The effects of the combination of biodegradable and synthetic polymers on the release behaviour of Nateglinide matrix tablets.

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ABSTRACT

The present work was to study the effect of biodegradable and synthetic polymers on sustained release (SR) matrix tablets of Nateglinide based on *in vitro* performance. The SR tablets were formulated with various concentrations of chitosan and/or Eudragit® RLPO or HPMC K100M by direct compression. The tablets were tested for drug-polymer interaction, weight variation, thickness, hardness, friability, drug content, *in vitro* drug release and stability. The NG06 SR matrix tablets were able to sustain the release of the drug over 12 hours (CDR=98% ± 1.47) and showed optimum post-compression properties. The *in vitro* release data of NG06 also showed a good linear relationship with the Korsmeyer-Peppas model (r^2=0.9975) while n=0.750 indicated non-Fickian transport. Formulation NG06, which included 12.5 mg chitosan and 12.5 mg Eudragit® RLPO, showed optimum characteristics to achieve the objectives of this study.

KEY WORDS: Nateglinide, sustained release, matrix tablets, chitosan, Eudragit® RLPO, HPMC K100M, *in vitro* dissolution, excipients

INTRODUCTION

Nateglinide (NG) is a derivative of meglitinide analogues and widely used for the management of type-2 diabetes. NG has a short biological half-life of 1.5 ± 0.7 hours (1) whilst exhibiting fluctuations in plasma concentration. The short biological half-life of the drug and the fluctuations in the drug concentration in plasma favours the development of a sustained release formulation (2) which would additionally allow for a reduction in the dosing frequency of NG. A sustained release (SR) dosage form of NG would have advantages over conventional dosage forms such as decreased frequency of dosing, thus improving patient compliance. An appropriately formulated SR dosage form could also reduce the *in vivo* fluctuation of the drug concentrations thus increasing the therapeutic efficacy and minimising the risk of adverse events such as hypoglycemia and hepatic impairment (3).

Sustained release formulations can be developed at low cost by incorporating the drugs into a matrix system that contains a hydrophilic or hydrophobic rate-controlling polymer. Chitosan have been widely used in the development of SR formulations. It is a linear-chain copolymer composed of D-glucosamine and N-acetyl-D-glucosamine and obtained by the partial deacetylation of chitin. The structure of chitosan is very much like that of cellulose and is the second most abundant natural polymer after cellulose (4). Chitosan

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cannot be dissolved in water, organic solvents or aqueous bases. However, it dissolves after stirring it into acetic, nitric, hydrochloric, perchloric and phosphoric acids. Chitosan can have different degrees of deacetylation (DD) and different molecular weights. Generally, a typical commercial chitosan has a DD of 66-95% (5). Chitosan has good complexing capacity and can form a complex with an oppositely charged polymer such as poly (acrylic acid), sodium salt of poly (acrylic acid), carboxymethyl cellulose, xanthan, carrageenan, Eudragit®, alginate, pectin and so on (6). Eudragits® are synthetic polymers obtained by polymerization of acrylic acid and methacrylic acids or their esters such as butyl ester or dimethylaminoethyl ester whose physicochemical properties are determined by their functional groups.

Due to its wide range of molecular weights, hydroxypropyl methylcellulose (HPMC) is also considered a versatile excipient to use in the formulation of soluble matrix tablets for sustained release formulations. HPMC provides an effective control of the viscosity of the gel. HPMC is also widely accepted as a pharmaceutical excipient for the formulation of sustained release matrix tablets (7). For example, an Azithromycin insert was prepared using 1.5% HPMC and 3% Eudragit® RL100, and the authors were able to show that it extended the drug release over 12 hours (8).

NG has been developed as sustained release formulations using natural polymers such as guar and xanthan gums to extend drug release and reduce dosing frequency (9). The concept of blending biodegradable polymers with synthetic polymers has received considerable attention from researchers due to the increased bio-based content. Combining synthetic and natural polymers can produce new polymeric materials, which have biocompatible and biodegradable properties, but at the same time maintain optimum thermal and mechanical properties (10). Matrix systems are extensively used in SR formulations due to their ability to achieve the desired drug release profile, the minimal influence of physiological variables on the release behaviour, cost-effectiveness, and broad regulatory acceptance (11).

Direct compression is extensively used for the preparation of Eudragit®-based matrix tablets. Ceballos *et. al.*, prepared extended-release theophylline matrix tablets using direct compression of the drug and various pH-dependent (Eudragit® L 100, S 100 and L 100-55) and time-dependent (Eudragit® RLPO and RSPO) polymer combinations. Matrix tablets containing the combination of the desirable erodable properties of Eudragit® L 100 with the swelling properties of Eudragit® RLPO and Eudragit® RSPO polymers gave the best results (12). Eudragit® RLPO and Eudragit® RSPO can reduce drug release rates because they have low water affinity. The higher the concentration of Eudragit® incorporated into the formulation, the more hydrophobic the environment, thus the lesser the permeation of the dissolution medium into the matrix, thereby causing a delay in the drug release (13).

There has not been previously any NG sustained release formulations using the combination of biodegradable and synthetic polymer. In this study, chitosan and/or Eudragit® RLPO or hydroxyl propyl methyl cellulose (HPMC K100M) were incorporated as drug retardants in the SR matrix tablets. Chitosan is a biodegradable, non-toxic polymer that has a gel-forming ability at low pH while both Eudragit® RLPO and HPMC K100M are synthetic polymers which are commonly used in the formulation of sustained release dosage forms due to their capability of forming a matrix system.

MATERIALS AND METHODS

Nateglinide was purchased from Wuhan Vanz Pharm Inc, China. Eudragit® RLPO was a gift supplied by Nice Chemie Pvt. Ltd., Mumbai, India. High molecular weight Chitosan was obtained from Sigma Aldrich, USA. HPMC K100M, pharmaceutical grade magnesium stearate (vegetable source) and microcrystalline cellulose 102 (MCC) were obtained from Merck Chemicals, Germany, whereas talcum powder BP and lactose analytical reagent grade were acquired from Fisher Scientific (M) Sdn Bhd, Malaysia.

Compatibility studies

A compatibility study was carried out using FT-IR spectroscopy (Thermoscientific Nicolet iS5) over

the region 400-4000 cm^{-1}. The spectra obtained were evaluated for signs of drug-excipient interaction (7).

Preparation of sustained release matrix tablets

SR Nateglinide matrix tablets were prepared using the formulations shown in Table 1. Direct compression was used because it is the easiest, most effective and least complicated method for compressing tablets (11, 14). The formulations were optimized for the total weight 500 mg per tablet. The excipients used in this study have good compressibility properties, making them suitable for direct compression. All the ingredients were passed through a number 60 sieve, carefully weighed and placed into a plastic bag. Chitosan and/or Eudragit® RLPO or HPMC K100M were added into the bag. After each addition, the bag was sealed and manually shaken for several minutes to mix the ingredients thoroughly. Then MCC and lactose were added as diluents to adjust the total weight of each tablet. Finally, talc and magnesium stearate were added as lubricants into the powder blend to improve flow properties. The powder blend was fed manually into the die cavity of a rotary tablet press (Rimek Mini Press 1) and compressed into tablets (3).

Table 1 The composition of the SR matrix tablets of Nateglinide

INGREDIENTS (MG)	NG01	NG02	NG03	NG04	NG05	NG06
Nateglinide	60	60	60	60	60	60
Chitosan	20	-	-	10	-	12.5
Eudragit® RLPO	-	20	-	10	-	12.5
HPMC K100M	-	-	20	-	25	-
Lactose	205	205	205	202.5	200	200
MCC	205	205	205	202.5	200	200
Mg Stearate	5	5	5	10	10	10
Talc	5	5	5	5	5	5
Total weight	500	500	500	500	500	500

Evaluation of sustained release matrix tablets

Pre-compression properties

Pre-compression properties of the powder blend were evaluated using standard protocols including angle of repose, compressibility index and Hausner ratio (15).

Post-compression properties

Post-compression properties of the sustained release matrix tablets were evaluated including weight variation, uniformity of thickness, hardness and friability.

Drug content

Ten tablets were weighed and crushed into powders and the equivalent of the average weight of one tablet was weighed and dissolved in 5 mL of methanol in a 100 mL volumetric flask, the volume made up by adding water. The aliquots of the samples were analysed using a UV spectrophotometer (Spectrum Instruments SP-UV500DB) at 210 nm (16).

In vitro drug release

The dissolution test was performed by adding 900 mL of 0.75% SLS in 0.01 M HCl using a paddle method with a Type 2 dissolution apparatus (Electrolab Dissolution Tester) at 37°C±0.5°C at 50 RPM (3). 5 mL of samples were withdrawn by using a syringe at predetermined time intervals up to 12 hours and replaced with an equivalent amount of buffer after each withdrawal of the sample to maintain the volume in the vessel. The collected samples were analysed using a UV spectrophotometer at 210nm (16).

Drug release kinetics

The mechanism of drug release was determined by fitting the *in vitro* dissolution data into five different types of mathematical models: zero order as cumulative % of drug released versus t, first order as log cumulative percent drug remaining versus t, the Higuchi equation as cumulative percent drug released versus log t, the Korsmeyer-Peppas equation as log cumulative percent drug released versus log t and the Hixson-Crowell equation as cube root of % drug remaining versus t (17).

Best fit was evaluated using r^2 (correlation coefficient) values. The Korsmeyer-Peppas equation indicates that the value of the release constant can be used to identify the mechanism of drug release (18).

Table 2 The mechanism of drug release based on release constant (17).

RELEASE CONSTANT, *N*	MECHANISM OF DRUG RELEASE
0.45	Fickian release (case I)
0.45<*n*<0.89	Non-Fickian release (anomalous)
0.89	Super case II release

Swelling and erosion of the tablets

Swelling and erosion studies of the tablets were carried out in 0.75% SLS in 0.01 M HCl medium. The tablets were placed in the medium for a predetermined time up to 12 hours before taking them out and drying them in the oven (Memmert 500) at 40°C for 2 days (19). The dried tablets were reweighed to determine the matrix erosion and the percentage of swelling and erosion were calculated using Equations 1 and 2 respectively:

$$\%\,\text{Swelling} = \frac{\text{Wet weight - Dry weight}}{\text{Dry weight}} = 100 \qquad \text{Eq. 1}$$

$$\%\,\text{Erosion} = \frac{\text{Original weight - Dry weight}}{\text{Dry weight}} = 100 \qquad \text{Eq. 2}$$

Accelerated stability studies

The optimized formulation was packaged in an aluminium foil and subjected to accelerated storage conditions at a temperature of 40±2°C and 75±5% RH over a period of three months (90 days). Samples were drawn at predetermined time intervals to measure physical parameters and drug content.

Statistical analysis

The results obtained are presented as the mean ± standard deviation (SD). GraphPad Prism version 7.0 was used for statistical analysis. The results obtained from the drug release and accelerated stability studies (*in vitro* drug release) were analysed using two-way analysis of variance (ANOVA). Two-way ANOVA was used because there are two independent variables in the drug release study, i.e., time and various polymers and in the accelerated stability studies, the independent variables are time and different months. A post hoc Tukey-HSD test was performed when the results showed a statistically significant difference. A statistically significant difference was considered when $p < 0.05$.

RESULTS AND DISCUSSION

Compatibility studies

Figure 1 shows that there was no significant shifting or masking of drug peaks. There were also no significant changes in the positions of the wave numbers indicating that all the polymers in the tablet formulations were fully compatible with the drug (Nateglinide).

Evaluation of sustained release matrix tablets

Pre-compression properties

The results of the pre-compression properties are shown in Table 3. Initially, three formulations NG01, NG02 and NG03 were prepared. These all indicated fair to passable flow based on the values obtained from both the compressibility index and Hausner ratio. Therefore, to improve flow properties, magnesium stearate, which acts as a lubricant, was increased from 1% to 2% for formulations NG04, NG05 and NG06. Table 3 shows that NG04 still had a fair to passable flow and NG05 and NG06 showed good flow properties indicated by the angle of repose, compressibility index and Hausner ratio, all complying with USP Standards (20).

Post compression properties

Table 4 shows that all the tablets prepared in this study met USP Standards for weight variation tolerance. Friability was <1% for all the formulations whereas the drug content was in the range of 94.76% ± 1.78 to 105.90% ± 1.46, also within USP limits (20).

Compatibility studies

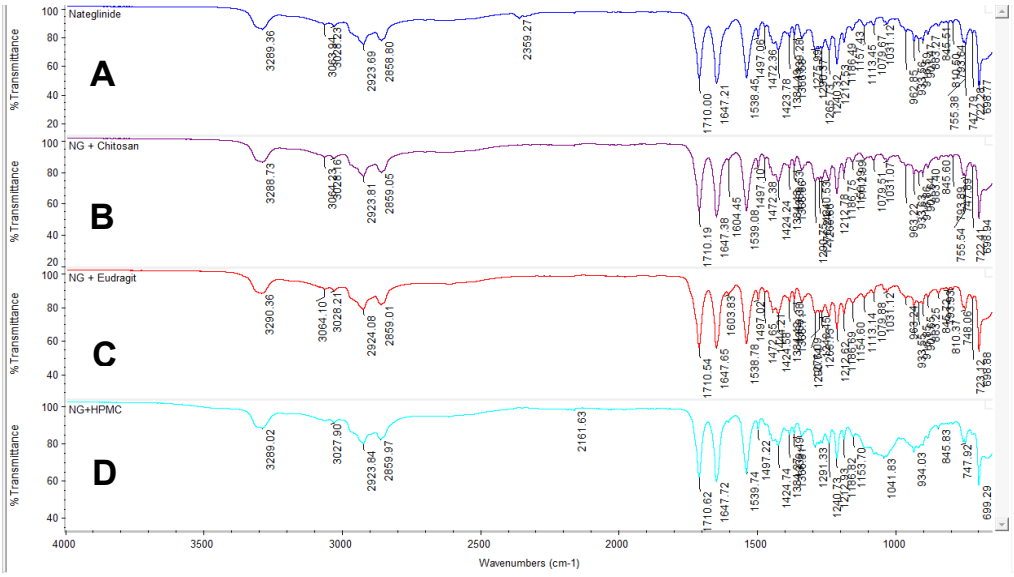

Figure 1 FTIR spectra for Nateglinide (A); Nateglinide with Chitosan (B), Nateglinide with Eudragit® RLPO (C) Nateglinide with HPMC (D)

In vitro drug release studies

A variation in drug release profile for all formulations was observed because of the different polymer compositions included. A two-way ANOVA analysis was conducted whereby the effect of the different polymers and drug release time was examined. There was a statistically significant interaction between the effects of the different polymers and time of drug release, whereby $F(12, 84) = 2.693$ and $p < 0.0001$. The drug release between the different polymers ($p<0.0001$) and the drug release between time ($p<0.0001$) were also both statistically significant, whereby $p<0.05$.

Carbinatto *et al.*, made the assumption that the rate of drug release from a polymeric matrix depends on the

Table 3 Pre-compression properties of powder blend.

FORMULATION	BULK DENSITY (g/cm³) ± S.D.	TAPPED DENSITY (g/cm³) ± S.D.	COMPRESSIBILITY INDEX (%) ± S.D.	HAUSNER RATIO ± S.D.	ANGLE OF REPOSE (°) ± S.D.
NG01	0.50±0.023	0.61±0.025	18.03±2.324	1.22±0.026	34.80±1.082
NG02	0.55±0.015	0.71±0.026	22.54±1.457	1.29±0.021	36.30±0.624
NG03	0.55±0.010	0.67±0.010	17.91±2.339	1.22±0.023	31.80±1.058
NG04	0.61±0.017	0.77±0.017	20.78±0.462	1.26±0.028	34.10±0.500
NG05	0.65±0.020	0.75±0.040	13.33±1.961	1.15±0.024	29.96±2.917
NG06	0.59±0.036	0.67±0.030	11.94±1.774	1.14±0.023	29.89±1.147

Table 4 Post-compression properties of Nateglinide SR matrix tablets

FORMULATION	WEIGHT (mg) ± S.D.	HARDNESS (kg/cm²) ± S.D.	THICKNESS (mm) ± S.D.	FRIABILITY (%) ± S.D.	DRUG CONTENT (%) ± S.D.
NG01	494±0.16	4.5±0.42	4.49±0.35	0.52±0.02	100.38±1.24
NG02	491±0.36	4.8±0.34	4.53±0.31	0.56±0.03	99.16±1.17
NG03	494±0.36	5.0±0.34	4.61±0.31	0.43±0.04	105.90±1.46
NG04	495±0.36	4.46±0.34	4.49±0.30	0.62±0.01	99.92±1.33
NG05	496±0.04	5.0±0.52	4.61±0.43	0.61±0.05	94.76±1.78
NG06	495±0.35	5.8±0.33	4.59±0.31	0.49±0.03	99.31±1.31

swelling of polymer matrix, which is dependent on the characteristics and ratio of the incorporated polymers (21). The hydrophilic polymers HPMC K100M and hydrophobic polymer Eudragit® RLPO have different drug release mechanisms. The HPMC K100M forms a hydrated gel barrier through which the drug must diffuse, whereas the hydrophobic polymer Eudragit® RLPO forms channels or pores in the tablet matrix through which the drug diffuses (22).

The combination of chitosan and Eudragit® polymers in NG04 showed a better drug release profile compared to formulations prepared using a single polymer (chitosan (NG01), Eudragit® (NG02) and HPMC K100M (NG05) (shown in Figure 2). Higher concentrations of chitosan alone and Eudragit® RLPO alone did not show further delay in the drug release. Ryakala *et al.*, also reported that drug release was not sustained as long as 12 hours when only a single polymer is incorporated (16). Based on this a combination of polymers (chitosan and Eudragit® RLPO (formulation NG04) were incorporated into the NG formulation. However, NG04 was not able to sustain the drug release for as long a 12 hours. Therefore, the amounts of chitosan and Eudragit® RLPO in formulation NG04 were increased from 10 mg to 12.5 mg for NG06 in order to delay the drug release (23). Due to

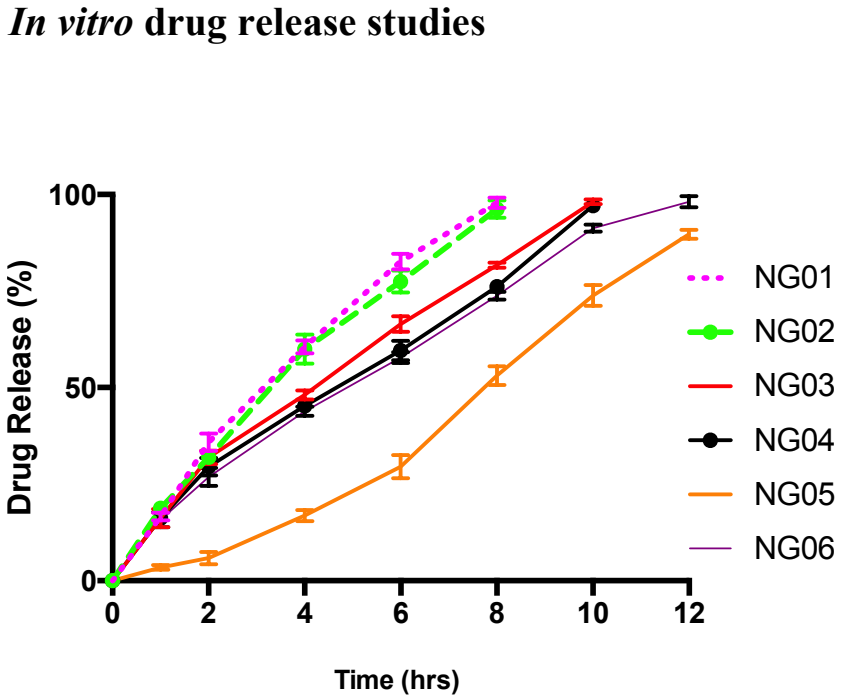

Figure 2 Comparison of percentage drug release of Nateglinide from SR matrix tablets for all the formulations.

the low water affinity of Eudragit® RLPO, the greater the quantities of the polymer, the less the permeation of dissolution medium into the matrix (13). Thus, less channels or pores are formed resulting in a reduction in the total porosity of the matrices (initial porosity plus porosity due to the dissolution of the drug), which caused a delay in drug release (22).

Based on the values in Figure 2, NG06 showed CDR of 98±1.47 in 12 hours, which was the objective of this study. Therefore, formulation NG06, which included 12.5 mg Chitosan and 12.5 mg Eudragit® RLPO, was considered the optimum formulation and selected for further testing. There was a statistically significant difference in drug release between NG04 and NG06 at 10 hours ($p=0.0011$) at $p<0.05$.

Although formulation NG05 was able to sustain drug release up to 12 hours, the drug release did not fulfil the USP requirements, which states that not less than 70% of the drug should be released in the eight hours (CDR = 53±2.44 in 8 hours) (14). All the results were expressed as mean values of three determinants ±S.D.

Drug release kinetics

The *in vitro* release data of the SR matrix tablets of Nateglinide was fitted into different mathematical models and equations to determine the drug release mechanism. The mathematical models used were zero order, first order, Higuchi, Korsmeyer-Peppas and Hixon-Crowell models. DD Solver an Excel add-in was used to calculate the regression coefficient, as well as, release constant and the values are shown in Table 5. The *in vitro* drug release profile of the optimized formulation, NG06, was best represented by Korsmeyer-Peppas model as it showed highest linearity ($r2=0.9975$) (Table 5). From the Korsmeyer-Peppas equation, the release constant (n) obtained was 0.750 which showed that the drug released through anomalous transport otherwise known as a non-Fickian release. In a non-Fickian release, the release of the drug follows both diffusion and erosion mechanisms simultaneously (24). Due to erosion, specific narrow channels through which the drug release takes place are produced in the matrix (25).

The Korsmeyer-Peppas equation has been widely used to identify the mechanism of drug release (24). Reddy *et al.*, obtained an n-value of 0.71 for a matrix tablet of nicorandil (11) whereas Fassihi and Ritschel (26) obtained an n-value of 0.70 for a matrix tablet of theophylline. Meanwhile, Sharma *et al.*, reported an n-value of 0.66 for a matrix tablet of Nateglinide (27). The above studies all concluded, based on the release exponent value obtained using the Korsmeyer-Peppas equation, that an anomalous diffusion acted as the mechanism for the drug release.

Swelling and erosion behavior

Formulation NG06 showed an increase in percentage weight gain until reaching maximum (152.5±2.76) at 12 hours, indicating maximum swelling. Swelling occurred due to the entry of water into the polymeric matrix. This resulted in the decrease of the glass transition temperature of the matrix to that of the dissolution medium. As the amount of water inside a matrix increases, the crystalline state is converted to a gel state. A hydrophilic gel barrier, which functions to retard drug release, is formed. The intake of water also induced stress within the polymeric matrix, resulting in relaxation of the polymeric matrix, which led to swelling (28).

Because drug release occurs through the hydrophilic gel layer surrounding the matrix tablets, the formation and viscosity of the gel layer, as well as, the tablets' swelling, and erosion rates are key factors that affect drug release rates (11). Table 6 shows that the optimimum formulation NG06 had a slow release rate. This is due to the rapid formation of a highly viscous gel layer around the matrix tablets, which delays the release of the drug.

As the mechanism of drug release of the formulation includes both diffusion and erosion simultaneously, the erosion properties of the matrix tablets were also investigated. Similarly, a directly proportional relationship was observed for the percentage weight loss, showing that the erosion rate after 12 hours was 66.9±2.46.

Table 5 Drug release kinetics of SR matrix tablets of Nateglinide

MODEL	NG01	NG02	NG03	NG04	NG05	NG06
Zero Order						
R^2	0.9684	0.9718	0.9665	0.9762	0.9429	**0.9666**
K_0	13.299	12.869	10.435	10.029	7.034	**8.971**
First Order						
R^2	0.9726	0.9752	0.9730	0.9641	0.8369	**0.9674**
K_1	0.258	0.242	0.198	0.181	0.101	**0.173**
Higuchi						
R^2	0.9439	0.9452	0.9522	0.9391	0.7223	**0.9489**
K_H	31.790	30.751	27.799	26.618	19.346	**26.066**
Korsmeyer-Peppas						
R^2	0.9962	0.9981	0.9986	0.9966	0.9979	**0.9975**
n	0.763	0.767	0.745	0.786	1.572	**0.750**
K	20.493	19.682	17.534	15.501	1.940	**15.575**
Hixson-Crowell						
R^2	0.9922	0.9926	0.9880	0.9803	0.8710	**0.9859**
K_S	0.071	0.067	0.055	0.050	0.030	**0.048**

Accelerated stability studies

The results from the accelerated stability studies are shown in Table 7. The results suggest that the physical parameters, including the appearance and drug release profile of the optimized formulation, remained within the set limits. There was also no statistically significant difference in drug release between different months ($p=0.2899$), showing that the drug release remained unchanged (above 97%) throughout the test period. Consequently, the formulation (NG06) optimized in this study was considered stable after three months at accelerated storage conditions.

CONCLUSION

The optimized formulation, NG06, which included 12.5 mg chitosan and 12.5 mg Eudragit® RLPO had the best characteristics to achieve the objectives of this study. The SR matrix tablets formulated using NG06 was able to sustain the release of the drug over 12 hours and showed optimum post compression properties,

Table 6 Swelling and erosion data for the optimized formulation NG06

TIME (HOURS)	ORIGINAL WEIGHT (mg) ± S.D.	WET WEIGHT (mg) ± S.D.	DRY WEIGHT (mg) ± S.D.	PERCENTAGE WEIGHT GAIN (%) ± S.D.	PERCENTAGE WEIGHT LOSS (%) ± S.D.
1	498.3±0.012	941.0±0.004	470.2±0.007	100.2±3.91	6.0±1.06
2	497.6±0.006	975.7±0.001	440.1±0.007	121.6±3.94	13.1±1.23
4	500.9±0.010	787.7±0.003	338.1±0.003	132.8±2.55	48.2±4.24
6	506.9±0.007	776.9±0.002	329.2±0.008	136.2±2.45	54.1±2.04
8	501.2±0.009	755.4±0.001	313.7±0.002	141.1±0.95	59.8±2.47
10	500.3±0.009	762.0±0.002	308.8±0.003	147.2±1.93	62.0±1.43
12	500.8±0.008	757.3±0.003	300.1±0.002	152.5±2.76	66.9±2.46

Table 7 Parameters for the optimized formulation NG06 during accelerated stability study

PARAMETERS	INITIAL	1 MONTH	2 MONTHS	3 MONTHS
Appearance	Yellowish-white, flat and round shaped	Yellowish-white, flat and round shaped	Yellowish-white, flat and round shaped	Yellowish-white, flat and round shaped
Weight variation (mg)	495±0.35	495±0.28	496±0.22	495±0.31
Hardness (kg/cm²)	5.8±0.33	5.8±0.24	5.8±0.30	5.8±0.27
Thickness (mm)	4.59±0.31	4.71±0.33	4.69±0.25	4.66±0.29
Drug Content (%)	99.31±1.31	99.29±0.87	99.38±0.89	99.33±0.72
Dissolution (cumulative % drug release in 12 hrs)	98.34±1.47	98.61±1.28	99.76±0.75	97.7±1.31

as well as, stability after three months. *In vitro* release studies also showed a good linear relationship with the Korsmeyer-Peppas model (r^2=0.9975) while n=0.750 indicated a non-Fickian transport mechanism. Therefore, the optimized Nateglinide sustained release formulation could effectively extend the drug release and thus decrease the dosing frequency.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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