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Review Article

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A Review on Gastro-retentive Floating *In-situ* Gel.

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Keywords

Gastro-retentive;
Floating;
Biodegradable;
Polymers;
Sustained.

Abstract

The present investigation deals with the formulation and evaluation of sodium alginate based In situ gelling system for controlled delivery of Lisinopril for the treatment of hypertension. Sodium alginate was used as a polymer and CaCO3 was used as a crosslinking agent varying concentration of sodium alginates were dissolve in distilled water containing sodium citrate and calcium chloride. This mixture was heated in 90^0 C and cooled to 40^0C then add Lisinopril and calcium chloride added with continuous stirring still to form uniform dispersion. The formulation of gel depends upon factors like temperature modulation, pH changes, presence of ions and ultra-violet irradiation, from which drug gets released in sustained and controlled manner. The objective of this study was to develop a novel in- situ gel. The system utilizes polymers that exhibit sol-to-gel phase transition due to change in specific Physico-chemical parameters. In-situ gel was formed at a biological ph. In vitro release studies were conducted in simulated gastric fluid and cumulative amount of drug release was analysed by spectrophotometry. From designed set of experiments, it was evident that formulation containing 0.5-1.5 % of sodium alginate control the release of drug for longer duration. The in-situ gel exhibited the expected, viscosity, drug content, pH, *in vitro* gelling capacity, *in vitro* floating ability and sustained drug release.

Introduction & Physiology of GIT

GRDDSs (Gastro-retentive drug delivery system) is one novel approach in this area. Dosage forms which can be retained in the stomach are called GRDDs. These dosage forms can improve the controlled release of drugs for a longer period of time before it reaches its absorption site.

GRDDSs also prolonging the gastric retention of the drugs for achieving therapeutic benefits of drug that are absorbed from GIT (gastro intestinal tract) or those are less soluble in or are degraded by alkaline pH.[1]

GRDDS are beneficial for such drugs by improving their

- Bioavailability
- Therapeutics efficiency and
- Possible reduction of the dose.

Drugs which easily absorbed from GIT and have short half-lives are eliminated quickly from the body. These drugs are required to be given in frequently doses to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a longer period of time.

The GIT is a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat, oesophagus, stomach, small intestine and large intestine. The wall of the gastrointestinal tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents. A full cycle consists of four phases, beginning in the lower oesophageal sphincter/gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum. Phase III is termed the housekeeper wave as the powerful contractions in this phase tend to empty the Stomach of its fasting contents and indigestible debris.

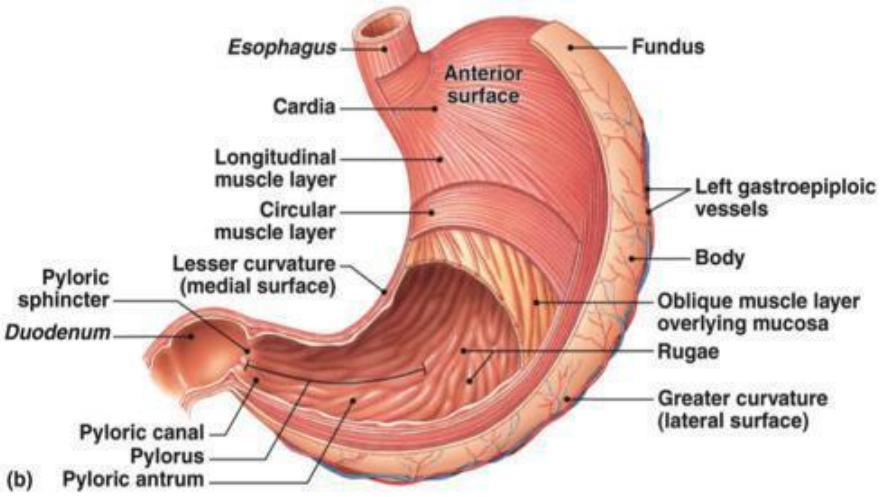


Figure – Physiology of GIT

During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the inter digestive myoelectric cycle, which is further divided into following 4 phases.[1]

Phase I: (basal phase) Period of no contraction.

Phase II: (pre-burst phase) Period of intermittent contraction

Phase III: (burst phase) Period of regular contraction at the maximal frequency that migrate distally.

Phase IV: Period of transition between phase III and phase I After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state.

Factors affecting gastric retention time of the dosage form [2]

Size: Dosage form units with a diameter of more than 7 mm are reported to have a increased gastric retention time compared with those with a diameter of 10 mm.

Density: Gastric Retention Time is a function of dosage form buoyancy that is dependent on the density.

Shape of dosage form: Ring and tetrahedron shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch are reported to have better gastric retention time 91% to 100% retention at 24 hours compared with other.

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 that occurs every 1.5 to 2 hours.

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.

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.

Biological factors: Diabetes and Crohn's disease.

Practical approaches for designing of floating drug delivery system

Different approaches have been introduced to increase the retention of oral dosage forms in the stomach. Some are formulated as single component whereas others are formulated as multi-component dosage forms. GRDDS can be broadly categorized into floating and non-floating system.

- Floating Drug Delivery System
- Non-floating Drug Delivery system:

Floating Drug Delivery System (FDDS):[3]

The floating system is intended to float in and over the gastric content resulting in prolonged gastric retention time (GRT). It is a low density approach which has a bulk density lower than gastric fluids and hence remains buoyant in the

stomach, releasing the drug slowly without affecting the gastric emptying rate for a prolonged period of time. After the drug is released from the stomach, the delivery system is expelled.

Mechanism of floating drug delivery system:[4]

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the Surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side as shown in fig. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

Classification of floating drug delivery system:

Based on the bouncy mechanism, floating system is classified as follows:

(A) Effervescent drug delivery system:

1. Gas generating system
2. Volatile liquid containing system.

(B) Non- effervescent drug delivery system:

1. Colloidal gel barrier system
2. Micro porous compartment system
3. Floating microspheres
4. Alginate floating beads
5. Raft forming system

Table : Dosage Form of FDDS with example of various drugs[5,6]

Sr. No.	Drug(s)	Dosage Form	Polymer(s)	Method of Preparation
1	Melatonin	Microspheres	Chitosan	Ionic Interaction
2	Repaglinide	Microspheres	Eudragit S	Solvent emulsion
3	Fluorescein Sodium	Beads	Casein-Gelatin	Emulsification Extraction
4	Acetohydraximic Acid	Microspheres	Eudragit E Carbopol	Novel Quassi emulsion
5	Verapamil	Microparticles	Polypropylene foam powder, Eudragit RS, Ethylcellulose, Methylacrylates	Solvent Emulsion
6	Nifedipine, Nicaedipine, Verapamile, Dipyridimol	Hollow Microspheres	Celluose Acetate	O/W emulsion

7	Riboflavin	Microballoons	HPMC,Eudragit S 100	Solvent emulsion
8	Meloxicam	Beads	Sodium alginates, Flurite RE	Ionotropic gelation
9	Piroxicam	Hollow Microspheres	Polycarbonates	Solvent Evaporation
10	Captopril	Tablet	HPMC, Carbopol, Na-alginate	Direct compression
11	Misoprostol	Capsule	HPMC	Conventional
12	Diltiazem HCL	Granules	Gelucire 43/01,HPMC,Ethocel 20 FP	Melt Granulation
13	Amoxycillin	Hydrogel	Chitosan, Carbopol	Ionic Interaction
14	Serratiopeptidase	Capsule	Glycerylmonooleate, Gelucire 43/10	Conventional

Table : Gastro-retentive product available in the market

Sr.No	Brand Name	Active Ingredient
1	Cifran OD	Ciprofloxacin
2	Madopar	Levodopa and benserazide
3	Valrelease	Diazepam
4	Topalkam	Aluminium-Magnesium Antacid
5	Almagate Flatcoat	Antacid
6	Liquid Gaviscon	Acid and Sodium bicarbonate

Formulation of *In-Situ* Gelation Mechanism [7,8]

The development of in situ gel systems has received considerable attention over the past few years. In situ gel forming drug delivery systems are principle, capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. Different mechanism which leads to in situ gel formation are:

- Ionic cross-linking
- pH change
- Temperature modulation

Polymers such as gelling gum, pectin and sodium alginate etc contains divalent ions which are

Complexes with sodium citrate which are braked down in acidic environment of stomach to release free divalent ions (Ca^{+2}) that causes in situ gelation of oral solution. It forms double helical junctions by aggregating double helical segments to form a dimensional network by complexation with cations and hydrogen bonding with water.

Various attempts are made to obtain retention of dosage form in stomach by increasing RT of stomach. These include introduction of different gastro retentive dosage forms as floating system (gas generating system and swelling and expanding system), muco adhesive system, high density systems, modified shape systems, gastric-empting delaying devices and co-administration of gastric empting delaying drugs. From this the floating drug delivery system (FDDS) is most commonly used. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolong period of time. When the system floats on gastric contents the drug is released slowly at the desire rate from the system.

After the drug is released, the residue is emptied from the stomach. This results in increasing the gastric empting time of stomach as well as controlling the fluctuations in PDC.

F = F buoyancy- F gravity= (Df- Ds) gv--- (1)

Different Approaches for *In-Situ* Gelling System [9,10]

There are different mechanisms reported for the formation of in-situ gel formation:

Chemical Stimuli

a. Ionic cross linking method

Physiological stimuli

a. Temperature-sensitive.
b. pH-sensitive.
c. Ion-sensitive.
d. Dilution sensitive.
e. Electrical signal-sensitive.
f. Light-sensitive.
g. Glucose-sensitive

Materials and Method: [11,12,13]

Materials

List of Materials/ chemicals

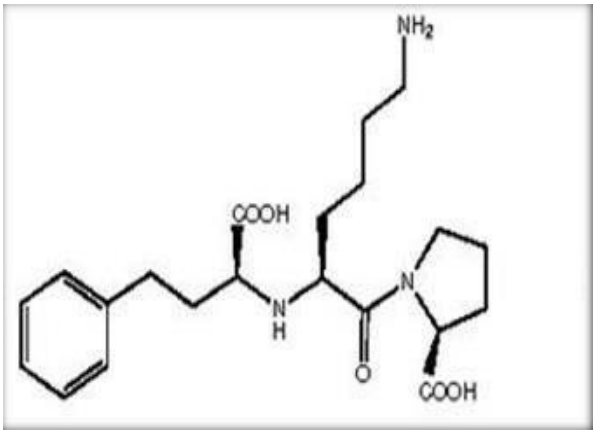
Table - List of Material/Chemicals used for dissertation work.

Sr.No	Name of Ingredients	Name of supplier
1	Lisinopril	Taj Pharmaceuticals, Mumbai
2	Sodium Alginates	Lobachemie Pvt. LTD. Mumbai
3	Calcium Chloride	Research lab fine chem. Industries, Mumbai.
4	Calcium carbonate	Research lab fine chem. Industries, Mumbai.
5	Sodium citrate	Research lab fine chem. Industries, Mumbai.
6	Hydrochloric acid	Research lab fine chem. Industries, Mumbai.
7	Methyl paraben	Lobachemie Pvt. LTD. Mumbai
8	Propyl paraben	Lobachemie Pvt. LTD. Mumbai

Drug and excipient profiles:

Polymers such as sodium alginate, calcium chloride, calcium carbonate contains divalent ions which are complex with sodium citrate which are braked down in acidic environment of stomach to release free divalent ions (Ca^{+2}) that causes in situ gelation of oral solution. It forms double helical junctions by aggregating double helical segments to form a dimensional network by complexation with cations and hydrogen bonding with water.[14,15]

Lisinopril Structure:



Structure of Lisinopril.

Molecular formula: C21H31O5N3

Synonym: (S)-1-(N2-(1-carboxy-3-phenylpropyl)-L-lysyl)-L-rolinedihydrate.

Molecular weight: 441.52

Appearance: white crystalline powder

Solubility: Very soluble in water, sparingly soluble in methanol, partially soluble in acetone and in ethanol.

Category: ACE inhibitor

Uses: Anti-hypertensive.
Dose: 2.5- 40mg

Storage: Preserve in tightly close container at cool and dark place.

Absorption: Approximately 25%

Protein binding: None

Elimination: renal, 100% unchanged.

Half life: 12 hrs

Binding : ACE only.

Characterization of drug and excipient

Organoleptic properties

Appearance and pH – The pH of a solution can be determined by using a digital pH meter.
Color– A small amount of drug was taken in butter paper and View in Dark place.
Odour –A Small amount of drug was taken and gets a smell.
Melting point determination - Melting Point of drug was determined by using capillary method.

Special characterization[16]

The λ_{max} determination

The 0.01g drug was dissolved in sufficient quantity of distilled water. This stock solution (i.e.100 µg/ml) was used further to make dilutions. According to the range obtain the dilutions where made between 4-24 µg/ml. This

solutions where then scanned from 200-400 nm on the double beam UV visible spectrophotometer in Wavelength of 205 nm (Shimadzu, UV-1650, Japan).

FT-IR study

The FT-IR study showed that there are no significant changes observed in the position of specific absorption bands of groups and bonds. The spectra of pure drug and mixture showed slight changes but there is no change in the absorption bands of drug which indicate that there is no interaction between drug and excipients. So, lisinoprildihydrate, sodium alginates, and all excipients were found to be compatible with each other.

Differential scanning colorimeter

DSC is frequently a preferred thermal analytical technique because of its ability to provide detailed information about both the physical and energetic properties of a substance. This is often information that cannot be obtained as accurately, easily, or quickly using any other technique. In differential thermal analysis, the difference in temperature between a sample and a reference material is measured as a function of a pre-programmed temperature cycle. The sample and reference thermocouples are located beneath the pans in an electrically heated furnace. The sample thermocouple is used by the microcomputer to control the furnace temperature, so that the sample temperature increases linearly. The difference in temperature between the sample and reference is plotted against sample temperature, Thermo gram of pure drug, drug loaded capsule of optimize batch were obtained.

Experimental method[17,18]

Calibration Curve of lisinopril in 0.1 N HCl

Calibration curve of lisinopril was taken on UV Visible Spectrophotometer (Shimadzu, UV-1800, Japan) by scanning diluted solution was prepared in range of 3-18 µg/ml and analyzed the solution and absorbance was taken.

Calibration Curve of lisinopril in water

Calibration curve of lisinopril was taken on UV Visible Spectrophotometer at 205nm (Shimadzu, UV-1800, Japan) by scanning diluted solution was prepared in range of 4-24 µg/ml and analyzed the solution and absorbance was taken

Experimental Design (3^2 factorial design)

The 3^2 full factorial design was constructed and the concentration of sodium alginates (X_1) and calcium carbonate (X_2) where the two factors selected. The concentration of two factors was selected on basis of preliminary studies carried out during experimental work and the other parameters where kept constant throughout the experimental work.

Preparation of floating *in-situ* gelling solution

Sodium alginate, at varying concentration of 0.5-1.5 W/V were dissolve in deionize water, previously containing sodium citrate (0.25% W/V) and calcium chloride (0.016% W/V). The sodium alginate containing mixture will be heated in 90^0C with stirring continuously on magnetic stirrer. Then cool below 40^0C various concentrations of calcium carbonate and drug will be added after cooling the solution below 40^0C with continuously stirring to form a uniform dispersion

Evaluation of floating *in-situ* gel of Lisinopril [19]

i. Measurement of viscosity of *in-situ* gelling solutions

Viscosity of the solution prepared using various concentrations of gelling agents can be determined by viscometers like Brookfield viscometer, Cone & plate viscometer etc., Viscosity of the formed gel can also be determined to estimate the gel strength.

ii. In-vitro gelation study

In general the gelling capacity of an *in situ* gel forming system can be determined by formulating a colour solution of *in situ* gelling system for visual observation. By adding the in-situ gelling formulation to a medium (simulating gastric fluid), various parameters like the time taken for *in situ* gel formation, its stiffness and the duration for which formed gel remains intact, can be estimated.

iii. In-vitro buoyancy study

After adding a fixed volume of *in situ* gelling formulation to a medium (simulating gastric fluid ,0.1N HCL,1.2 pH), the parameters like the time taken for the system to float over the surface of medium (floating lag time) and the time the formed gel constantly float over the surface of the dissolution medium (floating time) can be estimated.

iv. In-vitro drug release study

The release rate of drug from in situ gel can be determined using USP dissolution rate testing apparatus I (basket covered with muslin cloth) at 50 rpm. 900 ml of 0.1 N HCl can be used as dissolution medium and temperature of 37+0.5oC can be maintained. 5 ml samples can be withdrawn at various time points for estimating the drug release using UV-Visible spectrophotometer. Same volume of fresh medium has to be replaced every time the sample is withdrawn. measured at 206nm on double beam UV visible Spectrophotometer (Shimadzu, UV-1650, Japan).

v. Stability Studies

A stable product is one that shows no significant degradation or changes in its physical, chemical, microbiological, and biological properties, with the product remaining within its specification. The stability of pharmaceutical ingredients and the products containing them depends on (*a*) the chemical and physical properties of the materials concerned (including the excipients and container systems used for formulated products) and (*b*) environmental factors such as temperature, humidity, and light and their effect on the substances in the product. Stability data on the drug substance and the formulated product are required in connection with applications for marketing authorizations for pharmaceutical products containing new active substances, for products containing known active substances (including reformulations), for additional strengths or dosage forms, for new containers, and for amendments or variations to existing marketing authorizations, including new sources for active ingredients, extensions to the shelf life, and soon. The optimized formulation was sealed in the vials and kept in humidity chamber maintained 40 ± 2^0C/ 75±5% RH for 1 month. After 30 days samples were retrieved and analyzed for drug content, viscosity, pH, in-vitro drug release etc.[20]

Conclusion

The lisinopril was selected for the preparation of the in situ gelling system for its sustained drug delivery in stomach. lisinopril is a Class 3 drug & it has a high solubility and low permeability. lisinopril is a ACE inhibitor & it is used as a treatment of heart failure, hypertension, kidney failure, prevent the congestive heart failure, and myocardial infraction. Lisinopril has a just 25% Bioavailability. drug has a narrow therapeutic index & it less absorbed in stomach, so lisinopril is suitable for a gastro-retentive drug delivery system.

The gastro-retentive floating in situ gel was prepared using calcium chloride as a cross linking agent. When sodium alginates and calcium carbonate used at varying concentration 0.5-1.5 % in preparation of in situ gelling solution. When sodium alginates was dissolved in Distilled water previously containing sodium citrate and calcium chloride. This solution was heated at 90^0C. then this solution cooled at 40^0C, then drug added in cooled solution, completely dissolved the drug, then add calcium carbonate in solution with continuously stirring still to form a uniform dispersion.

The drug and excipient characterization was done by using Differential Scanning Colorimetric (DSC), FT-IR Spectroscopy, UV-Visible Spectroscopy analysis showed drug pure and compatible with all polymer and excipient used in formulation. The calibration curve of drug was done by 0.1 N HCL and water which showed linearity & r^2 values obtained were 0.9987 & 0.997 respectively.

The evaluation parameter of formulation was done such as pH of solution, gelling capacity, floating lag time, duration of floating, viscosity of gelling solution, drug content, in vitro drug release, drug release kinetic of optimized batched and finally the stability studies was done..

The viscosity of optimized batch (F7) was found to be 283 cps & had good flowability. The floating lag time of lisinopril floating in situ gelling solution was less than 3 minutes. The duration of floating was up-to 22 hrs. & gelation is within few seconds. The drug content of optimized batch was found to be 97.64 % and drug release was found to be 93.78 % at 10 hrs.
The formulation was prepared for sustained drug release in form of floating in-situ gel and it there was no significant change in the viscosity, drug content and in-vitro drug release of formulation.

The Gastro-retentive Floating in-situ gel was successfully fabricated by ionic cross linking method. According to result obtained the in-situ gel gelling property depends on concentration of gelling agent and concentration of calcium carbonate. Concentration of gelling agent increase floating lag time and hardness of gel also increase. Also the concentration of calcium carbonate increase and viscosity of formulation also increase.

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