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FORMULATION AND EVALUATION OF GASTRORETENTIVE IN SITU GELLING SYSTEM OF SAXAGLIPTIN

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ABSTRACT

Gastroretentive floating In-situ gel refers to a polymer solution of low viscosity which upon coming in contact with the gastric fluids; undergoes change in polymeric conformation and a viscous strong gel of density lower than the gastric fluids is produced. The gelation can be triggered by temperature modulation, pH change, and ionic crosslinking. Insitu gels can be administered by oral, ocular, rectal, vaginal, injectable and intra-peritoneal routes.

Moreover, presence of $CaCl_2$ shows significant increase in gel strength, the degree of rigidness of gel increases due to increasing degree of crosslinking of divalent Ca^{2+} ions with the polymer chains. The $CaCl_2$ which upon contact with 0.1N HCl (pH 1.2) the liquid polymeric solution should undergo a rapid sol-to-gel transition by means of ionic gelation. The composition of gastric fluid is rich in Cl^- ions; hence on interacting with $CaCl_2$ as cross-linking agent, in-situ gel formed rapidly. In-situ gel formed should preserve its integrity without dissolving or eroding so as to localize the drug at absorption site for extended duration. *In-vitro* and buoyancy study test gave a good indication about the gastroretentive property of the selected formula (F3) in the activity of drug and it agreed with the in-vitro results and the proposed mathematical modeling for release kinetics.

Key words: In-situ Gel, Polymer matrix, Gastroretentive floating system, Effervescent system, Photo-polymerization.

1 INTRODUCTION

In-situ is a Latin word which means ‘In its original place or in position’ Extensive researches focused on the development of new drug delivery systems with improving efficacy and bioavailability together, thus reducing dosing frequency to minimize side effects. As a progress, they design in-situ forming polymeric delivery systems sparked by the advantages of easy administration, accurate dose as well as prolong residence time of drug in contact with mucosa compared to conventional liquid dosage form, improved patient compliance and comfort[1]

In-situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition upon administration . Gels are an intermediate state of matter containing both solid and liquid components. The solid component comprises a 3D network of inter connected molecule or aggregates which immobilizes the liquid continuous phase. Gels may also be classified (based on the nature of the bonds involved in the 3D solid network): chemical gels arises when strong covalent bonds hold the network together and physical gels when hydrogen bonds, electrostatic and Vander walls interaction maintain gel network. Hydrogels are aqueous gel having high molecular weight, hydrophilic, cross-linked polymers or copolymers that form a 3D network in water. These gels have been shown to combine significantly longer residence time with increased drug bioavailability. The hydrogels are polymers which have the ability to absorb and retain large amounts of water and biological fluids; in addition, they swell and induce a liquid-gel transition.[2,3]

1.1 Approaches of Designing In-Situ Gel System

1.1.1 Physically Induced In-Situ Gel System

A) Swelling

In situ formation occurs when material absorbs water from surrounding environment and expands to give the desired space. Example of substance is myverol 18-99 (glycerol mono-oleate), which is polar lipid that swells in water to form liquid crystalline phase structures. It has some bioadhesive properties and can be degraded in vivo by enzymatic action.[4]

B) Diffusion

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be useful solvent for such system.[5,6]

1.1.2 Chemically induced in-situ gel systems

A) Ionic crosslinking

Certain ion sensitive polysaccharides such as iota carrageenan, gellan gum(Gelrite®), pectin, sodium alginate undergo phase transition in presence of various ions such as k^+ , Ca^{2+}, Mg^{2+}, Na^+ · In- situ gel formation involves administration of aqueous liquid solutions, once administered they form gel under certain conditions involve the use of gelling agent which can form a system that contain the dispersed drug and other excipients. The gelling of this system is achieved by using polymer solutions such as gellan gum & sodium alginate triggered by ionic complexation that contains divalent-ions complexed with Na-citrate which breakdown in acidic environment of stomach to release free divalent ions (Ca^{2+}) due to change in pH. The free Ca^{2+} ions get entrapped in polymeric chains thereby causing cross linking of polymer chains to form matrix structure causes the in situ gelation of orally administered solution[7,8]

1.2 situ gel formation based on physiological stimuli

1.2.1 Temperature dependent in-situ gelling

These hydrogels are liquid at room temperature (20ºC-25ºC) and undergo gelation when contact body fluids (35ºC-37ºC), due to an increase in temperature. This approach exploits temperature-induced phase transition. Some polymers undergo abrupt changes in solubility in response to increase in environmental temperature (lower critical solution temperature, LCST) and formation of negative temperature sensitive hydrogel in which hydrogen bonding between the polymer and water becomes unfavorable, compared to polymer–polymer and water–water interactions. Also, an abrupt transition occurs as the solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure[9].

1.2.2 pH dependent in-situ gelling

Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymers. The pH is an important signal, which can be addressed through pH-responsive materials. Gelling of the solution is triggered by a change in pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. For example: carbomer and its derivatives as anionic polymer[10].

2. EXPERIMENTAL WORK

2.1 Characterization of Saxagliptin

2.1.1 Determination of melting point

The melting point of drug was determined by capillary tube method according to the USP which is 103-107ºC.

2.1.2 Determination of Solubility

Solubility of drug in two different solvents 0.1N HCl and distilled water was checked by preparing saturated solutions of drug in respective solvents by using the shake-flask method at 37º C. Saturated solutions were prepared by adding excess of drug to vehicles, then samples were allowed to shaken in sonicator for 24 hrs overnight. After 24 hours, the solutions were filtered and analyzed spectrophotometrically. Freely soluble in methanol, soluble in 0.1N HCl and slightly soluble in water[11].

2.1.3 Preparation of Oral saxagliptin Solution as In- Situ Gel

Using the magnetic stirrer, fluidity enhancer agent was added in 100 ml of distilled water. Gelling agent was added when the temperature reached 70˚ C, and then release retard polymer was added. The temperature was maintained at 70˚ C and then stirred continuously to obtain a clear solution. The obtained clear solution was cooled to 40˚ C and then cross-linking agent was added. The temperature was maintained at 40˚ C, finally the drug, preservative and sweetening agent were added in the solution along with gas uniform solution was obtained.[12]

Table1: Composition of in situ gel formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Saxagliptin (mg)	5	5	5	5	5	5	5	5	5	5	5	5
Sodium alginate (% w/v)	0.25	0.5	0.75	-	-	-	-	-	-	-	-	-
Iota Carrag -eenan (% w/v)	-	-	-	0.25	0.5	0.75	-	-	-	-	-	-
Gellan gum (% w/v)	-	-	-	-	-	-	0.25	0.5	0.75	-	-	-
Sodium CMC (% w/v)	-	-	-	-	-	-	-	-	-	0.25	0.5	0.75
Tri-sodium citrate (% w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPMC K100M (% w/v)	1	1	1	1	1	1	1	1	1	1	1	1
Calcium chloride (% w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium bicarbonate (% w/v)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Methyl paraben (% w/v)	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Saccharin sodium (% w/v)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Distilled water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

3. EVALUATION OF FLOATING IN-SITU GEL SOLUTION

All the formulations (F1-F12) prepared were evaluated for different parameters like: gel strength, gelation time, content uniformity, floating lag time, floating duration, pH measurement, water uptake and swelling index, the results are summarized.[20]

3.1 Gel Strength Determination

Solution of 5 ml was taken in the cylinder followed by addition of 25 ml of GF 0.1 N HCl (pH 1.2) for gelation. After gelation the HCl was drained off leaving the formed gel mass, and then the device was rested on to surface of the gel. At the free end of the device a light weight pan (4 g) was attached to which the weights were added. The gel strength was reported in terms of weight required to pass the apparatus through the gel mass[13].

3.2 Gelation Time Determination

Gelation time was evaluated visually; it was measured by placing 5ml of GF 0.1 N HCl (pH 1.2) in test tube and maintained at 37±1° C. One ml of each formula was taken with pipette and transferred slowly on the surface of the fluid, as the solution come in contact with gastric fluid solution; it was immediately converted into gel like structure. The gelation time was evaluated triplicate on basis of time period for which gel formed[14].

3.3 Swelling Index

The percentage of swelling index of in-situ gel of the formulations was determined. In situ gel formed by putting 5 ml of each formula in a petri dish and 40 ml of GF 0.1 N HCl (pH 1.2) was added. Then 0.1N HCl solution was removed from the gel and the excess of 0.1N HCl solution was blotted out with filter paper. The initial weight (W_o) of the gel was recorded, to this gel 10 ml of distilled water was added and after 60 minutes the water was decanted and the final weight (W_t) of the gel was recorded, this process was repeated for 5 hrs and the difference in the weight was calculated and reported.[15].

3.4 Viscosity Measurements

The viscosity of the prepared solutions was measured out using sample of 100ml. Measurements were performed using suitable spindle number 64 and sheared at a rate of 3, 4, 5, 6, 10, 12, 20, 30, 50, 60, 100 rpm, and the temperature was maintained at 37° C. The viscosity was read directly after 30 seconds. All measurements were made in triplicate. The rheological velocity was explained by plotting viscosity against angular velocity.[16]

3.5 In-vitro Buoyancy Study

In vitro buoyancy study was carried out triplicate using USP dissolution apparatus type II using 900 ml medium of 0.1N HCl (pH 1.2). The medium temperature was kept at 37 $\pm$ 0.5° C. Accurately 10 mL of the prepared in-situ gel formulation was drawn up using disposable syringe and placed into the petri dish (4.5 cm internal diameter) and finally the petri dish containing the formulation was placed carefully in the dissolution vessel. The time the formulation took to emerge on to the medium surface (floating lag time) and the time over which the formulation constantly floated on the dissolution medium surface (duration of floating) were reported [17].

3.6 pH Measurement

The pH of the prepared solution for all formulations was measured by digital pH meter at 25 ± 0.5° C after it is calibration using standard buffer solutions of pH 4, 7, 9 then the measurements of pH were recorded.

3.7 Determination of Drug Content

Accurately, 5 ml of liquid solution from all formulations was taken and to which 70 ml of 0.1N HCl was added, then the sample was sonicated for 30 min until clear solution is made. The volume completed to 100 ml. From this solution, 1ml sample was withdrawn and diluted to 10 ml with 0.1N HCl. Contents of drug was determined spectrophotometrically. [18]

3.8 Water Uptake Study

From each formulation the gel portion from the 0.1 N Hydrochloric acid separated and the excess solution was blotted out with a tissue paper. The initial weight of the gel taken was weighed and to this gel 10 ml of distilled water was added and after every 30 minutes of the interval water was decanted and the weight of the gel recorded and the difference in the weight was calculated and reported.[19].

Table 2: Evaluation of preliminary formulations F1 – F12

Formulation	pH determination	Viscosity in cPs		Floating Lag time in sec.
		Solution	Gel	
F1	7.56 ± 0.028	265.66 ± 2.04	1353.3 ± 1.69	4.66 ± 0.47
F2	7.59 ± 0.012	288.20 ± 2.33	1450.0 ± 2.16	4 ± 0.81
F3	7.4 ± 0.021	327.26 ± 2.77	1536.6 ± 2.86	3 ± 0.43
F4	7.26 ± 0.028	247.6 ± 2.98	1045.0 ± 1.41	35 ± 3.74
F5	7.23 ± 0.016	265.83 ± 4.01	1152.0 ± 3.74	42.66 ± 2.05
F6	7.30 ± 0.020	296.93 ± 4.04	1224.3 ± 3.39	50.33 ± 2.05
F7	7.66 ± 0.038	312.33 ± 3.23	882 ± 3.74	22.66 ± 1.24
F8	7.61 ± 0.038	333.56 ± 4.56	1008.3 ± 4.64	25.33 ± 2.05
F9	7.69 ± 0.030	363.23 ± 1.91	1250.3 ± 2.86	22 ± 2.44
F10	7.84 ± 0.024	254.03 ± 4.39	942.66 ± 3.39	54.66 ± 3.09
F11	7.86 ± 0.026	283.73 ± 2.90	1135.6 ± 3.29	48.66 ± 2.62
F12	7.86 ± 0.028	317.03 ± 2.77	1217 ± 4.32	55.33 ± 1.24

3.9 In vitro Drug Release Study

The *in vitro* release of drug from buoyant in-situ gel solutions was studied using USP type II (paddle type) dissolution test apparatus. Five ml from each formulation was transferred using disposable syringe. The syringe plunger depressed slowly to extrude 5 ml into a petri dish with an internal diameter of 4.5 cm already containing 10 ml of 0.1N HCl. This petri dish containing formulation was placed on the surface of the medium and plunged into a dissolution vessel containing 900 ml of 0.1N HCl (pH 1.2). Five ml samples were withdrawn form dissolution medium with disposable syringe at predetermined time intervals of one hour and contents in the aliquots was determined spectrophotometrically. [21]

Table 3: Evaluation of preliminary formulations F1 – F12

Formulation Code	Total Floating time (hours)	% Drug content	% Water Uptake study	Gelling strength in sec.	Swelling index (%)	Gelation time (sec)
F1	> 12	98.13 ± 0.11	9.04 ± 2.51	12.09 ±0.81	46.1	11 ±0.05
F2	> 12	96.85 ± 0.26	11.69 ± 0.75	14.04 ±1.01	65.6	2 ±0.01
F3	> 12	99.21 ± 0.63	16.47 ± 0.30	16.31 ±0.47	91.2	2 ±0.001
F4	> 12	94.65 ± 0.67	4.77 ± 1.46	4.11 ± 0.68	63.7	10 ±0.07
F5	> 12	95.29 ± 0.82	8.06 ± 1.48	6.65 ± 0.33	75.6	6 ±0.11
F6	> 12	96.15 ± 0.48	10.31 ± 2.10	8.07 ± 0.43	84.2	7 ±0.06
F7	> 12	89.06 ± 0.15	5.90 ± 1.40	3.31 ± 0.07	8.3	2 ±0.01
F8	> 12	88.08 ± 0.26	8.00 ± 1.10	5.74 ± 0.30	10.1	10 ±0.09
F9	> 12	85.19 ± 0.45	9.13 ± 1.26	6.3 ± 0.74	12.2	3 ±0.02
F10	> 12	87.54 ± 0.14	3.18 ± 0.69	7.45 ± 1.78	60.9	5 ±0.03
F11	> 12	89.37 ± 0.34	6.19 ± 0.67	10.98 ±0.54	64.4	4 ±0.08
F12	> 12	91. ± 0.93	8.42 ± 0.25	12.39 ±0.84	42.5	5 ±0.04

4 CONCLUSION

Oral saxagliptin solution can be formulated as in-situ gel preparation by using Na alginate and iota carrageenan. Viscosity of the solution increased significantly with increasing concentrations of Na alginate and iota carrageenan. Gelation time reduced significantly with addition of $CaCl_2$. Swelling index increased significantly with increasing Na alginate concentration and it is affected by type of secondary polymer. Floating duration and floating lag time reduced significantly by the presence of sodium

bicarbonate. In-vitro test gave a good indication about the gastro retentive property of the selected formula (F3) in the activity of drug and it agreed with the in-vitro results and the proposed mathematical modeling for release kinetic. It was concluded that the formulation of saxagliptin as a floating in-situ gel is promising for sustain release with minimal toxicity.

Table 4: Invitro Drug release of formulations

Time	% CDR											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0	0	0	0	0	0	0	0	0
1	14.26	13.09	21.6	11.47	12.6	7.60	14	11.75	15.07	7.42	6.52	5.85
2	26.67	25.49	35.53	17.02	22.52	14.71	25.72	27.56	17.22	13.09	11.60	10.60
3	40.18	40.98	52.74	32.50	27.91	20.68	37.30	47.33	29.65	20.81	17.83	18.27
4	52.19	53.18	57.39	37.14	37.42	39.52	52.94	54.12	48.31	32.17	24.22	23.23
5	54.73	55.63	60.59	47.82	52.21	46.08	56.29	57.56	53.70	42.97	28.32	29.30
6	58.50	58.81	63.98	52.63	57.63	50.65	58.49	59.18	54.90	54.86	37.47	38.95
7	62.28	61.11	67.66	58.05	59.83	54.89	61.69	61.98	58.26	56.74	51.22	53.52
8	65.77	65.09	70.82	60.35	62.81	58.57	66.30	65.87	62.54	60.83	53.62	56.42
9	75.35	73.68	73.85	64.45	65.90	62.53	67.65	71.36	66.66	63.50	58.55	58.98
10	79.40	77.32	78.03	67.77	67.88	64.85	69.5	74.58	69.40	64.56	60.17	62.45
11	80.73	78.81	81.33	72.01	70.22	69.56	72.30	76.87	74.50	66.67	68.51	70.71
12	82.60	80.31	92.50	74.64	72.04	73.09	76.24	77.78	79.58	71.79	77.83	75.55

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