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FORMULATE AND EVALUATE THE FLOATING CONTROLLED RELEASE SYSTEM OF NEBIVOLOL HYDOCHLORIDE

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ABSTRACT
Drug delivery through the numerous gastro-retentive approaches has opened a new horizon for effective way of increasing patient compliance and increasing bioavailability of variety of drugs through oral rout. Many approaches with use of different polymers and other constituents can produce different range of gastro-retentive systems. Especially the swellable bioadhesive drug delivery system is the most widely used in gastro- retentive dosage forms. However a lot of work is still needed to be done to overcome the different physiological and pharmaceutical barriers to develop the more effective gastro- retentive dosage forms. Natural gums are polysaccharides consisting of numerous sugar units such as glucose, galactose, rhamnose, arabinose, xylose, mannose and uronic acids. Due to their availability, safety and biodegradability, they are preferred over synthetic polymers. The majority of the gums are safe enough to be consumed and are hence, widely used in the field of drug delivery and as food additives. The objective of the present work was to formulate swellable extended release tablets for increased residence time in the stomach and also for controlling drug delivery using natural polymer (bioadhesive) for retardant release. Nebivolol hydrochloride is a class II drug that selectively blocks β1 receptor with therapeutic applications as antihypertensive and can also used as monotherapy for initial management of uncomplicated hypertension. Nebivolol is having very low oral bioavailability. Hence, the main objective of this current research work is to improve its oral bioavailability by swellable solid dosage forms by compaction. Earlier research was done using a single volatile solvent as a vehicle. In the current research, compacts were prepared by using combination of swelling polymers as novel carriers to improve its oral bioavailability.

KEYWORDS: GRDDS, Swelling polymers, Natural gums, Polysaccharide polymers, Bioadhesive Polymer.

INTRODUCTION
The field of pharmaceutical science is witnessing a remarkable evolution, with researchers and healthcare professionals continually seeking new and innovative drug delivery systems to optimize therapeutic outcomes and enhance patient compliance. Among the multitude of drugs used in the management of various medical conditions, Nebivolol Hydrochloride has gained significant prominence for its role in the treatment of cardiovascular diseases. While Nebivolol is an effective beta-blocker with proven therapeutic benefits, it faces certain challenges due to its rapid absorption and short half-life. These characteristics necessitate frequent dosing, which can lead to fluctuations in therapeutic drug levels, thereby increasing the potential for side effects and patient inconvenience. In this context, the development and application of floating controlled release systems for Nebivolol Hydrochloride offer an exciting and promising solution.

This paper explores the concept, development, and evaluation of floating controlled release systems as an advanced drug delivery strategy for Nebivolol Hydrochloride. Such systems are designed to ensure sustained and controlled drug release at the desired site of absorption, thus addressing some of the limitations associated with conventional dosage forms.[1] The primary innovation behind these systems lies in their ability to enable the drug to remain buoyant in the gastric fluids, prolonging its residence time in the stomach and subsequently the upper small intestine. This extended gastric retention facilitates a consistent and controlled release of Nebivolol Hydrochloride, improving its bioavailability and reducing the frequency of administration.[2]

The rationale behind adopting floating controlled release systems for Nebivolol Hydrochloride stems from the recognition of its pharmacokinetic profile. Nebivolol is characterized by rapid absorption and a relatively short

half-life, typically necessitating multiple daily doses for the treatment of cardiovascular conditions. This frequent dosing regimen can lead to patient non-compliance, suboptimal therapeutic outcomes, and potential side effects. Therefore, there is a compelling need to develop a dosage form that ensures the sustained and controlled release of Nebivolol, extending the duration of therapeutic action and reducing the frequency of administration.[3]

Floating controlled release systems offer a compelling solution by taking advantage of the unique physiological features of the gastrointestinal tract. These systems are designed to float on the gastric fluid, resisting the peristaltic movement and gastric emptying, which leads to prolonged drug release. This buoyant behavior is primarily achieved through the use of specific excipients and polymers that impart buoyancy to the dosage form. Consequently, the drug remains in the stomach for an extended period, releasing Nebivolol Hydrochloride gradually and consistently.[4]

Formulation strategies for floating controlled release systems of Nebivolol Hydrochloride involve careful selection of excipients, polymers, and drug loading techniques. Excipients like hydrocolloids, effervescent agents, and low-density fillers are commonly used to enhance the buoyancy of the system. These excipients ensure that the dosage form remains afloat in the gastric environment, effectively delaying its transit to the small intestine. Moreover, specific polymers like HPMC (hydroxypropyl methylcellulose) can be employed to modulate drug release kinetics, achieving the desired release rate over time.[5,6]

A successful formulation must consider factors like drug solubility, drug-polymer interactions, and the need for dose adjustment. Nebivolol Hydrochloride, being a water-soluble drug, necessitates particular attention in formulating controlled release systems to maintain adequate drug release over an extended period. This involves the selection of suitable hydrophilic polymers, often in combination with lipophilic components to optimize drug release kinetics.[7]

The effectiveness of floating controlled release systems for Nebivolol Hydrochloride is evaluated using a range of in vitro and in vivo techniques. In vitro assessments include dissolution studies, buoyancy tests, and drug release kinetics experiments. These experiments help in understanding the release profile of Nebivolol from the dosage form and its behavior in simulated gastric and intestinal fluids. The extent of buoyancy is also determined, as it is a key factor in ensuring prolonged gastric retention.[8]

The development and application of floating controlled release systems for Nebivolol Hydrochloride represent a significant advancement in pharmaceutical science. These systems hold the promise of improving patient compliance, reducing side effects, and enhancing the therapeutic efficacy of this vital cardiovascular drug. As the research in this field continues to evolve, the potential benefits extend beyond Nebivolol, with the prospect of transforming the landscape of drug delivery for a range of medications. This paper will delve deeper into these aspects, providing a comprehensive understanding of the development, evaluation, and future prospects of floating controlled release systems for Nebivolol Hydrochloride.

METHODOLOGY

Analytical Method Development for Nebivolol

Preparation of Stock solution of Nebivolol: 100 mg of Nebivolol was taken in 100 ml of volumetric flask, added few ml of methanol to solubilized drug then added freshly prepared 0.1 N Hcl up to 100 ml. It gives 1.0 mg/ml of drug (stock-I).

Determination of λmax: The drug λmax determined by 20 µg/ml standard solution of Nebivolol. The prepared drug solution was scanned at 200 – 400 nm by using UV spectrophotometer (Shimadzu 1800). Accurately weighed 50 mg of drug sample was soluble in 50 ml of simulated gastric fluid containing 0.1 N HCl in 50 ml volumetric flask. The mixture was sonicated with the help of sonication in bath sonicator for 20 min to get 1000 µg/ml solution. The prepared solution was named as **Stock-I**. Withdrawn 1 ml of prepared solution was again diluted up to 100 ml with same solvent separately with sonication for 20 min to obtain 10 µg / ml solution. The spectrum of these solutions was run in 200 – 400 nm range in double beam UV spectrophotometer.

Determination of Nebivolol calibration curve: The standard solution of Nebivolol was subsequently diluted with 0.1 N Hcl to gives 10- 80 µg/ml of solution. The dilutions was analyzed at 282 nm using the 0.1 N Hcl as blank. Accurately weighed 50 mg of drug sample was soluble in 50 ml of simulated gastric fluid containing 0.1 N HCl in 50 ml volumetric flask. The mixture was sonicated with the help of sonication in bath sonicator for 20 min to get 1000 µg/ml solution. The prepared solution was named as **Stock-I**. From the above stock solution 10 ml was again diluted with 100 ml of dissolution medium to obtain 100 µg / ml solution. From above prepared solution was withdrawn as 0.2 ml, 0.4 ml, 0.6 ml upto 2.0 ml and diluted up to 10 ml with respective solvent in 10 ml volumetric flasks to get concentration of 2 µg / ml, 4 µg / ml, 6 µg / ml, upto 20 µg / ml respectively. The absorbance of each solution was measured separately at 230 nm for 0.1 N HCl.

Solution Stability: The stability of Nebivolol hydrochloride in plasma was tested by two different standard samples at low and high. The samples are stored for 24 hrs at room temperature in plasma on short time storage collected samples at 6, 12 and 24 hrs, these are analysed by the extraction from plasma and then

reconstituted with 50 % acetonitrile and was assessed in triplicate.

Preformulation Studies for Nebivolol: Objective of pre-formulation study is to develop the elegant, stable, safe and effective dosage form by establishing compatibility with the other ingredients and to establish physicochemical parameters of new drug substance. The preformulation studies were carried out in terms of tests for identification (physical appearance, melting point, IR spectra and UV spectrum), solubility profile, drug excipients interaction.

Organoleptic parameters identification: Organoleptic parameter of drug was checked by visual inspection.

Physical Characteristics: The density of drug powder was exactly weighed (M) and poured gently through a glass funnel into graduated cylinder and the volume was noted and bulk density was determined.

Particle size: The drug particle size was determined by using a microscope fitted with ocular micrometer and stage micrometer.

Micromeritic properties: Tap density of pure drug was determined using tap density tester and % Carr's index was calculated. Angle of repose was assessed to know the flowability of microspheres by a fixed funnel method.

Angle of repose: A weighed quantity of drug powder was passed through a funnel fixed on a stand at a specific height upon a graph paper. A static heap of powder with only gravity acting upon it was tending to form a conical mound. The height of the heap (h) and radius (r) of lower part of cone were measured and calculated.

$$\theta = \tan\text{-}1h/r$$

Where θ = angle of repose, h = height of cone and r = radius of cone base

Carr's index: The Carr's index was evaluated for the flow ability of the powder by comparing the pour density and tapped density of microspheres and was calculated using:

$$\text{Carr's index} = \{(\rho t\text{-}\rho b) \times 100\}/\rho t$$

Hausner's ratio: Hausner's ratio (H), another index of flow ability, was calculated using:

$$H = \rho t/\rho b$$

A value < 1.2 is preferred for free flow; however, a value close to 1 indicates good flow properties.

Formulation of swellable tablets: The tablets prepared by direct compression method. Drug, Guargum, Xanthan gum, Carbopol and HPMC, Magnesium stearte and MCC used for formulation. The tablets were prepared by direct compression method. Nebivolol, Guargum, Xanthan gum, Carbopol and HPMC were sieved through #30 sieves. Magnesium stearte and MCC were sieved through #60 sieves before the use. All the materials were accurately weighed and blended using hand blender and directly compressed on a manual single punch tablet compression machine into 90 mg tablets using flat-faced, round punches 4 mm in diameter. 9 batches of the formulation were prepared using guargum and xanthan gum, carbopol 940 and HPMC as polymers, upto total weight of 90 mg.

Table 6.1: Various composition of swellable GRDDS tablets.

F. Code	Drug (mg)	Guargum (mg)	Xanthan gum (mg)	Carbopol 940 (mg)	HPMC (mg)	Magnesium stearate (mg)	Microcrystalline cellulose (mg)
NST1	5	35	20	10	5	5	10
NST2	5	30	25	10	5	5	10
NST3	5	20	35	10	5	5	10
NST4	5	35	20	7.5	7.5	5	10
NST5	5	30	25	7.5	7.5	5	10
NST6	5	20	35	7.5	7.5	5	10
NST7	5	35	20	5	10	5	10
NST8	5	30	25	5	10	5	10
NST9	5	20	35	5	10	5	10

Post Compression Evaluation

Weight variation: The average weight by more than the percent shown below and none deviates by more than twice that percent.

Hardness: Hardness of tablet is defined as the force required to break a tablet a in a diametric direction. A tablet was placed between two anvils. Hardness is thus the tablet crushing strength. Monsanto tester is used for hardness testing.

Friability: Weigh 10 tablets and place in a friabilator chamber rotated at 25 rpm and they are dropped on distance of 6 inches and allowed to rotate for 100 revolutions. The difference in the weigh is calculated and the weight loss should not be more than 1%.

Thickness: The thickness of tablets was performed on 20 tablets from each formulation by using Vernier caliper.

In-vitro buoyancy lag time: The Buoyancy lag time and total floating time were determined by immersion of tablets of different formulation in 0.1 N HCL at 37±.5°C.

Swelling index (%): Swelling ratio was determined using following equation: Swelling Ratio (%) = $(A_t - A_0) / A_{tablet} * 100$
A_t, weight of the tablet and basket at time t (g);
A_0, weight of the tablet and basket at the beginning (g);
A_{tablet}, weight of the dry tablet (g).

The prepared tablets were placed in the wire basket of six basket dissolution apparatus. The basket was immersed in a beaker containing 0.1 N HCl (900 ml) for 2 h and allowed to swell at 37 ºC. The tablets were removed and changes in weight were measured before and after swelling.

Percent Drug content estimation: Crushed 10 tablets from all batches in pestle- mortar and weighed equivalent 150 mg as drug dose using for single tablet was taken in volumetric flask (100ml) and dissolved in 0.1 N HCL and filtered. This solution was analyzed in UV spectrophotometer at λmax 263nm.

RESULT AND DISCUSSION

Analytical method development

Method Development using UV-Spectrophotometer: It was scanned on a double- beam UV- visible spectrophotometer (Shimadzu 1800) between wavelength 200- 400 nm and UV spectrum was recorded. Nebivolol maximum Absorbance was found at 282 nm. Therefore 282 nm was chosen for determination of drug in the samples (Table 7.1 and Figure 7.1).

Table 7.1: Nebivolol maximum absorbance using UV-Spectrophotometer.

Wavelength (nm)	Absorbance
339	0.002
282	0.267
214	0.373

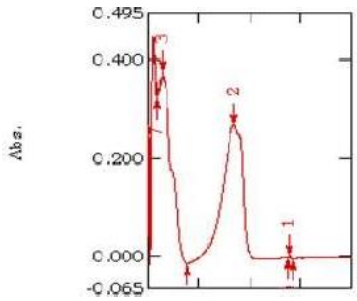

Figure 7.1: Nebivolol maximum absorbance using UV-Spectrophotometer.

Calibration Curve: The stock solution will be made in concentration range of 20-100 µg/ml. The standard graph of Nebivolol was plotted by standard samples absorbencies on y-axis and their concentrations on x-axis. Regression coefficient value found to be 0.999 (Table 7.2 and Fig. 7.2). Which suggest that it obeys the Beer- Lamberts law.

Table 7.2: Standard Nebivolol in 0.1 N HCl.

Concentration (µg/ml)	Absorbance
0	0
10	0.12
20	0.24
30	0.35
40	0.48
50	0.59
60	0.72
80	0.96

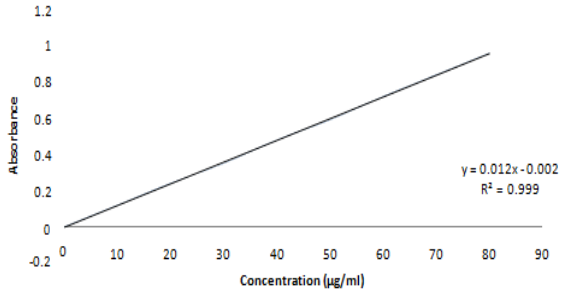

Fig. 7.2: Standard Nebivolol in 0.1 N HCl.

Preformulation studies: Objective of pre-formulation study is to develop the elegant, stable, safe and effective dosage form by establishing compatibility with the other ingredients and to establish physicochemical parameters of new drug substance. The preformulation studies were carried out in terms of tests for identification (physical appearance, melting point, IR spectra and UV spectrum), solubility profile, drug excipients interaction.

Organoleptic parameters identification: Organoleptic parameters of drug will be checked by visual inspection.

Melting Point determination: The melting range of drug will be determined using open capillary method.

Solubility Test: The Nebivolol solubility in water is very poor; Amelia Avachat and coworkers have been reported 0.7 mg/ml as an increase concentration of co solvent to increase solubility of drug. In this study observed that Nebivolol solubility was increased in 0.1 N Hcl upon addition of various co solvents in different strength. The maximum solubility of drug resulted in 20% of Glycerol, Methanol and DMSO 1.21±0.82, 1.08±0.79 and 1.12±0.96 mg/ml respectively. Based on these results 20% of glycerol in 0.1 N Hcl preferred as diffusion medium for maintaining better sink condition over the drug release studies.

Pre Compression Characterization: Pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were evaluated for powder blend. Swellable mucoadhesive tablets were prepared by the direct compression method, using

Carbopol, HPMC, Guargum and xanthan gum as swellable polymers for swellable agent. The effect of the nature of polymers was studied by preparing various formulations of swelling of mucoadhesive tablets. In all these formulations, a constant amount of drug (5 mg) was maintained and the prepared granules was initially characterized for flow properties and all other parameters. The different characterization as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio includes angle of repose (26.02), bulk density (0.174 g/cm^3), tapped density (0.173 g/cm^3), Carr's index (23.31 %) and Hausners ratio was found to be (1.18).

Table 7.3: Flow properties of various swellable mucoadhesive tablets.

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)
NST1	0.152	0.133
NST2	0.163	0.157
NST3	0.185	0.171
NST4	0.143	0.137
NST5	0.162	0.165
NST6	0.174	0.121
NST7	0.191	0.173
NST8	0.143	0.112
NST9	0.131	0.122

Table 7.4: Flow Properties of Various Swellable Mucoadhesive Tablets.

Formulation code	Carr's index (%)	Hausner Ratio	Angle of Repose
NST1	19.32	1.1	26.71
NST2	20.33	1.17	22.33
NST3	23.21	1.12	26.12
NST4	22.51	1.17	24.81
NST5	22.24	1.21	21.25
NST6	23.21	1.31	27.24
NST7	26.31	1.58	22.22
NST8	23.21	1.16	25.15
NST9	23.31	1.18	26.02

Post Compression Evaluation: The oral sustained release dosage form with prolonged residence time in the stomach helps in absorption of the drugs which are less soluble or unstable in the alkaline pH and those which are absorbed from the upper gastrointestinal tract. GRDDSs help in maintenance of constant therapeutic levels for prolonged periods and produce therapeutic efficacy and thereby reduce the total dose of administration. In the present study an attempt was made to develop a mucoadhesive buoyant tablet of Nebivolol with variation in polysaccharide polymeric combination with different ratios to increase mucoadhesion at gastric mucosa. Such type of proposed formulations increases the gastric residence time, thus increase the bioavailability.

The other characterization includes thickness, hardness, friability, weight variation, drug content and in-vitro drug release. The thickness of all the tablets was in the range of 4.01 to 4.09 mm. The average weights of the entire prepared tablet were 240.17 mg to 240.71 mg which was within the specified limit. The hardness of all the formulated tablets was found to be in the range of 5.04 to 5.36 kg/cm^2. Friability was found to be 0.31 to 0.38%. The preliminary and screening studies were performed using different polymers and the polymers Carbopol 940, HPMC, guargum and xanthan gum promised excellent properties for controlled release and muco-adhesion. Using selected polymers, the final batches were prepared by direct compression method and were evaluated for buoyancy lag time and total buoyant time, swelling index, drug content, ex- vivo mucoadhesive strength, in-vitro dissolution study. The formulation NST4 was found to be the best formulations in terms of sustained drug release. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer- Peppas and Higuchi's equation. The regression coefficient (r^2) value of various models was found to be non-fickinon drug release diffusion mechanism and followed supercase II transport mechanism respectively.

Table 7.5: The Various Characterization of Swellable Mucoadhesive Tablets.

Formulation code	Weight variation (mg)
NST1	91.21±.49
NST2	89.17±.01
NST3	91.12±.02
NST4	90.19±.04
NST5	91.21±.01
NST6	90.15±.05
NST7	91.11±.01
NST8	91.73±.03
NST9	90.21±.06

Table 7.6: The Various Characterization of Swellable Mucoadhesive Tablets.

Formulation code	Thickness (mm)
NST1	4.09±.01
NST2	4.01±.02
NST3	4.06±.01
NST4	4.04±.01
NST5	4.03±.03
NST6	4.01±.02
NST7	4.06±.03
NST8	4.09±.03
NST9	4.06±.02

Table 7.7: The Various Characterization of Swellable Mucoadhesive Tablets.

Formulation code	Hardness (kg/cm^2)
NST1	5.51±.11
NST2	5.54±.12
NST3	5.31±.13
NST4	5.04±.18
NST5	5.14±.11

NST6	5.36±.10
NST7	5.25±.44
NST8	5.11±.27
NST9	5.10±.21

Table 7.8: The Various Characterization of Swellable Mucoadhesive Tablets.

Formulation code	Friability (%)
NST1	0.36±.13
NST2	0.31±.16
NST3	0.38±.11
NST4	0.32±19
NST5	0.34±.17
NST6	0.38±.16
NST7	0.35±.17
NST8	0.32±.13
NST9	0.34±.13

Table 7.9: The Various Characterization of Swellable Mucoadhesive Tablets.

Formulation code	Swelling Index (%)
NST1	150.23±0.17
NST2	159.55±0.28
NST3	156.17±0.21
NST4	158.18±0.22
NST5	157.62±0.03
NST6	156.71±0.31
NST7	157.58±0.11
NST8	156.59±0.25
NST9	156.25±0.19

Table 7.10: The Various Characterization of Swellable Mucoadhesive Tablets.

Formulation code	Percent Drug content (%)
NST1	99.52±0.26
NST2	99.08±0.18
NST3	99.29±0.98
NST4	99.15±0.15
NST5	98.65±0.14
NST6	99.91±0.32
NST7	99.16±0.44
NST8	99.14±0.08
NST9	101.32±0.16

Table 7.11: Ex-vivo Bioadhesive Strength of Swellable Mucoadhesive Tablets.

Formulation Code	Bioadhesive strength (gm)
NST1	21.03±0.5
NST2	24.52±0.1
NST3	29.36±0.4
NST4	31.02±0.5
NST5	23.12±0.1
NST6	20.17±0.2
NST7	22.24±0.4
NST8	21.25±0.2
NST9	28.56±0.2

Table 7.12: In-Vitro Drug Release Study of The Prepared Swellable Mucoadhesive Tablets (NST1 – NST9).

Time (h)	NST1	NST2	NST3	NST4	NST5	NST6	NST7	NST8	NST9
0	0	0	0	0	0	0	0	0	0
1	3.2	4.3	3.1	2.1	2.5	2.8	3.1	3.5	3.8
2	14.6	14.8	12.2	10.5	11.4	11.1	10.5	12.5	15.4
3	25.3	24.3	23.3	21.4	21.6	20.8	22.2	25.6	28.6
4	40	39.1	37.4	33.6	35.3	32.3	38.7	38.2	42.7
5	46.4	46.2	46.3	41.7	45.5	45.5	44.4	45.9	48.4
6	54.1	56.2	53.1	49.3	52.6	52.2	54.3	52.8	55.3
7	66.2	63.2	61.1	57.3	61.5	62.2	60.6	64.7	68.4
8	72.4	70.2	67.6	60.4	68.4	67.9	68.2	69.5	73.6
9	80.5	79.8	75.4	69.2	75.1	74.6	76.7	76.4	82.7
10	85.1	85.3	82.2	76.5	80.3	82.6	81.4	84.3	88.3
11	90.6	89.3	89.5	84.3	87.4	87.3	88.3	88.3	90.6
12	98.6	98.1	97.1	95.5	96.1	96.9	96.6	97.7	99.7

SUMMARY AND CONCLUSION

The present investigation aimed at formulation and evaluation of gastroretentive tablets based on combination of natural polymer. Oral sustained release dosage form with prolonged residence time in the stomach helps in absorption of the drugs which are less soluble or unstable in the alkaline pH and those which are absorbed from the upper gastrointestinal tract. GRDDSs help in maintenance of constant therapeutic levels for prolonged periods and produce therapeutic efficacy and thereby reduce the total dose of administration. In the present study an attempt was made to develop a mucoadhesive buoyant tablet of Nebivolol with variation in polysaccharide polymeric combination with different ratios to increase mucoadhesion at gastric mucosa. Such type of proposed formulations increases the gastric residence time, thus increase the bioavailability. A major problem in gastric delivery is the attainment of an optimal concentration at site of action with maximum bioavailability of drugs. The problem is associated with the conventional dosage form for peptic ulcer diseases is frequent dosing due to the low half life. The bioavailability of an instilled compound is generally low from 1.5 – 3.0 h and low solubility, with only a small fraction reaching the target site. The preliminary and screening studies were performed using different

polymers and the polymers Carbopol 940, HPMC, guargum and xanthan gum promised excellent properties for controlled release and muco-adhesion. Using selected polymers, the final batches were prepared by direct compression method and were evaluated for buoyancy lag time and total buoyant time, swelling index, drug content, ex-vivo mucoadhesive strength, in-vitro dissolution study. The formulation NST4 was found to be the best formulations in terms of sustained drug release.

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