table no.6 The plot of cumulative percentage drug release V/s time (Hr) were plotted and depicted in Graph no-5 .

Table no: 6 % Cumulative drug release of Formulations (F_1-F_{15} & optimised Batch)

Time (Hrs) / Sr.No	% DR- (9-12)Hr
1	96.5
2	94.5
3	75
4	96.5
5	96.5
6	84
7	83.4
8	96.5
9	75
10	87.8
11	86
12	92
13	96.5
14	83
Optimize	88

Table No - 6



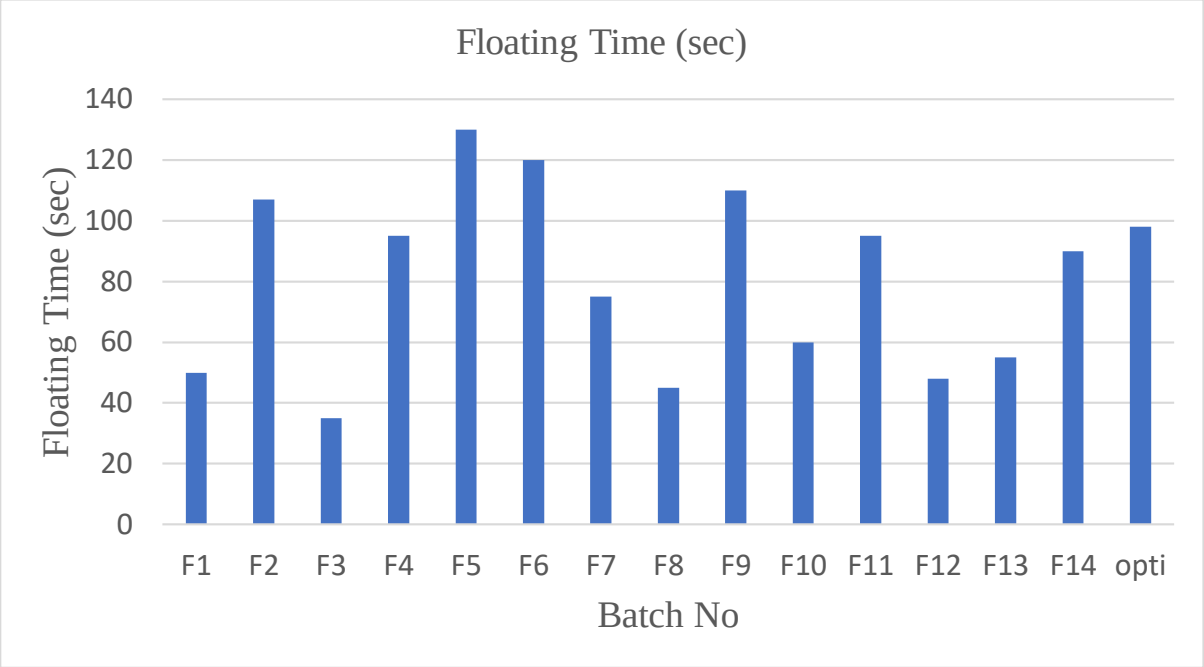
Graph No-5

1. Floating Lag Time:

The floating properties of the beads were evaluated in a flask filled with 250 mL of pepsin-free simulated gastric fluid (SGF) (0.1 N HCl, pH 1.2). For each formulation, 100 beads were placed in the flask and were then shaken in a horizontal shaking water bath at 50 rounds per minute and 37±1oC. The number (percentage) of floating beads was determined in table no-7

Batch no	Floating Lag Time (sec)
1	50
2	107
3	35
4	95
5	130
6	120
7	75
8	45
9	110
10	60
11	95
12	48
13	55
14	90
Optimised	88

Table No - 7



Graph No-6

Conclusion

Floating mucoadhesive alginate beads prepare different trials batches by using design expert.

Enhance buoyancy of alginate beads in stomach by using calcium carbonate.

Improvement of mucoadhesive strength by using Chitosan and retard drug release rate using sodium alginate.

Above the different trials batches the mucoadhesive strength batch no F6 & F10 maximum mucoadhesive was obtained.

Entrapment efficiency of above batch no F4,F9 and F12 maximum drug entrapment was obtained.

Above formulation batch no F5 and F6 sustained rate of drug release was obtained.

Acknowledgement

I deeply convey my special thanks and express deep sense of gratitude with sincerity to respected my guide Dr. S. F. Sayyad, Prof. & HoD of Pharmaceutics, Amrutvahini College of Pharmacy, Sangamner for his inspiring and instrumental role in providing me the research & infrastructure facilities at the college and encouragement for the successful completion of my project work. I express my sincere thanks to respected Dr. M. J. Chavan, Principal, Amrutvahini College of Pharmacy, Sangamner for providing me enthusiastic academic environment and industrial facilities required for research work.

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