Journal of Chemical Health Risks

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JCHR (2023) 13(4), 2299-2308 | ISSN: 2251-6727

Formulation and In-Vitro Evaluation of Gastroretentive Expandable Film of Nateglinide

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(Received: 05 June 2023 Revised: 14 October 2023 Accepted: 24 November 2023)

KEYWORDS

Nateglinide, Gastroretentive film, Hydroxyl Propyl Methyl Cellulose, Polyethylene Glycol 400.

ABSTRACT:

The present work was based on the development and characterization of unfolding type gastro retentive dosage form appropriate for the controlled release of Nateglinide (NAT), a drug with a narrow therapeutic window. Gastroretentive films were formulated using hydroxypropyl methylcellulose (HPMC) as a film-forming agent, and polyethylene glycol 400 (PEG) as a plasticizer. The drug-loaded polymer film of hydroxypropyl methylcellulose (HPMC) as a film-forming agent and polyethylene glycol 400 (PEG) as a plasticizer was folded into hard gelatin capsules. The prepared films were evaluated for several parameters like physical appearance, surface texture, weight variation, thickness, folding endurance, swelling index, tensile strength, unfolding behavior, drug content, and In vitro drug release studies. Drug and polymers were found to be compatible as revealed by Fourier transform infrared spectroscopy (FTIR) study revealed uniform dispersion of NAT in polymeric matrices. The best release for gastroretentive film was shown by formulation F19 (HPMC 15cps and PEG 400). Formulation F19 exhibited a good appearance, better mechanical strength with acceptable flexibility. Formulation F19 was given 90% NAT release after 12 hr, 95.15±0.18% drug content, and found to be stable. The results indicate that the unfolding type gastro retentive drug delivery system offers a suitable and practical approach for the prolonged release of drug over an extended period and thus oral bioavailability, efficacy, and patient compliance is improved.

INTRODUCTION

Several difficulties are faced in designing sustained release and controlled release systems for better absorption and enhanced bioavailability [1]. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs [2]. Prolonged gastric retention improves bioavailability, reduces drug wastage, and improves solubility for drugs that are less soluble in a high pH environment.

Gastroretentive Dosage Form (GRDF) extend significantly the duration of time over which the drugs may be released. They not only prolong dosing intervals but also increase patient compliance. GRDF will bring about new and important therapeutic options. Several strategies including, a floating drug delivery system, mucoadhesives, and co-administration of agents that prolong gastric residence have been developed. Other approaches and drug carriers have been designed that unfold or expand in the stomach to form a complex geometric shape to obstruct its escape through the pyloric sphincter [3].

NAT is used in the treatment of type 2 diabetes mellitus. The usual dosage regimen is 60-120 mg three times/day. Nateglinide belongs to BCS class II and exhibits low and variable oral bioavailability (73%). It majorly absorbs from the stomach. Nateglinide has a short biological half-life of 1.5 hours and is eliminated rapidly. It is commercially available as conventional tablets. To achieve

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JCHR (2023) 13(4), 2299-2308 | ISSN: 2251-6727

maximum therapeutic effect with a low risk of adverse effects, gastric-retention formulation is preferred[4].

Based on the practical aspects of designing floating and unfolding type polymeric films, the present investigation aims to provide optimal drug release in the upper gastrointestinal tract and deliver immediate release (IR) to attain the therapeutic drug concentration in a short period, as well as controlled release to maintain the concentration for the anticipated time.

METHODOLOGY

Materials

NAT was gifted by Alembic Pharmaceutical Ltd, Vadodara, India. HPMC15cps, HPMC50cps, PVPK30, and Ethylcellulose were obtained from Astron Research Ltd, Ahmedabad, India. Polyethylene glycol 400, Methanol, and Dicholormethane were obtained from ACS Chemicals, Ahmedabad, India. All other reagents and chemicals were of suitable analytical grade and were used as received.

Preparation of standard calibration curve of Nateglinide in 0.1N HCL

NAT (100 mg) was added into 40 mL of 0.1N HCl and mixed for about 20 min on a mechanical shaker to obtain a clear solution [5-7]. After achieving a clear solution, add the remaining amount of 0.1 N HCl and makeup to 100 ml. From the above solution, various dilutions were prepared to get concentrations of 5, 10, 15, 20, and 30 mcg/ml. The absorbance of the various solutions was measured against 0.1N HCl as a blank at 210nm using a double-beam UV visible spectrophotometer. The graph of absorbance v/s concentration was plotted and data were subjected to linear regression analysis in Microsoft Excel (Figure 1).

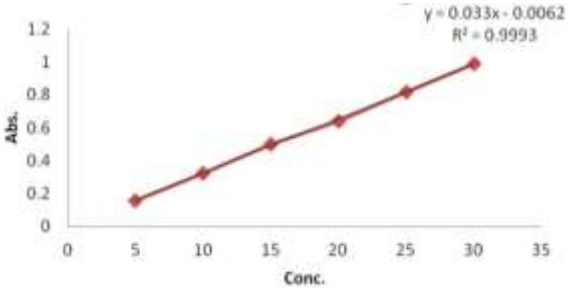

Figure 1: Standard calibration curve of Nateglinide in 0.1N HCL at 210nm.

Preparation of Gastroretentive Film

The screening of Blank film (without NAT) was performed with (I) different amounts of plasticizer (F1-F5) and (II) different amounts of solvents (F6-F8) (III) various polymer (F9-F15) (Table 2) [8]. Based on film appearance, thickness, Folding endurance, and quality, Plasticizer amount (0.4 ml), Methenol: DCM ratio (12.5:12.5), HPMC15cps, and HPMC50cps were finalized. NAT-loaded films were prepared as per formulation F16-F22 (Table 3). The amount of NAT in the film was 120 mg in a 4*2 cm^2 film piece. An appropriate amount of NAT was dissolved in a suitable amount of solvent mixture (1:1) on a magnetic stirrer. NAT solution was added to the polymer solution (e.g.HPMC 50cps) slowly with continuous stirring using a magnetic stirrer. Finally, a selected amount of plasticizer was mixed homogeneously into a NAT-polymer mixture with continuous stirring. The resulting solution was poured into a Petri dish, dried at room temperature, and stored in a desiccator until further used (Figure 2) [9-10].

Table 2: Screening of Plascitizer amount, Solvents amount, and polymers(Blank Films)

Batch code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
HPMC15cps (mg)	1500	1500	1500	1500	1500	1500	1500	1500	---	---	1500	---	1800	---	---
PVPK30 (mg)	---	---	---	---	---	---	---	---	800	900	---	---	---	---	---
HPMC50cps (mg)	---	---	---	---	---	---	---	---	---	---	---	1200	---	1400	---

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HPMCK4M (mg)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1000
EC (mg)	---	---	---	---	---	---	---	---	400	400	250	200	---	---	---
PEG 400 (ml)	0.2	0.3	0.4	0.5	0.6	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Methanol(ml)	10	10	10	10	10	10	12.5	15	12.5	12.5	12.5	12.5	12.5	12.5	12.5
DCM (ml)	10	10	10	10	10	10	12.5	15	12.5	12.5	12.5	12.5	12.5	12.5	12.5

Table 3: Formulation of NAT-loaded gastroretentive films

Batch CODE	**F16**	**F17**	**F18**	**F19**	**F20**	**F21**	**F22**
NAT (mg)	660	660	660	660	660	660	660
HPMC 15cps(mg)	2000	1800	1500	1200	---	---	---
HPMC 50cps(mg)*	---	---	---	---	1500	1200	1000
PEG 400 (ml)	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Methanol(ml)	12.5	12.5	12.5	12.5	12.5	12.5	12.5
DCM (ml)	12.5	12.5	12.5	12.5	12.5	12.5	12.5

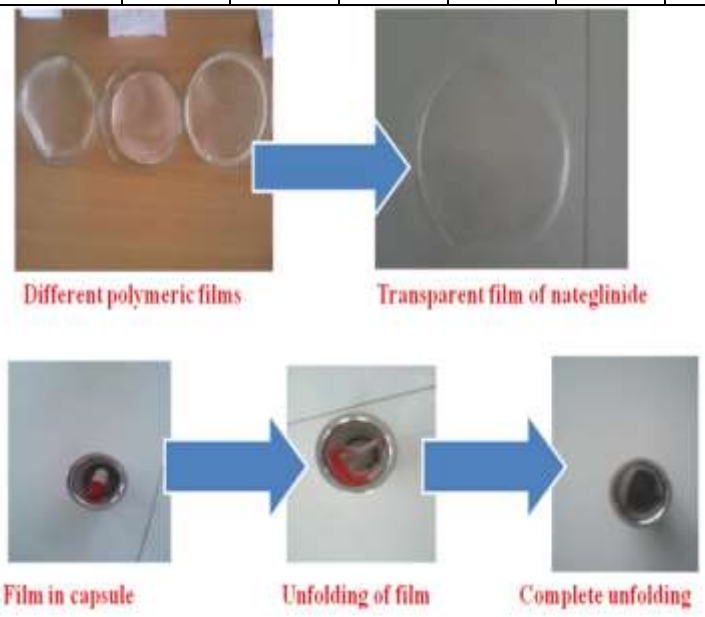

Figure 2. Photographs of Gastroretentive Films and its unfolding pattern.

In-vitro unfolding behavior study [11]

Films were folded by two methods. In the first method, the film was rolled in a single direction, In the second method the film was folded in a zigzag manner and both films were inserted into individual capsules (Size 00). In each case, six capsules were taken for an in vitro dissolution study in 900mL aqueous hydrochloric acid pH 1.2 at 37±0.5ºC using the USP Apparatus-I (basket) at 100rpm. Baskets were removed after 5, 10, 15, 20, 30, 60, 120, 240, 480, and 720 min, and the films were examined for their unfolding behavior, and photographs were taken (Figure 3).

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A) Rolling method **B) Zigzag method**

Figure 3: Photographs of the folding pattern of gastroretentive film (F19)

FTIR Analysis

The interaction of the drug with other polymers was studied through Fourier Transform Infrared Spectroscopy. This test is used to determine the compatibility of the drug with the polymers and the final formulation.

Evaluation of Gastroretentive Films

Physical appearance and surface texture of films

This parameter was checked simply by visual inspection of films and evaluation of texture by feel or touch.

Weight uniformity of films

Three films of the size 4*2 cm^2 were weighed individually using digital balance and the average weights were calculated.

Thickness of films

The thickness of the film was measured using a screw gauge with a least count of 0.01 mm at different spots of the films. The thickness was measured at three different spots of the films and an average was taken.

Folding endurance of films

The flexibility of films can be measured quantitatively in terms of folding endurance. The folding endurance of the films was determined by repeatedly folding films at the same place till it broke. The number of folding at the same place, without breaking gives the value of folding endurance [12].

Swelling index of films

The swelling index of the films was determined by immersing the preweighed film in 50 ml water. The films were taken out carefully at 5, 10,15,20,25, and 30 min intervals, blotted with filter paper, and weighed accurately [13]. The swelling index is calculated by,

% Swelling Index = Wet weight − Dry weight/Dry weight *100

Surface pH of films

Surface pH was determined by the films were allowed in contact with 1ml of distilled water [14]. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of the films and allowing equilibration for 1 min.

Tensile strength of films

The tensile strength of the film was determined with a digital tensile strength tester (Tinius-Olsen) [15]. The sensitivity range of the machine is 1-10 Newton's. It consists of two load cell grips. The lower one was fixed and the upper one was movable. The test film of size (4x2 cm^2) was fixed between these cell grips and force was applied till it broke. The tensile strength of the film was directly taken from the dial reading in Newton's, which was converted into kilogram [16].

Tensile strength =Force at break/Initial cross-sectional area of the sample(cm^2)

Drug content

The film was dissolved in a suitable solvent in a specific volume. Then the solution was filtered through a filter medium and analyzed the drug content with the UV spectrometry method at 210 nm.

In vitro drug release studies

Drug release from the formulations was studied by using USP dissolution tester XXIII Apparatus1 (basket) at 100 rpm in 900mL aqueous hydrochloric acid pH 1.2 at 37ºC ± 0.5ºC. A

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sample of 5ml was withdrawn at a predetermined time interval and replaced with a fresh medium. The samples were filtered through Whatman filter paper and examined by UV at 210nm. The average cumulative percentage of drug release was determined [17]. The dissolution profile of formulations was subjected to various models such as Zero order kinetics, First order kinetics, Higuchi, and Korsemeyer-Peppas to assess the kinetics of drug release from prepared NAT GREF.

Stability study

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors [18]. To assess the drug and formulation stability, stability studies were done as per ICH guidelines. Films were placed in a glass beaker lined with aluminum foil and kept in a humidity chamber maintained at 40±2ºC and 75±5% relative humidity for 1 month. Changes in the appearance, in-vitro release, and unfolding behavior of the stored films were investigated.

RESULT AND DISCUSSION

Screening of Plascitizer amount, volume of solvents and polymers (Blank films)

Gastroretentive expandable films (GREF) of nateglinide (NAT) were prepared by solvent casting technique by using different types of polymers such as HPMC15cps, PVPK30, HPMC50cps, HPMCK4M and ethylcellulose, and PEG400 as a plasticizer. Optimizations of the solvent system, plasticizer concentration as well and selection of polymer and its concentration were done (Table 4). It was found that the polymer concentration is a major factor affecting the drug release and unfolding behavior of gastroretentive films.

Batch F1 to F5 were prepared with various quantities of PEG400 as a plasticizer. It was found that less than 0.2ml of PEG400 was insufficient and imparts lower elasticity to the film. Plasticizer concentration between 0.3 to 0.5 ml yielded satisfactory flexibility to the films. Further increasing the concentration of plasticizer above 0.5ml increased the drying time of the film. Therefore, a PEG400 volume of 0.4 ml was selected for further optimization (Table 4). In the case of batches F6 to F8, it was found that a solvent volume of 25ml was sufficient to cast the film. Formulation F6 produced a viscous solution because the solvent volume was 20 ml hence complete transfer of the solution could not be ensured and film was not produced. In the case of batch F8, the solvent volume was 30 ml and it took more time to evaporate the solution during the preparation of the film (Table 4). Various polymers were evaluated for the preparation of the NAT GREF. The result of the prepared batches is shown in Table 4. The result revealed that the HPMC 15cps and HPMC50cps were suitable for the preparation of GREF.

Table 4: Screening of F1-F15 batches for plasticizer amount, volume of solvents and polymers

Formulation Code	Appearance	Thickness (mm)	Folding endurance	Quality
F1	Non-sticky, Brittle	< 1	<200	Poor
F2	Non-sticky, Brittle	< 1	<250	Poor
F3	Non-sticky, Good flexibility	< 1	>300	Best
F4	Good flexibility, slightly sticky	< 1	>300	Good
F5	Good flexible, but sticky	< 1	> 300	Good
F6	Viscous solution formed	--	--	Poor

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F7	Sufficient volume of solvent	--	--	Good
F8	With more volume of solvent, higher evaporation time	--	--	Poor
F9	The film easily breaks, and hazy film forms	< 1	< 200	Poor
F10	The film was easily broken, hazy film forms.	< 1	< 200	Poor
F11	Cracks found in film	< 1	< 200	Poor
F12	Transparent but cracks were found	< 1	> 250	Poor
F13	Transparent & flexible	< 1	>300	Good
F14	Transparent & flexible	< 1	>300	Good
F15	Transparent & flexible	< 1	>300	Good

FTIR Analysis

Fourier transform infrared spectroscopy (FTIR) was employed for compatibility between NAT and the selected polymer(HPMC 50cps and HPMC 15cps). NAT and NAT with excipients were scanned separately. The FTIR spectra of all samples are shown in Figure 4. NAT spectrum displayed distinctive peaks at 3358.18 cm^{-1} due to stretching of the -2 NH, 2852.72 cm^{-1} for the -CH atom, 16477.26 cm^{-1} for the C=O atom, 1411.94 cm^{-1} for the OH atom, and 1246.06 cm^{-1} for aromatic CO stretching. FTIR spectra of physical mixtures of polymers with the drug retain the characteristic peaks of the drug (Figure 4). It indicated that there was no interaction between the drug and polymers because the IR spectra of all physical mixtures show all the main peaks of NAT. It presumably suggests that the drug molecule is present in an unchanged state in the film.

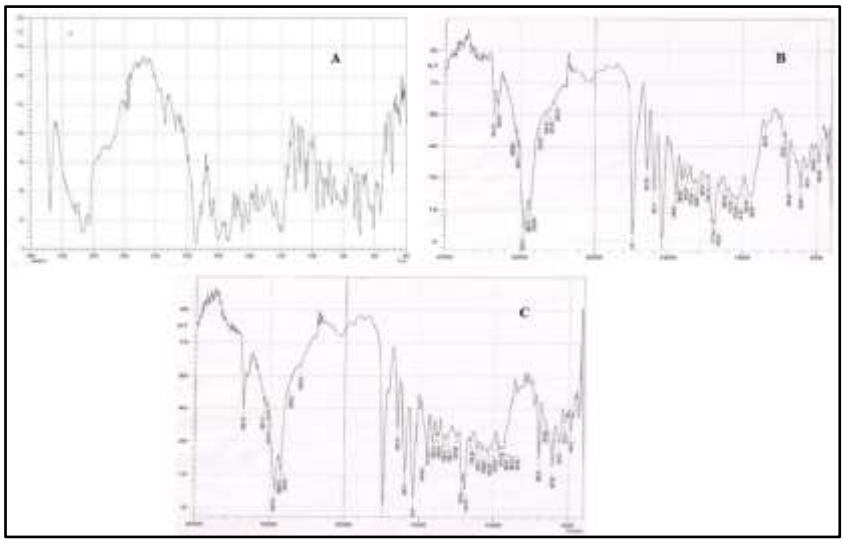

Figure 4 (A)FTIR Spectra of NAT, (B) FTIR Spectra of NAT-HPMC 15cps, (C) FTIR Spectra of NAT-HPMC 50cps.

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Evaluation of NAT-loaded GREF

Appearance, Thickness, Weight variation and Folding endurance

After the screening of the solvent system, plasticizer concentration as well and polymer selection and its concentration, NAT-loaded films were prepared and evaluated (Batch F16-F22). Prepared NAT GREF was smooth, flexible, and good in appearance. The evaluation studies of all the formulations were performed by standard methods.

The weight of the films was determined using digital balance and the weight uniformity of batches F16 to F22 films was given in Table 5. The drug-loaded films were tested (4*2 cm^2) for uniformity of weight. The films were found uniform in weight. The thickness of the films prepared was found to be satisfactory and less than 1 mm in all the prepared batches. The folding endurance gives the idea of the flexible nature of films. The folding endurance was measured manually, films were folded repeatedly till they broke, and it was considered as the endpoint. The folding endurance was found optimum and has more than 300 folds. Therefore, the films exhibited good physical and mechanical properties (Table 5).

Table 5: Appearance, Thickness, Weight variation, and Folding endurance

Formulation Code	Appearance	Thickness (mm)	Weight variation (mg)	Folding endurance
F16	Transparent & flexible	0.889 ± 0.003	345 ± 0.577	337±9.16
F17		0.789 ± 0.002	332 ± 1.527	344±13.01
F18		0.725 ± 0.004	323 ± 2.081	351±16.82
F19		0.704 ± 0.016	310 ± 2.645	327±13.61
F20		0.774 ± 0.002	323 ± 0.577	334±10.50
F21		0.730 ± 0.002	298 ± 1.527	342±9.53
F22		0.704 ± 0.010	281 ± 1.527	331±11.01

Surface pH, Swelling Index and Drug Content and tensile strength

The surface pH of the batch F16 to F22 was found to be in the range of 6.52±0.025 to 6.78±0.032. The swelling index of batch F16 to F22 was found to be in the range of 22.06±2.041 to 31.94±3.012. There was no more significant difference observed among grades of HPMC 15cps and HPMC 50cps in swelling index. The drug content in batches F16 to F22 was in the range of 93.23 to 97.56% (Table 6). The tensile strength of the optimized formulation was found to be 5.45±0.585 kg/cm^2. The results showed that PEG with optimum concentration provides a better plasticizing effect for the polymeric film.

Table 6: Surface pH, Swelling index, and Drug content

Formulation Code	Surface pH	% Swelling Index	Drug content (%)
F16	6.72 ± 0.026	22.48 ± 1.612	96.26 ± 0.251
F17	6.59 ± 0.055	25.67 ± 1.140	93.23 ± 0.152
F18	6.77 ± 0.025	24.50 ± 0.931	94.60 ± 0.300
F19	6.52 ± 0.025	31.94 ± 3.012	95.60 ± 0.916
F20	6.64 ± 0.040	22.06 ± 2.041	97.56 ± 0.251
F21	6.78 ± 0.032	25.44 ± 1.849	93.46 ± 0.750
F22	6.60 ± 0.051	27.78 ± 2.613	96.50 ± 0.402

In-vitro unfolding behavior study

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Gastroretentive films were prepared by rolling and zigzag methods and evaluated for their in vitro unfolding behavior. It was observed that the rolling method had more time for unfolding than the zigzag method. The Zig zag method had an unfolding time was 15-20 min for optimized formulation (Figure 5). Hence, a zigzag method was chosen for the determination of the unfolding behavior of films.

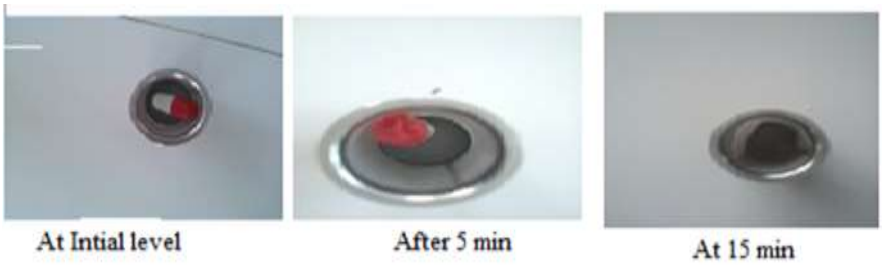

Figure 5: Unfolding behavior of batch 19

In vitro drug release studies

In vitro dissolution study of formulations was carried out in an acidic buffer pH 1.2 (Table 3). Film F16 shows the lowest drug release while film F19 shows the highest drug release for drug release at the first hour(Q1) and drug release at 12 hour (Q12) (Figure 6). The result revealed that formulation F16-F19 (HPMC15cps) and F20-F22 (HPMC 50cps) showed that as the polymer amount was reduced more drug release in Q1 and Q12 was observed. Hence, formulation with a high proportion of HPMCs in total polymer content was found to have a slow release rate of the NAT from the polymeric film over time. HPMCs make channels from which the NAT leaches out more initially and later releases slowly by diffusion from the polymer matrix. During the hydration of HPMC, there is a formation of a gel layer around the dry core of HPMC and swelling of the polymer takes place which is attributed to be used as an oral controlled drug delivery system because of its high swellability.

The data obtained from dissolution studies of batch F19 was analyzed using different mathematical models for the determination of release kinetics(Table 8). Batch F19 followed first-order release kinetics (R^2=0.9933). The release exponent (n=0.56) value can be used to explain why the NAT release followed non-Fickian diffusion in the Korsmeyer-Peppas model. A value less than 0.49 displays Fickian diffusion of the drug and a value of 0.49 and more shows the non-Fickian diffusion mechanism.

Table 7. % In vitro drug release profile of formulations in acidic buffer pH 1.2.

Formulation code	F16	F17	F18	F19	F20	F21	F22
Q1	13.21±1.39	14.31±1.54	16.33±1.34	22.14±2.56	12.23±1.67	14.12±3.54	15.22±2.24
Q12	63.15±1.44	73.22±1.74	86.59±1.65	90.24±3.14	79.54±1.89	83.36±3.71	85.21±2.47

Table 8: Drug release kinetic models with correlation coefficient value (R^2)

Formulation	Zero-Order	First-Order	Higuchi Model	Korsmeyer-Peppas Model	
				R^2	n
F19	0.9514	0.9933	0.9869	0.9890	0.56

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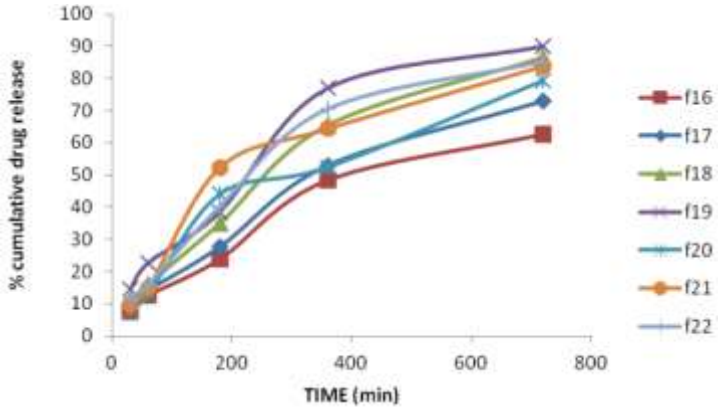

Figure 6: In vitro drug release profile of formulations in acidic buffer pH.

Accelerated stability study

The formulated films were stored in a glass beaker lined with aluminum foil and kept in a humidity chamber maintained at 40±2°C and 75±5% relative humidity for 1 month. The physical and chemical parameters were investigated for a month. The stability studies were carried out on the optimized formulation F19. There was no significant difference in drug content, folding endurance, flexibility, and stickiness. The in vitro drug release of the films changed as the reduction in polymer porosity led to slower penetration of the dissolution medium could happen when they were exposed to accelerated humidity and temperature conditions.

Table 9: Results of Stability study of Formulation F19.

Time	Initial	After one month
Visual Appearance	Flexible, Nonsticky	Flexible, Nonsticky
Folding endurance	327±13.61	320±11.61
Drug content(%)	95.60 ± 0.916	94.85 ± 0.56
In vitro Drug Release (%) (After 12 hr)	90.24±3.14	88.02±2.14

CONCLUSION

The Gastroretentive expandable films (GREF) of nateglinide (NAT) a drug with a narrow absorption window, were successfully formulated. The formulated batches were characterized through various physicochemical parameters, release characteristics, unfolding behavior, and stability study. It consists of a NAT and HPMC15cps polymeric film, folded in two different patterns inside a hard gelatin capsule. The result revealed that the zigzag folding pattern was appropriate in comparison with the roll folding pattern in simulated gastric fluid. The presence of HPMC15cps in polymeric film was crucial to provide an immediate and sustained effect. The floating and mechanical performance of the film indicated the gastroretentive potential of the dosage form. We may investigate this drug delivery approach further through its in vivo evaluation studies, which could result in enhanced bioavailability and assured therapy with other similar drugs that are currently on the market.

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