Formulation and Evaluation of Oral In-Situ Gel of Esomeprazole

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Abstract **- The 'In situ gel' system emerged as one of the best Novel Drug Delivery System used for sustain and control drug delivery by its special characteristic feature of 'Sol to Gel' transition. Generally, Esomeprazole is used as Proton pump inhibitor which belongs to class II of BCS Classification i.e., Low solubility and High permeability. The half-life of drug is found to be less than 2 hrs, so in order to prevent repetitive administration of drug and to improve patient compliance (Bed ridden patients), the present study focus on formulation and Evaluation of Sustain release of oral 'In situ gel'. Sodium alginate is used as Gelling polymer and Calcium carbonate was used as a cross linking agent. Other polymers such as Pectin, HPMC, and PEG 4000 are used to enhance the gelling capacity and also act as drug release retarding polymers. Methyl paraben is used as Preservative and sorbitol is used as sweetening agent. Sodium bicarbonate and calcium carbonate contributes to floating capability. Totally Nine formulations are prepared by varying different concentrations of Sodium alginate, PEG 4000 and HPMC. These are further evaluated for Viscosity, Gelling Time, Floating Time, Assay and Invitro release studies in order to select the best optimized formulation.**

Index Terms **- 'In situ gel', Esomeprazole, Sodium alginate, Methyl paraben.**

INTRODUCTION

Gels: Gels are Intermediate state of matter containing both liquid and solid components.
It consists of Three-dimensional solid networks. As it has three-dimensional solid network, Gels are mainly classified into two types based on the nature of the bonds.

Physical gels
It arises when weak bonds like hydrogen bonds, electrostatic bonds and Vander Waal bonds constitute together to maintain the gel network.

Chemical gels
It arises when strong covalent bonds constitute to maintain the gel network. The network indicates the presence of cross-links which helps to avoid the dissolution of the hydrophilic polymer in an aqueous medium.

Hydrogels:
Hydrogels are the three-dimensional structures that have polymeric networks which have the capacity to absorb and retain large amounts of water and biological fluids to swell.

Classification of Hydrogels: It is of two types:
Preformed Hydrogels
These are defined as simple viscous solutions which do not undergo any modification after administration.

In-situ gels
These are the solutions or suspensions that undergo Gelation after reaching the particular site due to Physico- chemical changes.

In-situ gelling system:
In-situ gelling system has become one of the most prominent among novel drug delivery systems due to many advantages such as improved patient compliance, reduced frequency of drug administration. 'In-situ' is a Latin word which means 'in position'.
There are many triggering mechanisms in in-situ gel formation some of them are pH change, temperature modification and solvent exchange. As the gel formed from in-situ gelling system, being lighter than gastric fluids float over stomach contents due to the presence of bio adhesive nature of polymers resulting in prolonged gastric retention time. So, this type of formulation mainly comes under Gastro Retentive

Floating drug delivery system .In-situ gels are the formulations that are in sol form before administration in the body, but once administration undergo gelation to form gel. Various routes of administration of In-situ gelling systems is oral, nasal, ophthalmic, vaginal, Injectable, Intraperitoneal and rectal route.1

Oral in situ gel forming system also known as stomach specific systems have provided a suitable way of providing the controlled drug delivery within stomach with enhanced gastro- retention. This new concept of production a gel in-situ was suggested first time in the early 1980s.

In situ gelling drug delivery system is capable of releasing drug in a sustained manner, maintaining relatively constant plasma conc time profiles. In-situ gel forming polymeric formulations is in sol form before administration undergo gelation in situ to form a gel. These in situ solutions are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. Floating In- situ gel drug delivery systems have been used to deliver many drugs which are used either for their systemic (or) for their local effects in the stomach .Gelation occurs via the cross linking of polymer chain that can be achieved covalent bond formation (chemical cross linking) or non-covalent bond formation (physical cross linking).2

Advantages:

Simple manufacturing process, ease of administration, reduced frequency of administration, improved patient compliance and comfort, compared to conventional dosage form.

It also promotes deliverance of accurate dose as well as prolongs residence time of drug at the site of administration.

In situ gel formation occurs due to one or combination of different stimuli like change in pH, temperature or solvent exchange, ionic cross linkage, ionization, UV irradiation.

Low dose is required for treatment

Minimum local and systemic side effects

Increased residence time and improved bioavailability

It can also be administered to unconscious patient.

It shows local action and site specificity by acting directly onto the targeted site.

Disadvantages:

It is more susceptible to stability problems due to chemical degradation.

It requires high level of fluids.

IMPORTANCE OF IN SITU GELLING SYSTEM:3

The major importance is the possibilities of administrating accurate &reproducible quantities compared to already formed gel.

In-situ forming polymeric delivery system such as ease of administration &reduced frequency of administration improved patient compliance & comfort.

IDEAL CHARACTERISTICS OF POLYMERS

A polymer used to in situ gels should have following characteristics:

It should be biocompatible.

It should be capable of adherence to mucus.

It should be good tolerance.

FORMULATION DESIGN

The design of In-situ gel formulation depends on the physicochemical properties of the drug molecule, the diseased condition for which treatment is required, the patient population and the marketing preference. Physicochemical factors include molecular weight, lipophilicity and molecular charge). While formulation factors include clarity, pH, gelation temperature, viscosity, osmolarity, spread ability.

MATERIALS AND EQUIPMENTS

The following materials were used as supplied by the manufacturers.

Materials Used

S. No.	Chemicals	Supplied by
1	Esomeprazole Magnesium Trihydrate	Gift Sample
2	HPMC	Oxford Laboratories, Mumbai
4	Sodium Alginate	S.D. Fine Chem. Ltd, Mumbai
5	Sodium Bicarbonate	S.D. Fine Chem. Ltd, Mumbai
6	Pectin	Signet chemicals Ltd.
7.	PEG 4000	Signet chemicals Ltd.
8	Caco3	Oxford Laboratories, Mumbai
9	Sodium citrate	Signet chemicals Ltd.

10	Methyl paraben	Signet chemicals Ltd.
11	Mannitol	Signet chemicals Ltd.

Table 1: Materials used Equipments Used

S. No.	Equipment	Supplied by
1	Dissolution test apparatus	Lab India
2	Mechanical stirrer No. 1A323	REMI
3	UV-Visible Spectrometer Model	SCHIMADZU UV-Vis spectrometer
4	Dryer: Hot Air Oven	Asian test Equipments
5	Electro Balance	Sartorious precision balance
6	P^h Meter	Thermo
7	Brooke –field viscometer	Wensar

Table 2: Equipments used

EXPERIEMENTAL METHODOLOGY

Preformulation study
Method of Preparation
Post formulation study

Preformulation study
Following are the tests performed for the preformulation study:
Organoleptic properties
Melting point
UV Scanning
Construction of Calibration curve
Gelling nature of Polymers

Organoleptic Properties
The Esomeprazole drug is evaluated for color ,odor and appearance.

Melting point
The melting point of Drug is determined by using melting Point apparatus and is noted

UV Scanning
The Spectrum for drug is observed by using uv spectrophotometer. For this 100mg drug is taken and dissolved using DMSO solvent and is make upto 100 ml using 0.1N HCl P^h1.2 .From this 10 ml is taken and make upto 100 ml using same above buffer. From Stock II a known concentration of 10mcg/ml is prepared by taking 1ml and diluted to 10 ml. For the above concentration the spectrum is run at uv range of 200-400 nm to obtain a curve. From this curve λ max is recorded.

Construction of standard calibration curve of Esomeprazole [17]:
For this 100mg drug is taken and dissolved using DMSO solvent and volume was made up to 100 ml in 100 ml volumetric flask (Stock I) to obtain (1000mcg/ml). From This stock I solution 10 ml was taken and further diluted to 100 ml with (0.1 N HCl, pH 1.2) to obtain solution of
100 mcg/ml (Stock II). From this Serial dilution of 5,10,15,20 and 25 mcg/ml was prepared by taking 0.5, 1, 1.5, 2and 2.5 ml and diluted to 10 ml using 0.1N HCl . The absorbance of each solution was measured at λmax 285 nm using UV spectrophotometer. The standard curve was obtained by plotting absorbance v/s. concentration (µg/ml).

Gelling nature of Polymers
Weigh required quantity of all polymers i.e., HPMC, Alginate ,Pectin, PEG as per in formaulation table and transfer them individually into a beaker containing 50 ml of deionised water and stir it using Mechanical stirrer For 20 minutes .from this Beakers containing Polymers solutions pipette out 10 ml and transfer it into a beaker containing 100 ml of 0.1N HCl individually .The gelling nature of individual polymer is noted down.

Method of Preparation [18]
SA (sodium alginate) Solutions were prepared in distilled water by heating to 60ºC under continuous stirring. After cooling below 40ºC ingredients including drug, gelling agent and other excipients were weighed accurately and formulations were prepared as per given in the table. The resulting solution is mixed using Mechanical stirrer for a period of 15 minutes to ensure uniformity. Finally it is make up to required quantity using deionised water and stored in amber coloured bottles until further use.

Formulation of IN-SITU Gel Preparation F1 to F9

Formulations	Drug	Sodium alginate	Pectin	HPMC	PEG 6000	Caco3	NaHco3	Sodium citrate	Methyl paraben	Manni tol	Water
F1	0.2g	0.50g	0.1g	0.1g	-	0.20g	0.20g	0.02g	0.01g	0.02g	Qs to50 ml
F2	0.2g	0.75g	0.1g	0.1g	-	0.20g	0.20g	0.02g	0.01g	0.02g	Qs to50 ml
F3	0.2g	1g	0.1g	0.1g	-	0.20g	0.20g	0.02g	0.01g	0.02g	Qs to50 ml
F4	0.2g	0.50g	0.1g	-	0.1g	0.20g	0.20g	0.02g	0.01g	0.02g	Qs to50 ml
F5	0.2g	0.75g	0.1g	-	0.1g	0.20g	0.20g	0.02g	0.01g	0.02g	Qs to50 ml
F6	0.2g	1g	0.1g	-	0.1g	0.20g	0.20g	0.02g	0.01g	0.02g	Qs to50 ml
F7	0.2g	0.50g	0.1g	-	0.2g	0.20g	0.20g	0.02g	0.01g	0.02g	Qs to50 ml
F8	0.2g	0.75g	0.1g	-	0.2g	0.20g	0.20g	0.02g	0.01g	0.02g	Qs to50 ml
F9	0.2g	1g	0.1g	-	0.2g	0.20g	0.20g	0.02g	0.01g	0.02g	Qs to50 ml

Table 3 : Formulation of Esomeprazole F1 to F9

Post formulation study

Following are the tests performed for the post formulation study:

P^H Measurement.

Gelation Studies.

Floating behaviour

Viscosity Measurement.

Drug Content Determination.

In-vitro Drug Release Study.

Evaluation Parameters

PH Measurement

The pH was measured in each of the sodium alginate based in situ solutions, using a calibrated digital pH meter at room temperature. The measurements of pH of each data were noted.

Gelation Studies

Gelation studies were carried out using 0.1 N HCl. Take 5ml of Formulation and transfer into a beaker containing 100 ml of 0.1 N HCl. In this time required to obtain gel is recorded. In these studies the gelling capacity (gelling speed and extent of gelation) for all formulations were determined. Gelation characteristics were assessed ranging between + (poor), ++ (good), +++ (very good).

Floating behaviour

The floating ability of the prepared formulations was evaluated in (0.1N HCl, pH 1.2) Solution. The floating time of the prepared formulation took to emerge on the medium surface (floating lag time) was noted .The time the formulation constantly floated on the dissolution medium surface (duration of floating) was also evaluated

Viscosity Measurement

The viscosity value of prepared formulations were measured by using Brookfield viscometer with spindle LV 1 at 1.5, 3and 6 rpm at room temperature. The viscosity readings are noted.

Drug Content Determination

Formulation equivalent to 40 mg i.e., 10 ml of Esomeprazole was accurately taken and Transfer it to a 100 ml volumetric flask containing 100 ml 0.1 N HCl. Shaken vigorously for 30 min and then sonicated for 20 min and filter it. Dilution of filtrate were made with

0.1 N HCl. Absorbance of this solution was observed at 285 nm (λmax of Esomeprazole) values were substituted in the equation of calibration curve to obtain concentration.

In-vitro dissolution study:

In-vitro release profile was studied using USP apparatus TYPE II at 37° ± 1° C with a rotating speed of 50 rpm in dissolution media which containing o.1 N Hcl P^h 1.2 buffer. During the study, 5 ml of aliquots were removed at fixed time intervals (1, 2, 3, 4, 5, 6, 7, 8 hr) from the dissolution medium and replaced with fresh buffer to ensure sink condition and drug content can be determined by spectrophotometrically.

RESULTS

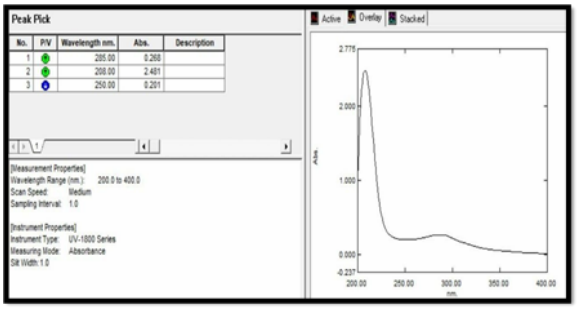
Pre-Formulation Studies:

Physical Appearance:

It appears as white to slightly colored crystalline powder

Melting Point: Its Melting Point Was found to be 155ºc.

SPECTRUM Results



Pre-Formulation Studies:

Physical Appearance:

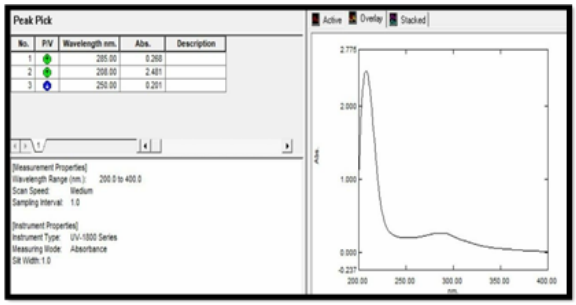
It appears as white to slightly colored crystalline powder

Melting Point:

Its Melting Point Was found to be 155ºc.

SPECTRUM OF ESOMEPRAZOLE UV SCANNING

The λ max was found to be 285 nm and Absorance value was found to be 0.268.



Standard calibration Curve of Esomeprazole

S.No	CONC	ABSORBANCE
1	5	0.084
2	10	0.203
3	15	0.285
4	20	0.375
5	25	0.455

Table 4: standard Calibration Curve:

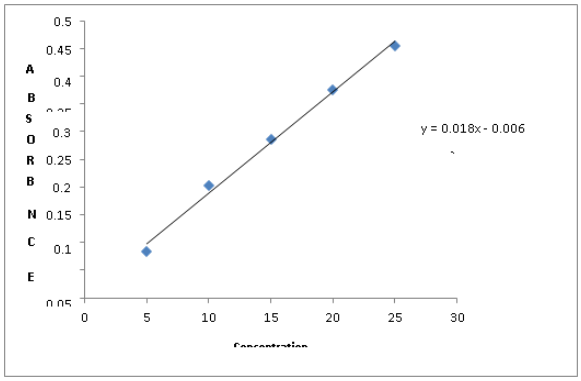


Fig 7: Standard calibration Curve

Formulation	% Drug Content
F1	86.83
F2	87.33
F3	88.83
F4	89.33
F5	89.83
F6	90.33
F7	90.83
F8	91.33
F9	91.83

Table :5 Determination of Absorbance

Formulation	PH	Formulation	Gelling Time
F1	7.04	F1	5 sec
F2	7.00	F2	4 sec
F3	7.67	F3	5 sec
F4	7.74	F4	5 sec
F5	7.60	F5	4 sec
F6	7.65	F6	4 sec
F7	7.89	F7	5 sec
F8	7.93	F8	5 sec
F9	7.01	F9	5 sec

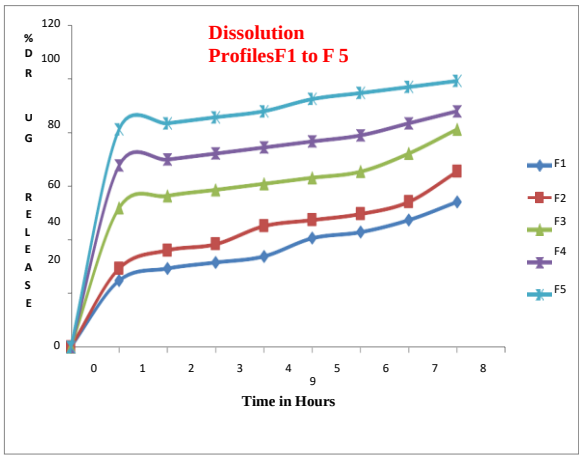
Table 6: Determination of Gelling Time Floating Time: Dissolution Profiles (F1 to F5):

Time	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	24.75	29.25	51.75	67.5	81
2	29.25	36	56.25	69.75	83.25
3	31.5	38.25	58.5	72	85.5
4	33.75	45	60.75	74.25	87.75
5	40.5	47.25	63	76.5	92.25
6	42.75	49.5	65.25	78.75	96.75
7	47.25	54	72	83.25	96.75
8	54	65.25	81	87.75	99

Table 07: Dissolution Profiles F 1 to F 5

Time	F6	F7	F8	F9
1	79	82	83	85
2	81.5	84.5	85.5	84.25
3	84.4	86.4	86.2	87.5
4	85.5	87.72	88.72	89.75
5	90.21	90.01	91.01	92.25
6	92.24	93.45	92.45	94.5
7	94.45	95.55	96.55	97.75
8	95.54	96.62	98.62	99

Table 08: Dissolution Profiles (F6 to F9)



Time (Hr)	Cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released	% Drug released
1	24.75	75.25	1.000	1.877	0.000	0.000	100
2	29.25	70.75	1.414	1.850	0.301	1.466	4.5
3	31.5	68.5	1.732	1.836	0.477	1.498	2.25
4	33.75	66.25	2.000	1.821	0.602	1.528	2.25
5	40.5	59.5	2.236	1.775	0.699	1.607	6.75
6	42.75	57.25	2.449	1.758	0.778	1.631	2.25
7	47.25	52.75	2.646	1.722	0.845	1.674	4.5
8	54	46	2.828	1.663	0.903	1.732	6.75

Table 09: Kinetics of Optimised Formulation (F1)

DISCUSSION

Controlled drug delivery can be greatly achieved by using various solid oral dosage forms but may not be suitable for patients with age related Dysphagia or clinical/pathological conditions like Tracheostomy, congestive heart failure, postoperative conditions etc. Identifying the clinical need of such controlled release dosage forms that suits to pediatric, geriatric, dysphagic or bed ridden patients can be well appreciated in this scenario. Oral administration of liquid dosage forms of suitable consistency and with sustained release characteristics may provide a suitable solution in the present situation which can be achieved by the development of *in situ* gelling solutions.

The development of *in- situ* gel systems has received considerable attention over the past few years because of their simpler method of formulation and cost effectiveness. *In situ* gel forming drug delivery systems in principle are capable of releasing drugs in sustained/controlled 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. These have a characteristic property of temperature dependent, pH dependent and cation induced gelation. Compared to conventional controlled release formulations, *in situ* forming drug delivery systems possess potential advantages like simple manufacturing process, ease of administration, reduced frequency of administration, improved patient compliance and comfort.

The '*In situ* gel' system emerged as one of the best Novel Drug Delivery System used for sustain and control drug delivery by its special characteristic feature of 'Sol to Gel' transition. Generally, Esomeprazole is used as Proton pump inhibitor which belongs to class II of BCS Classification i.e. ., Low solubility and High permeability. The half-life of drug is found to be less than 2 hrs, so in order to prevent repetitive administration of drug and to improve patient compliance (Bed ridden patients), the present study focus on formulation and Evaluation of Sustain release of oral *Insitu* gel. Sodium alginate is used as Gelling polymer and Calcium carbonate was used as a cross linking agent. Other polymers such as Pectin, HPMC, and PEG 4000 are used to enhance the gelling capacity and also act as drug release retarding polymers. Methyl paraben is used as Preservative and sorbitol is used as sweetening agent. Sodium carbonate and calcium carbonate contributes to floating capability. Totally Nine formulations are prepared by varying different concentrations of Sodium alginate, PEG 4000 and HPMC.

In this Thesis work sodium alginate was mainly used as gelling Agent, which was taken at a conc of 0.5 for F1 ,F4, F7 formulation ,0.75 g conc for F2, F5, F8 Formulation and 1g conc. For F3,F6,F9 formulations respectively .The pectin polymer was kept at constant ratio in all formulations i.e., 0.1 g. The HPMC polymer was used at conc of 0.1 g from F1 to F3 Whereas PEG was used at a concentration of 0.1 g from F 4 to F6 Formulations and 0.2g conc from F7 to F9.

Out of the Four polymers used here in this Formulations i.e., Sodium alginate, HPMC, PEG, Pectin only Sodium alginate polymer is responsible for

Formation of Insitu gel . Due to change in P^H the Sodium alginate cross links and forms a gelling like consistency. It can be observed in Fig 8 .A, 8.B ,8.C.

The Insitu gel appearance was found to be good both in consistency and appearance with PEG polymer Rather than HPMC polymer in all Formulations. It can be observed in Fig 9.A, 9.B But the drug Release studies With HPMC polymer justifies the sustain drug release rather than PEG polymer.

During first trial periods of our study excess concentration of Pectin, HPMC and PEG which was taken at a value of 0.5 g initially forms a good solution and upon transfer into O.1N Hcl leads to formation of gel, but after one week we noticed gelling of polymer in Amber coloured bottles which is mainly due to water absorbing capacity of pectin polymer so we reduced the polymer concentration to 0.1 g which was found to be stable.

The formulations were evaluated both for Gelling and Floating time. All the formulations tends to float and gel within seconds and the floating and gelling capacity were retained for a period of more than 9 hrs Even though the consistencty with PEG was found to be good but it fails in sustain drug release because within first hour itself for formulations F5 to F9 80 % drug has been released. So now we are considering Formulations with HPMC polymer i.e, F1 to F3 but for F3 formulation the drug release was fond to be 50 % within First hour. Comparing F1 and F2 formulations the Drug release for F1 is slow compared to F2.so now based on above discussion F1 formulation was choosen as optimised one compared with remaining Formulations

CONCLUSION

The Esomeprazole *Insitu* g*el* was prepared by using Sodium alginate polymer as gelling agent and HPMC as rate retarding Polymer. Mannitol is used as sweetening agent; sodiumbicarbonate enhances the effervescence which emphasizes floating of gel. The Optimised F1 formulation was prepared by using sodium alginate at 0.5 g conc and remaining polymers HPMC and pectin were taken at 0.1 g conc , Methyl paraben and Sodium citrate were used as preservatives. The Floating Time was greater than 9 Hr and gelling occurs within less than 5 seconds. The viscosity and P^H of F1 was found to be 83.97 cps and 7.04 .The assay value was found to be 86.83. The percentage Drug release from first hour to 8 hours ranges from 24.75 to 54 % which indicates that drug releases for more than 12 hrs justifying the sustain drug release of In-situ gel Formulation. Finally the kinetic release data shows that Drug release follows Zero order model and mechanism of Drug release was diffusion.

ACKNOWLEDGEMENT

All thanks and praises to God Almighty for his countless, abundant and never-ending blessings in completing this work. It is a proud privileged honor for us to express our hatful thanks and gratefulness to all the persons who backed us directly or indirectly through out of this research work as magnitude. Most importantly authors are thankful to patients and health care professionals.

Conflict of interest: No

Funding: Self

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