Poonam Shodh Rachna(ISSN 2456-5563)
(A Multidisciplinary, Peer Reviewed and Refereed Research Journal)
Vol. 3, Issue.V, May 2024, PSR-2405021

Exploring Natural Polymer-Based Raft Formulation for Gastro-Retentive Delivery of Anti-Hypertensive Drug

Neha Raghuwanshi
PhD Research Scholar, School of Pharmacy, RK University, Rajkot, Gujarat , India.
Corresponding author email: neharaghuwanshi41@gmail.com
Dr Vipul Patel , Associate Professor , School of Pharmacy, RK University , Rajkot, Gujarat

Abstract

The creation and assessment of floating in-situ gel comprising Metoprolol succinate with the purpose of treating hypertension. The preparation of the gastric floating in-situ gel was done with sodium alginate, Xanthan gum & excipients. The in situ gel that was made of Metoprolol succinate was assessed for floating lag time, gelling capability, pH, total floating time, viscosity, in-vitro release. All of the formulations displayed a very small floating lag time, according to the data. After a minute, the majority of the formulations floated. Every formulation showed a basic pH between 6.7 and 7.9, which is appropriate for stomach transport and oral ingestion. The batch G6 has adequate viscosity, gelling property, and floating lag time, making it the best batch choice.

Key words: *Floating drug delivery system; In situ gel; Xanthan gum; Metoprolol succinate; Sustained release*

Introduction

Any medicine delivered to the systemic circulation through oral administration is the most practical and recommended method. With the goal of achieving better therapeutic advantages—such as patient compliance, ease of dosage administration, and formulation flexibility—oral controlled release drug delivery has recently attracted more attention from the pharmaceutical industry. Short half-lives and easy absorption from the gastrointestinal tract (GIT) allow drugs to be rapidly removed from the systemic circulation. To obtain appropriate therapeutic activity, these medications must be dosed often. The creation of oral sustained-controlled release formulations is an effort to get around this restriction by releasing the medication gradually into the gastrointestinal tract and keeping an effective drug concentration in the systemic circulation for an extended period of time. So that the medication may be continually given to its absorption sites in the gastrointestinal tract , such a drug delivery would be kept in the stomach following oral administration and release the drug in a controlled manner.[1] An environment-specific gel forming solution that, when converted to gel, floats on the surface of the gastric fluids (owing to less density than gastric contents) is one potential method of providing regulated medication delivery within the stomach made possible by gastro-retentive in situ gel forming systems. Using this method, a low viscosity solution is employed, and when it comes into contact with the gastric fluids, the polymeric conformation changes, producing a viscous gel with a density that is lower than the gastric fluids. In addition to producing the much-desired gastro retention to extend the contact period, this low-density gel formation also produces the continuous and gradual release of the medicine. In situ gel-forming polymers, such as gellan gum, alginic acid, xyloglucan, chitosan, polycaprolactone, etc., might be synthetic or natural. The addition of effervescence-producing systems, such as bicarbonates or carbonates, with or without citric or tartaric acid, can further increase the gel's ability to float. This is because the gel will become considerably lighter due to the release of carbon dioxide (air production). The gel's capacity to generate a longer-lasting and more regulated

release can also be improved by increasing its viscosity (for example, by including viscosity enhancers like HPMC).[2]

Many studies have been conducted on in situ gel forming systems as means of delivering drugs continuously. The benefits of in situ forming polymeric delivery systems, including enhanced patient compliance and comfort, convenience of administration and decreased administration frequency, have generated interest in this field. One or more of the following stimuli, such as pH shift, temperature variation, and solvent exchange, can lead to in situ gel formation. When compared to traditional liquid dosage forms, the gastro-retentive in situ gelling technology helps to boost the drug's bioavailability. Due to the bioadhesive nature of the polymer, the gel created by the in-situ gelling system sticks to the gastric mucosa or floats over the contents of the stomach, producing gastric retention of the dosage form and lengthening the duration of the gastric residence, which prolongs the delivery of the drug throughout the gastrointestinal tract.[3,4]

A drug that blocks β-selective adrenergic receptors is metoprolol succinate. Due to the drug's approximately three to four hours half-life and the inability of traditional dosage forms to sustain the drug's plasma concentration over time, frequent administration is required. This makes the medication a good contender for the creation of formulations with continuous release, like in situ gel formulations. To sustain the drug's release in this investigation, metoprolol succinate was manufactured as a floating in situ gel. Calcium carbonate was employed as a cross-linking and gas-generating ingredient in the formulations of in situ gels that were created. Sodium alginate and Xanthan gum were used as the polymer blend that formed the gel.

Materials and Method

The materials used were Metoprolol Succinate (Gift sample IPCA Lab), Sodium alginate and Xanthan gum, Sodium Bicarbonate, Calcium carbonate, Citrate (SISCO CHEM).

Approach [5]:

The composition was created following the instructions in Table No. 1 by heating the polymer in deionized water to 60ºC while stirring constantly. Metoprolol succinate, the medication, gas-forming agent calcium carbonate, and buoyancy booster sodium bicarbonate were added while stirring continuously until the mixture had cooled to below 40ºC.

Table No1: Composition of Trial Batches (weights in %).

Components	Formulation Code					
	P1	P2	P3	P4	P5	P6
API (MG)	50	50	50	50	50	50
Sodium Alginate %	2.5	1.5	0.5	1.5	1.5	-
Xanthan Gum %	-	-		0.5	1	2
HPMC K4 M %	-	1	1	-	-	-
Calcium Carbonate %	0.15	0.15	0.15	0.15	0.15	0.15
Sodium Bicarbonate %	1	1	1	1	1	1
Methyl Paraben %	0.2	0.2	0.2	0.2	0.2	0.2

Assessment of in situ gel compositions of metoprolol succinate:

pH measurement [6]:

Utilizing a pH meter, the pH of every composition was found. Using solutions of pH 4 and pH 7, the pH meter was first calibrated.

Measurement of viscosity [7]:

A Brookfield viscometer was utilized to ascertain the viscosity of the compositions. Utilizing a room-temperature Helipath t-shaped spindle and spindle LV1, the 100 ml samples were evaluated at 12 rpm. Three separate measures of viscosity were made. Afterwards, the viscosity was computed using the subsequent formula:

Viscosity (in cPs) = Dial reading x Spindle factor

Gelling time [6]:

The gelation time and the amount of time the created gel stays in that state were the grading criteria: a) gel after a few minutes, b) dispersed quickly, and c) gelation instant, lasting for 12 hours.

Figure No1: Showing gelling ability of In Situ Gel formulation.

Floating lag time [7]:

In order to conduct this test, 900 ml of 0.1N HCl at 370C was combined with 10 ml of the in situ formulation. The term floating lag time refers to the amount of time the formulation took to appear on the dissolution medium's surface.

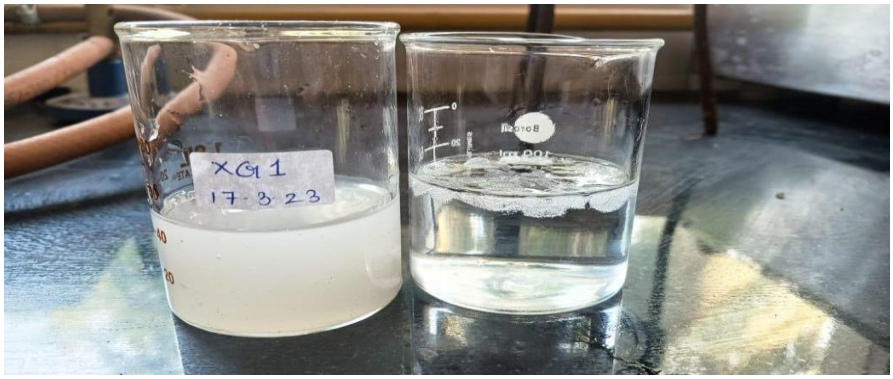

Figure No 2: Showing Floating lag time.

Determining the drug content [7]:

By putting 1 ml of the generated in situ gel formulations into a 100 ml volumetric flask and adding 50 ml of 0.1N HCl with a pH of 1.2 while shaking continuously, the drug content of the formulations was determined. With the use of 0.1N HCl at pH 1.2, the final volume was adjusted to 100 ml, and the mixture was then filtered. The concentration of the drug in the filtered solution was measured spectrophotometrically using a UV-Visible spectrophotometer (Shimadzu 1800, Japan) at the drug's appropriate wavelength.

Investigation of in vitro dissolution [9,10]:

Dissolution test equipment USP Type II (Paddle Method) was used to conduct an in vitro release investigation. With a pH of 1.2, a temperature of 37 ºC ± 0.2 ºC, and an RPM of 50, the dissolving medium had a volume of

900 ml. After removing 1 milliliter of sample every hour, 10 milliliters of 0.1 N HCl were added at 222 nm. To keep the sink condition, 1 milliliter of the sample was changed in the dissolving media.

RESULT AND DISCUSSION

The following test findings were obtained for the characterization of the oral in situ gel of metoprolol succinate: pH, viscosity, gelling time, floating lag time, floating duration, and content uniformity.

Table No 2: Characteristics of oral In-situ gel of Metoprolol succinate.

Formulation code	pH	Viscosity in cps	Gelling time (sec)	Floating lag time (sec)	Floating Duration in hr	Drug content (%)
P1	7.12	2217	Immediate	55 -65 sec	> 12	97.6 ±0.67
P2	7.26	2315	Immediate	45-65 sec	> 12	98.80 ±0.54
P3	7.42	1531	3-4 sec	Immediate	> 12	100.2 ±0.66
P4	7.21	1781	4-6 sec	Immediate	> 12	99.1 ±0.61
P5	7.35	1389	Immediate	Immediate	> 12	98.87 ±0.57
P6	7.53	1685	Immediate	45-55 sec	> 12	98.5 ±0.58

pH:

The pH of all batches was measured using a calibrated digital pH meter at 37 C and was found in the range of 7.12 to 7.53. The optimized batch P 5 showed pH 7.35 (as given in table no 2)

Viscosity:

The viscosity of all formulations was determined by a Brookfield viscometer using spindle number 62 with cup and bob setting at 12 rpm. All the prepared formulations showed viscosity in the range of 1389 to 2315cps. The optimized batch P5 show viscosity of 1389 cps. (as given in table no 2).

Figure No 3: Viscosity determination by Brookfield viscometer

Gelling time:

The gelling capacity of prepared formulations was observed by visual examination. All the prepared batches show gelling time from 4-6 second to immediate after entering in 0.1 N HCl. The optimized batch P 5showed

immediate gelling after getting in contact with 0.1 N HCl and remain in the form of gel for more than 12 hours. (as given in table no 2).

Floating lag time:

Floating lag time of all the prepared formulations was observed by visual examination. All the prepared formulations show Floating lag time from 55-65 seconds to immediate. And the optimized batch P 5 show immediate floating after entering in 0.1 N HCl and show floating for more than 12 hrs. (as given in table no 2)

Floating Duration:

All prepared formulation shows floating duration more than 12 hours. (as given in table no 2)

Drug Content Uniformity:

All the prepared formulations show drug content uniformity in the range of 97.6% to 100.2 %. The values are acceptable as per Indian pharmacopeia standards. (as given in table no 2).

In-vitro Dissolution Study for Oral Floating In-situ Gel of Metoprolol Succinate:

In-situ gel forming polymeric formulations are the drug delivery system that are in sol or suspension form before administration in body, but once administered, undergo gelation in situ, to form gel. In-situ gel forming system have been widely investigated as vehicle for sustain drug delivery system.

In the present study there was an examination of possibility of exploitation of in situ gelling characteristics of different polymers for oral drug delivery The formulation adopted were Sodium alginate, Xanthan gum, HPMCK4M polymers containing calcium chloride (as a source of Ca ions), and sodium citrate, which complexes the free Ca ions and releases them only in the highly acidic environment of the stomach. In this way, the formulation remains in liquid form until it reaches the stomach, when gelation is instantaneous.

Table No 5 : % Drug Release of Oral Floating Insitu Gel of Metoprolol Succinate

Batch No	**% Drug Release in Hrs**					
	1	2	6	8	10	12
P1	63.21	73.93	92.34	99.31	-	-
P2	41.96	47.86	62.67	83.45	97.34	-
P3	48.24	55.52	82.41	98.21	-	-
P4	37.43	48.85	68.36	83.24	98.91	-
P5	32.83	44.32	62.75	78.89	85.48	98.12
P6	46.96	57.86	72.68	95.45	-	-

In the formulation batch P1 (Sodium Alginate 2.5%) show in vitro release for 8 hours, batch P2 (Sodium Alginate 1.5%: HPMC K4M 1%) show in vitro release for 10 hours, batch P3 (Sodium Alginate 0.5%: HPMC K4M 1%) show in vitro release for 8 hours, as all the batches (P1 – P3) did not gave the drug release for 12 hours they were unable to give gastric retention. Batch P4 (Sodium Alginate 1.5%: Xanthan gum 0.5%) show in vitro release for 10 hours, batch P5 (Sodium Alginate 1.5%: Xanthan gum 1%) show in vitro release for 12 hours. In the batches P5 there was use of two natural polymers (sodium alginate 1.5%: (0.5 to 1 %) and Xanthan gum) which gave better gastric retention, it forms gel and it retard the drug release.

Summary

A range of synthetic and natural polymers have been used in varying ratios in the current work to combine organic: natural, organic: synthetic, and artificial: synthetic. However, in the prepared batches P1 to P4 and P6 didn't offer invitro release for 12 hours. In formulated batch P5 (Sodium alginate 1.5 % : Xanthan gum 1%) show in vitro release for 12 hours. It also gave floating lag time and floating time immediate, and floating duration more than 12 hours. As an outcome, it suggests that gastric retention could be induced by the gel-forming material sodium alginate and use mostly in In situ gel formulation and gellan gum is also gel formulating agent and it formulate and sustain the release at lower concentration so that form strong gel matrix formulation in 0.1 N HCl. Also it immediately after inclusion in 0.1 N HCl, construct the gel. It was discovered that the floating duration was greater than 12 hours.

CONCLUSION

It was determined through formulation and assessment investigations of oral floating insitu gel that the gas producing agents calcium carbonate 0.15% and sodium bicarbonate 1% each provide gel to float for more than 12 hours.
The creation of a metoprolol succinate matrix between Xanthan gum and sodium alginate results in a 12-hour delayed release. The goal of extending the stomach's residence period, lowering dosage frequency, improving safety, and other factors was accomplished.

References

- 1.Streubel, J. Siepmann, R. Bodmeier. Gastroretentive drug delivery system. Expert Opinion Drug Delivery (2006), 3(2), 217-233.
- 2. Archana D. Kajale, Dr. A. V. Chandewar, Oral Floating Insitu Gel – A Novel Approach For Gastro Retentive Drug Delivery, International Journal Of Research In Pharmaceutical Technology, (2015) 1(1) 1-7.
- 3. Nidhi R Doshi, In Situ Gel: A Novel Approach of Gastro Retentive Drug Delivery, Asian Journal of Pharmaceutical Sciences and Research, 3(3), March 2013.
- 4.K. Jain, Pharmaceutical Product Development, 3rd edition, 272.
- 5. P. Kushal, P. Agrawal , A. Dashora, D. Sahu, R. Garg, K. Pareta, M. Menaria , B. Joshi. Formulation and evaluation of oral floatable in-situ gel of ranitidine hydrochloride . Journal of Drug Delivery & Therapeutics (2013) 3(3) 90-97.
- 6. S. Shivaraju, S. Parthiban, S. Senthilkumar. Preparation and evaluation of ornidazole in situ gelling system for gastroretentive drug delivery. International Journal of Pharmacy (2013) 3(2) 62-69.
- 7. K. Rani, V. Garg, D. Goswami. Formulation and evaluation of stomach specific in situ gel of ofloxacin using natural, synthetic polymer. World Journal of Pharmaceutical Research (2013) 2(3) 631-645.
- 8. G. Sridevi, Y. Mahagen, V. Patidhar, Y. Balaram, P. Gopkumar. Formulation and evaluation of floatable in-situ gel for stomach-specific drug delivery of carbamazapine. Research And Reviews: Journal Of Pharmacy And Pharmaceutical Sciences (2014) 3(1) 37-43
- 9. S. Chaniyara, D. Modi, R. Patel, J. Patel, R. Desai, S. Chaudhary. Formulation & evaluation of floatable insitu gel for stomach-specific drug delivery of ofloxacin. American Journal of Advanced Drug Delivery (2013) 1(3) 285-299.
- 10. Geeta V Yadav, Sushma R Singh, Gastroretentive Drug Delivery System of Lamotrigine: In Vivo Evaluation, International Journal of Pharmacy and Pharmaceutical Sciences, (2014) 6(3) 279-285.