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Original Article

DEVELOPMENT OF OSMOTICALLY CONTROLLED ORAL DRUG DELIVERY SYSTEM FOR NATEGLINIDE AN ANTI-DIABETIC DRUG

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ABSTRACT

Objective: The purpose of the present study was to develop an oral push-pull osmotic drug delivery system for the drug Nateglinide which is a bio pharmaceutics classification system (BCS) class II drug.

Methods: The tablets were prepared by the wet granulation method using ingredients microcrystalline cellulose (Adsorbent), potassium chloride (Osmotic agent), poly ethylene glycol (4000 and 6000) (Hydrophilic polymer, Plasticizer), starch (Disintegrant), and aerosil. The granules were compacted by double compression method and were coated with eudragit by dipping method. Different batches were prepared to study the effect of the various ingredients and their effect on the release of the drug from the system by varying the concentrations of the ingredients in each batch. Dissolution was assessed using USP dissolution apparatus 2 in phosphate buffer pH 6.8 for 12 h.

Results: Certain key findings observed includes a decrease in micro crystalline cellulose content reduced the release of the drug due to the reduction of the hydrophilic content in the tablet which complements the uptake of water from the surroundings, and increase in the ethylene glycol leads to decrease in the release which resulted due to excess swelling and increase in the osmotic agent concentration lead to satisfactory release of the drug and followed zero-order release.

Conclusion: To conclude, the push-pull osmotic tablet of Nateglinide was able to deliver the drug in a controlled pattern for a prolonged period of time. This type of formulation can be used in conditions like hyperglycemia where the patient compliance can improve by reducing the dosing frequency and the plasma drug levels can be maintained, the total drug load is also reduced so that the dose related side-effects are also reduced.

Keywords: Controlled release, Push-pull osmotic pump, Nateglinide.

INTRODUCTION

Oral route of administration is one of the oldest and most extensively used route for the administration of drug providing convenient method of effectively achieving both local and systemic effect. In conventional oral drug delivery systems, there is little or no control over release of the drug and effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses. This kind of dosing pattern result is constantly changing, unpredictable and sub or supra therapeutic plasma concentrations, leading to marked side effects in some cases. Hence better dosage form design and delivery can minimize many of these problems. Oral controlled release (CR) systems continue to be the most popular amongst all the drug delivery systems [1] Because of pharmaceutical agents can be delivered in a controlled pattern over a long period. Among which the pulsatile drug delivery systems (PDDS)/ osmotic drug delivery system (ODDS) are gaining importance as these systems deliver the drug at specific time as per the pathophysiology need of the disease, resulting in improved patient compliance and therapeutic efficacy [2]. These systems work on the principle of osmotic pressure for controlling the delivery of the drug. The release of the drug is independent of physiological factors of the GIT to a large extent [3, 4].

Various approaches are made in designing the formulations, which will overcome the disadvantages of the conventional dosage forms, which include sustained/controlled drug delivery system [5-7]. Osmotic devices are the most promising strategy based system for controlled drug delivery [8]. Drug can be delivered in a controlled pattern over a long period of time by the process of osmosis. Surveys indicated that dosing more than once or twice daily greatly reduces patient compliance. Hence, the primary objective of controlling drug release is to deliver a pharmacologically active agent in a predetermined, predictable and reproducible manner [9].

Oral osmotically controlled release (OSCR) delivery system provide a uniform concentration/amount of drug at the site of absorption and thus after absorption, allow maintenance of plasma concentration within therapeutic range, which minimizes side effects and also reduces the frequency of administration [10]. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system [11, 12]. Nateglinide is derivative of D-phenylalanine that stimulates insulin secretion by blocking ATP-sensitive K+ channels in pancreatic cells. It acts by reducing postprandial glycemic elevations in type 2 Diabetes Miletus (DM) patients. Nateglinide is FDA-approved for use in type 2 DM. Nateglinide is metabolized primarily by the liver and should be used cautiously in patients with hepatic insufficiency [13, 14]. Nateglinide was prescribing to patients with Type 2 diabetes over the dose range of 60-240 mg three times a day for one week which is a major limitation of this drug because of reduced patient compliance [15, 16]. Hence the present study was attempted to design a novel drug delivery system for Nateglinide to sustain its release and action for prolonged time.

MATERIALS AND METHODS

Materials

Nateglinide was obtained as a gift sample from Dr. Reddys labs, India. Poly ethylene glycol (Molecular weight: 4000 and 6000), aerosil, talc, starch, magnesium stearate and potassium chloride were purchased from S.D Fine Chemicals, Chennai, India. Micro crystalline cellulose was obtained from Essel Fine Chem, Mumbai, India. Potassium bromide (IR grade) was purchased from Qualigen Fine Chemicals, Mumbai and Eudragit was purchased from Evonix, India.

Methods

Development of Calibration Curve for Nateglinide

A stock solution of Nateglinide was prepared by dissolving 100 mg of drug in 100 ml of phosphate buffer of pH 6.8 (1 mg/ml). From this

stock solution 20,40,60,80,100 µg/ml dilutions were prepared using phosphate buffer of pH 6.8. The λ max of the drug was determined by scanning one of the dilutions between 400 and 200 nm using a UV-visible spectrophotometer. At this wavelength, the absorbance of all the solutions was measured against a blank. Standard curve between concentration and absorbance was plotted and the intercept (C) and slope (K) values were noted

Compatibility Studies

Differential Scanning Calorimeter (DSC)

This is more advanced method of determination of purity of components. It scans the individual component or a mixture with a range if temperature and its effect on the sample [17]. The samples (Nateglinide, polyethylene glycol and eudragit) individually and their combination with the drug was studied for compatibility under DSC. Each sample scanned with DSC and found to be no interaction between the drug and polymer.

FTIR (Fourier transform infrared spectroscopy) Studies

The infrared spectrum matching approach was used for detection of any possible chemical interaction between the drug and the polymer. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 15 tons pressure. It was scanned from 4000 to 400 cm^{-1} in a Perkin Elmer FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers and matching was done to detect any appearance or disappearance of peaks using FTIR peak matching method [18].

Formulation Osmotic Tablets of Nateglinide

Tablet formulation was prepared by wet granulation technique and the detailed diagrammatic representation of preparation of tablets was shown as a flow chart in figure. 1.

Drug Layer

Drug was mixed with polyethylene glycol (4000), KCL, microcrystalline cellulose (MCC) and starch. All the excipients were passed through sieve # 120 before mixing. This mixture was moistened with 10% starch paste to proper wetness and granulated by passing through sieve #14 [19] and the quantities were taken accordingly for different batches as mentioned in Table no.1.

Table 1: Different batches of formulation

Compact	Ingredients	F (mg)	F1 (mg)	F2 (mg)	F3 (mg)
Drug Layer	Nateglinide	335	335	335	335
	PEG(4000)	60	60	70.7	60
	KCL	40	40	40	51.1
	MCC	10	15	10	10
	Mg.Stearate	1	1	1	1
	Starch	40	40	40	40
	Talc	10	10	10	10
	Aerosil	10	10	10	10
Push Layer	PEG(6000)	60	60	70.7	60
	KCL	40	40	40	51.1
	MCC	10	15	10	10
	Mg.Stearate	1	1	1	1
	Starch	40	40	40	40
	Talc	10	10	10	10

Push Layer

Polyethylene glycol 6000 was mixed with KCL, MCC and starch. This mixture was moistened with 10% starch paste and granulated by passing through sieve #14 and the quantities were taken accordingly for different batches as mentioned in table no: 1. these two layers were dried at 40 ^{0}C for 1 h separately and then passed through sieve #18. Finally talc, aerosil and magnesium stearate was added to the mixtures and compacted [20].

Coating

Tablets were coated by dipping method where the coating solution is prepared by dissolving 1 gm of eudragit (RLPO grade) in 8 ml of isopropyl alcohol [19]. The tablets are dipped in the coating solution and are allowed to dry at room temperature. Prior to the compression, the powder were evaluated for angle of repose, bulk density and compressibility index. After compression, post compression parameters like Weight variation, Disintegration and Hardness were done [22-24].

Dissolution Study

The dissolution studies of prepared Nateglinide tablets were carried out in simulated gastric acid fluid pH 1.2 and phosphate buffer pH6.8 respectively for 12 h using USP dissolution apparatus type 2 (The paddle method). The dissolution studies were performed at temperature 37^{0}C±0.5 ^{0}C and a rotation speed of 75 rpm. An aliquot sample of 5 ml was withdrawn at time intervals of 0, 1, 2, 4, 6, 8, 10 and 12 h respectively, simultaneously an equal amount of buffer was replaced back to maintain the sink conditions. The drug release at different time intervals was measured using UV Visible Spectrophotometer at λmax of 220 nm. It was made clear that none of the ingredients used in the matrix formulations interfered with the assay. The release studies were conducted in triplicate and the mean values were plotted versus time [25].

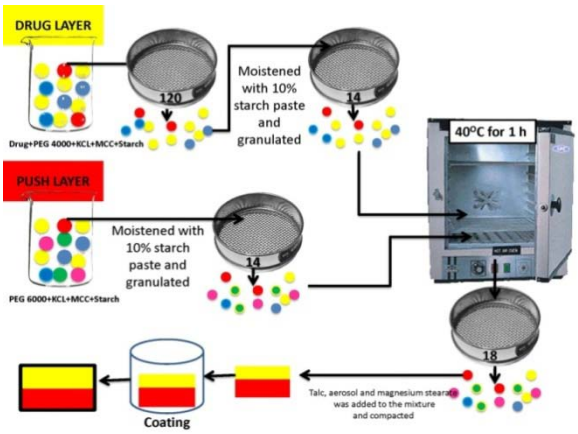

Fig. 1: Diagrammatic representation of preparation of Nateglinide osmotic tablets.

Mathematical Modelling

In vitro dissolution has been recognized as an important element in drug development. Under certain conditions it can be used as a

surrogate for the assessment of bioequivalence. Several theories/kinetic models describe drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where f_t is the function of t (time) related to the amount of drug dissolved from the pharmaceutical dosage system. To compare dissolution profiles between two drug products model dependent (curve fitting), statistic analysis and model independent methods can be used [26, 27]

In order to elucidate mode and mechanism of drug release, the *in vitro* data was transformed and interpreted at graphical interface constructed using various kinetic models such as Korsmeyer-Peppas, Higuchi release, Zero and first order release models. The interpretations of diffusion mechanisms from dosage forms are shown in Table. 2. Kinetic constant incorporates structural and geometrical characters of the drug/polymer system. For non-Fickian release, the n value falls between 0.5 and 1.0 ($0.5< n < 1.0$), whereas in the case of Fickian diffusion, n= 0.5; for zero-order release (case transport), n=1, and for Supercase II transport, n>1. The values of n as estimated by linear regression of log (M_t/ M_∞) vs log (t) of different formulations were calculated.

Table 2: Interpretations of diffusion mechanisms from dosage forms

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero order release
Higher than 1.0	Super case-II transport	t^{n-1}

RESULTS AND DISCUSSION

Preparation of calibration curve

Calibration curve of the drug (Figure. 2) was developed to find out the linearity between concentration of drug in the solution and its absorbance. It was concluded that the perfect linearity between the concentration and absorbance was observed when the concentration range was from 20µg/ml to 100µg/ml. Table 8 and Figure 10 shows the calibration of Nateglinide using phosphate buffer pH 6.8. The "Slope (K)" and "Intercept (C)" value was found to be 0.013 and 0 and linearity R^2 value was found to be 0.990.

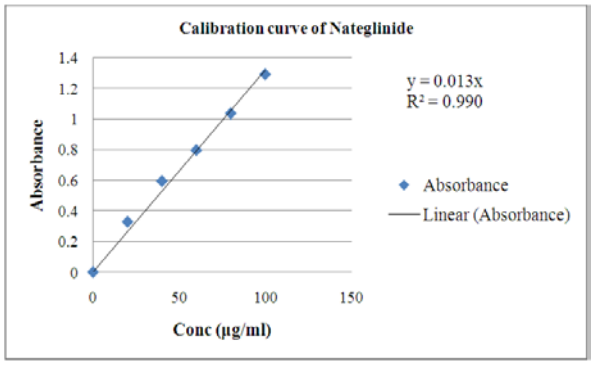

Fig. 2: Calibration curve of Nateglinide

Compatibility Studies (DSC)

The DSC graphs of individual samples and their mixture with drug are shown in figure 3,4 and 5. It has been found that there is no interaction between the drug and the polymers. The melting point of the Nateglinide (drug) was not interfered by the polymers. The drug exhibited an endothermic peak at 166.89°C, the same peak appeared at 165.7^0 C with eudragit and163.7°C with poly ethylene glycol indicating there is no interaction between the drug and polymers.

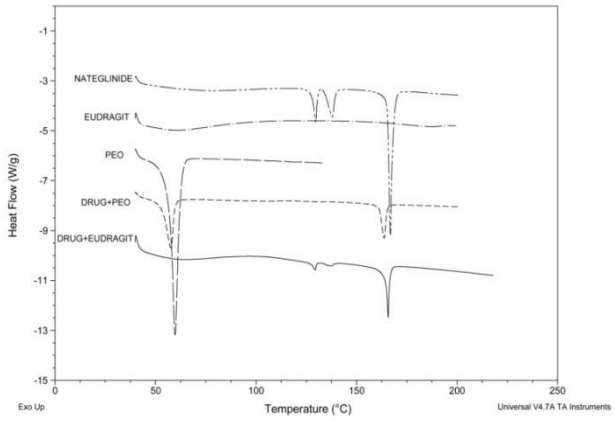

Fig. 3: Over lay DSC layout

FTIR Studies

The IR spectra of pure drug, polymer and the physical mixtures are shown in Figure 6,7 and the data was interpreted in Table. 3.

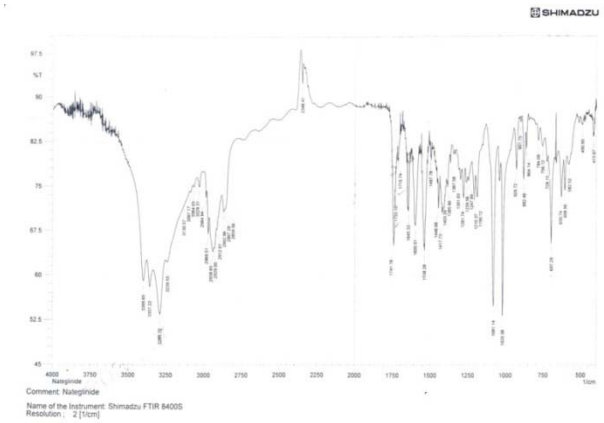

Fig. 6: FTIR graph of Nateglinide

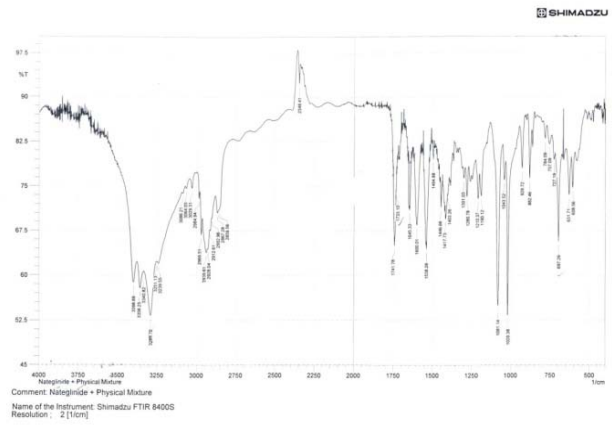

Fig. 7: FTIR graph of physical mixture

There was no appearance or disappearance of peaks in the polymer-drug mixture, which confirmed the absence of any chemical interaction between the drug and the polymers. After interpretation of the FTIR spectra's (Table. 3) it was confirmed that there was no major shifting, Loss or appearance of functional peaks between the spectra of drug and physical mixture of drug and excipients. From the spectra it was concluded that the drug was blended well with the excipients without any chemical interaction.

Table 3: FTIR compatibility studies for drug and physical mixture

Drug wave number (cm-1)	Physical mixture wave Number(cm-1)	Wave number region
2348.41	2348.41	O-H(Carboxylic acid)
1715.74	1715.74	C=O(Carboxylicacid)
1538.28	1538.28	N-H
1020.38	1020.38	C-N
687.29	687.29	C-C(Cyclic hexane)
3029.1	3029.1	C-H(Aromatic)
1600.01	1600.01	C=C(Aromatic)
1733.10	1733.10	C=O(Keto)
2969.51	2969.51	c-c(Alkyl)

Powder characteristics

The powder characteristics were performed for formulation F, F1, F2, F3 and shown in Table. 4. It was found that angle of repose is between 20-30 range, indicating a good flow property. Carr's Index was found to be in between 9-12 range, indicating good compressibility. Hausner's ratio was <1.25 indicating ease of powder flow.

Evaluation Parameters

Weight variation

The weight variation was determined using 20 tablets and it is shown in Table. 5. All the tablets were within range and not even a single tablet deviated more than 5 % from the average weight

Table 4: Powder characteristics for formulations (F, F1, F2 and F3)

Formulation	Angle of repose (°)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index	Hausner's ratio
F	29.9	0.6312	0.6939	9.035	1.099
F1	29.03	0.6114	0.6785	9.889	1.109
F2	28.43	0.6679	0.7346	9.07	1.099
F3	28.55	0.6136	0.6989	12.20	1.139

Table 5: Determination of weight variation of Tablets

S. No	Wt of Tablets (mg) (F)	% Deviation	Wt of Tablets (mg) (F1)	% Deviation	Wt of Tablets (mg) (F2)	% Deviation	Wt of Tablets (mg) (F3)	% Deviation
1	670	-1.39	655	-4.4	711	+0.70	625	-4.98
2	690	+1.54	715	-4.3	701	-0.84	685	+4.13
3	650	-4.33	682	-0.51	680	-3.81	635	-3.46
4	700	+3.0	692	+0.94	741	+4.6	675	+2.61
5	675	-0.66	660	-3.71	675	-4.5	673	+2.31
6	685	+0.80	715	+4.3	740	+4.6	637	-4.6
7	695	+2.28	675	-1.53	722	+2.1	686	+4.2
8	665	-2.13	695	+1.38	690	-4	626	-4.83
9	665	-3.60	690	+0.65	681	-3.6	678	+3.07
10	705	+3.75	681	-0.65	736	+2.9	631	-4.07
11	661	-2.72	671	-2.11	725	+2.5	650	-1.18
12	699	+2.86	699	+1.96	688	-2.6	660	+0.33
13	683	+0.51	667	-2.69	719	+1.6	645	-1.9
14	677	-0.367	703	+2.55	693	-1.9	665	+1.09
15	667	-1.838	661	-3.57	737	+2.8	669	+1.7
16	693	+1.985	709	+3.42	677	-4.2	671	+2.0
17	684	+0.66	659	-3.86	689	-2.5	663	+0.79
18	676	-0.514	711	+3.71	699	-1.1	667	+1.39
19	670	-1.39	679	-0.94	723	+2.2	654	-0.5
20	690	+1.54	691	+0.80	713	+0.84	661	+0.48

Hardness test was performed using Erweka TBH20 model hardness tester and the results was shown in Table. 6. It was found that hardness ranges from 5 and 6 kg/cm^2.Drug content (Table. 6) was estimated in the formulations F, F1, F2, F3 using phosphate buffer pH 6.8 and absorbance was taken at 210 nm and found that drug content was 99.62, 98.62%, 98.55%, 98.51%, 98.74% respectively in F, F1, F2 and F3.

Dissolution study

Dissolution studies were done for the formulations (F, F1, F2 and F3) and it is presented in Table. 7 and Figure. 8. Dissolution studies were performed for four formulations and the percentage release was calculated. The percentage release for formulation F was found to be 91.75 in 12 h, for formulation F1 was found to be 60.89% in 12 h and for formulation F2 was found to be 76.98% in 12hr and in F3 the release was found to be 83.16% in 12 h. In formulation F1 the MCC content is reduced so the release rate was found to be less when compared to other two formulations, and in F2 and F3 the PEG and KCL content were increase to 5% when compared to F and release rate was found to be increased when compared to F1.

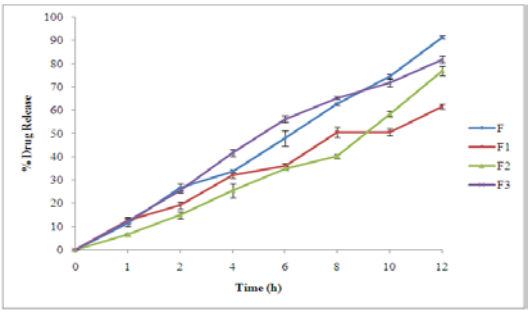

Fig. 8: Graphical representation of dissolution study for formulations

The kinetics was studied using release data modelling to predict the release behaviour of the drug from the polymer.

Release Drug Data Modelling

Release data modeling studies were performed using the Zero order, First order, Higuchi and Korsmeyer-Peppas model and data is shown in Figure. 9,10,11,12 and Table. 8. It was found that the formulation F followed first order and the other formulations (F1, F2, and F3) followed zero order release.

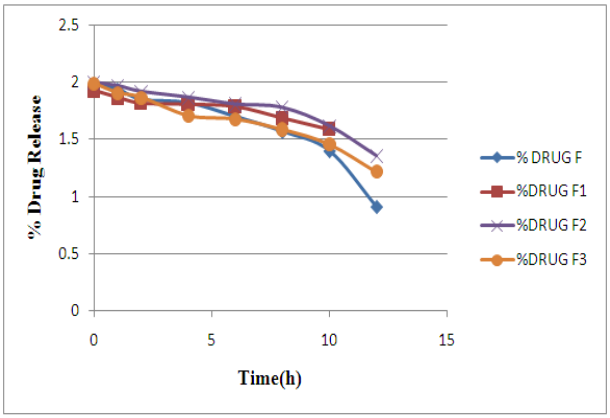

Fig. 9: Zero order models for formulation F, F1, F2 and F3.

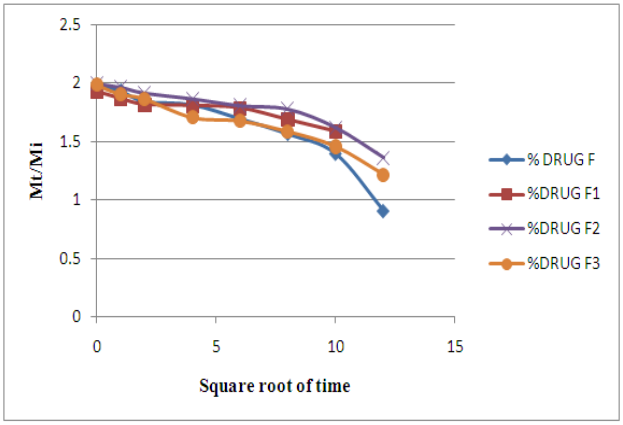

Fig. 10: Higuchi model for formulation F, F1, F2 and F3.

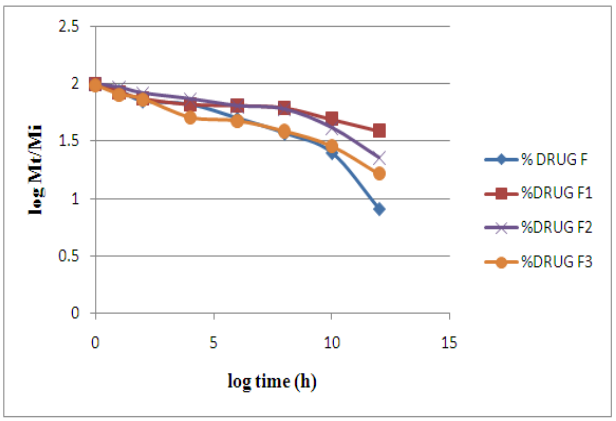

Fig. 11: Korsmeyer-Peppas model for formulation F, F1, F2 and F3.

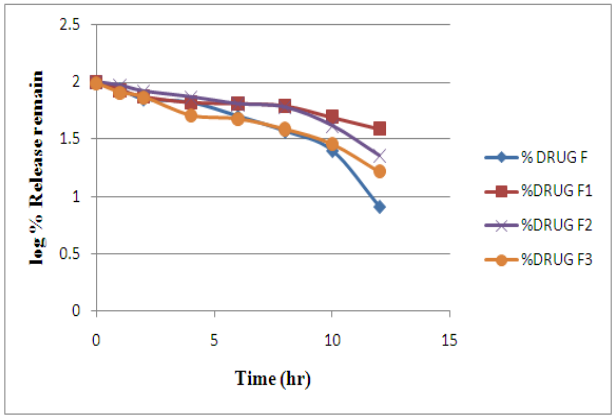

Fig. 12: First order model for formulation F, F1, F2 and F3.

Table 6: Hardness and Drug content of prepared formulations

Formulation	Hardness (kg/cm²)	Drug content (%)
F	5±0.02	98.62±0.06
F1	6±0.04	98.55±0.04
F2	6±0.01	98.51±0.10
F3	5±0.05	98.74±0.09

Table 7: Dissolution study for formulations F, F1, F2 and F3

Time (hr)	% Drug release (F)	% Drug release (F1)	% Drug release (F2)	% Drug release (F3)
0	0.07±0.05	0.07±0.01	0.03±0.05	0.08±0.02
1	11.53±1.52	12.62±1.15	6.50±0.57	12.49±1.52
2	26.86±1.52	19.13±1.52	14.95±1.52	25.46±1
4	33.76±0.57	32.10±1.15	25.53±3	41.73±1.56
6	47.96±3.21	35.99±1.16	34.97±1	56.24±1.65
8	62.69±0.57	50.41±2.30	40.16±1	65.29±0.57
10	74.40±1	50.62±1.52	58.35±1.15	71.91±1.73
12	91.42±0.54	61.56±1.15	76.98±2	81.83±1.52

*Standard Deviation (S.D) =3

Table 8: Consolidating all release models of formulation F, F1, F2 and F3

Model	R^2(F)	R^2(F1)	R^2(F2)	R^2(F3)
Zero order	0.9834	0.9532	0.9723	0.9593
Higuchi	0.9502	0.982	0.8878	0.9799
Korsmeyer-Peppas	0.9706	0.9878	0.9732	0.9739
First order	0.8829	0.9325	0.8889	0.9643

CONCLUSION

Osmotic drug delivery system was the most promising strategy based system for controlled drug delivery. These systems uses the osmotic pressure as driving force to deliver the drug; in a controlled pattern over a long period of time by the process of osmosis.

In the current research work, push pull osmotic tablets were prepared for Nateglinide which is used for the treatment of hyperglycemia (type 2 diabetes) and the half-life of the drug is 1.5 h. These tablets were prepared using starch, potassium chloride, poly ethylene glycol, aerosil and are coated with a semi-permeable membrane. Where starch is used as binding agent, KCL is used as osmogen, PEG acts as suspension as well as swelling agent.

Evaluation studies were performed namely weight variation, hardness test, dissolution. The results for the weight-variation hardness were found to be within the limit. The dissolution was performed using phosphate buffer pH 6.8. The results showed that the release profile of formulation F was 91.75%, F1 was 60.89%, F2 was 76.985 and F3 was 83.16% for 12 h.

To conclude, the push-pull osmotic tablet was able to deliver the drug in a controlled pattern for a prolonged period of time. This type of formulation can be used in conditions like hyperglycemia where the patient compliance can be improve by reducing the dosing frequency and the plasma drug levels can be maintained, the total drug load is also reduced so that the dose related side effects are also reduced.

CONFLICT OF INTERESTS

Declared None

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