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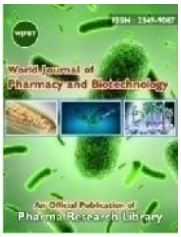

Research Article **Open Access**

Design, Characterization and Evaluation of Chrono-modulated Nateglinide using pulsatile Drug Delivery System

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A B S T R A C T

In present study pulsatile drug delivery system of nateglinide was developed to control early morning hyperglycemia to synchronize the circadian rhythm of diabetes mellitus. Nateglinide is a novel anti diabetic drug that lowers blood glucose levels by stimulating insulin secretion from the pancreas. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. The solubility of nateglinide was enhanced by using in situ micronization technique by using hydrophilic stabilizers like PVP K30, Hupu gum. The formed micro-crystals were evaluated for %practical yield, drug content, % drug release, FT-IR, DSC, XRD, and SEM. The optimized micro-crystals (F5) were selected as the best formulation for the development of pulsincap. Pulsincaps were formulated using body of the capsules treated with formaldehyde to modify its solubility and polymer plug of HPMC, Xanthan gum, lactose, gelatine was fitted in mouth of the capsule body. *In vitro* release study were carried out using pH 1.2 buffer for a period of 2 h then 6.8 pH phosphate buffer for a period of 6 hours. Batch P1 containing HPMC as a plug shows required lag time of 6 hours that release drug in the early morning hours.

Keywords: *In situ* micronization technique, Nateglinide, Pulsincap, Solubility.

A R T I C L E I N F O

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1. Introduction

Chronotherapeutics refer to a clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm including disease states to produce maximum health benefit and minimum harm [1]. A major objective of chronotheraphy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of disease. Pulsatile drug delivery system is the type of drug delivery system, where the delivery device is capable of releasing drug after predetermined lag time known as pulsatile drug delivery system. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time. Pulsincap is the one of the approaches for pulsatile drug delivery. Pulsincap system comprises of a water insoluble capsule body, soluble cap and hydrogel plug. When this capsule came in contact with the dissolution fluid, it dissolves and after a lag time, the plug pushed itself outside the capsule and rapidly releases the drug. The length of the plug and its point of insertion into the capsule controlled the lag time [2].

The capsule bodies of size 1 were treated with formaldehyde vapours to make capsule body water insoluble. The amino group in the gelatine molecular chain could react with an aldehyde group of formaldehyde by a Schiff's base condensation reaction to produce a water insoluble body. The formaldehyde solution concentration and exposure time to capsule bodies were optimized by solubility study of treated capsule bodies. The physical mixture of drug and excipients were filled in formaldehyde treated capsule body and filled with hydro gel plug. Then untreated cap was fitted on the body and the entire capsule device was coated with Eudragit S-100. After the cap opening in the dissolution media, the hydrogel plug came into contact with dissolution media and it hydrated and started to swell and after ejection of plug from the body, the drug was released immediately [3].

Nateglinide is an oral anti-hyperglycemic agent belongs to BCS class-II drug which has low solubility and high permeability. It belongs to the meglitinide class of short acting hypoglycemic agent and its effect is believed to effectively control postprandial blood glucose levels. Nateglinide is practically insoluble in water leading to poor dissolution and variable bioavailability indicating modest first pass effect. It is an anti-diabetic drug, which is widely used for the treatment of type-2 diabetes mellitus (non-insulin dependent diabetes mellitus). Fasting hyperglycemia is an important phenomenon observed in almost all individuals with diabetes. In non-diabetic individuals, fasting plasma glucose concentration was within normal limits and higher in the afternoon than in the morning. In diabetic patients, fasting plasma glucose concentration was not only abnormally high but was significantly higher in the morning than in afternoon. This shows the association between diabetes and morning hyperglycemias and this is also called as liver dump or dawn phenomenon and usually occurs between 4 am and 8 am. When hormone insulin is out of balance with other hormones (cortisol, glucagon and epinephrine), the liver will release too much glucose. The time of administration of the drug play a key role in the treatment of diabetes for effective therapy. Hence in this research work pulsatile delivery system of Nateglinide was developed at a predetermined lag time of 6h as a bed time dosing [4].

2. Materials and Methods

Materials

Nateglinide was supplied as a gift sample by A-Z pharmaceuticals, PVP K30 (S.D. Fine Chem Ltd., Mumbai), Guar gum (S.D. Fine Chem Ltd., Mumbai), HPMC, Gelatin, SSG, Lactose, Eudragit S-100, Methanol, Acetone. All other reagents used were of AR grade and procured locally.

Preparation of Nateglinide microcrystals

Nateglinide microcrystals were prepared by rapid solvent change method. In this method first, an organic solution of the drug was prepared by dissolving 1.7 gms of drug in 3 ml of methanol (solvent phase). Then measured quantity of aqueous solution (anti-solvent) containing 0.1% w/v of stabilizing agent was added rapidly under stirring to the drug solution. This caused super saturation with respect to the drug and subsequent nucleation and crystal growth. The mixture was stirred for 60 min by using magnetic stirrer. The crystals were collected by filtration using whatmann filter paper followed by three consecutive washings with 10 ml of cold water to remove any non-adsorbed excipients and dried at room temperature [5].

Characterization of Nateglinide microcrystals

Differential scanning calorimetry (DSC)

Thermal analysis of nateglinide and their micro-crystals were recorded with Netzsch DSC 200PC. The temperature axis and cell constant of DSC were previously calibrated with indium. A heating rate of 20°C/min was employed over a temperature range of 50- 350^0C with nitrogen purging.

X-ray diffraction study (XRD):

X-ray diffraction spectra of nateglinide and their micro-crystals were recorded with X-ray diffractometer with ray-flex software using Ni-filtered, Cu-K-α-radiation, a voltage of 40 kV and a current of 30 mA. The instrument was operating in continuous scan mode over a 2θ range of 20-60°C at a step time of 10.3 seconds. The relative intensity I/I_0 and the interplanar distance (d) corresponding to the 2θ values were reported and compared.

Scanning electron microscopy (SEM):

Scanning electron micrographs of nateglinide microcrystals and pure drug were taken using a scanning electron microscope. Samples were fixed on an aluminium stub with conductive double-sided adhesive tape and coated with gold in an argon atmosphere (50 Pa) at 50 mA for 50 sec.

In vitro release studies of microcrystals

In vitro dissolution studies of pure nateglinide and microcrystals were conducted by using USP type II apparatus (paddle type). The dissolution studies were performed using 900 ml phosphate buffer of pH 6.8 as dissolution medium at 37±0.5°C with 50 rpm speed.

Samples of each preparation equivalent to 100 mg of drug were added into the dissolution medium. At predetermined time intervals aliquots was withdrawn and replaced by an equal volume of dissolution medium to maintain constant volume. Withdrawn samples was filtered and suitably diluted with phosphate buffer pH 6.8 and analysed for their drug content by using UV spectrophotometer at a wavelength of 210 nm. Percentage of drug dissolved at various time intervals was calculated by plotting time on X-axis against Percent cumulative drug release on Y-axis[6].

Formulation of pulsincap dosage forms

The optimized microcrystals equivalent to 120 mg of drug& appropriate quantities of sodium starch glycolate (super disintegrant) and lactose (diluent) were was incorporated into the formaldehyde treated body of empty hard gelatin capsule shell. Then it was plugged with formulated hydrogel plug and fixed the gelatin capsule cap. Then the joint of the capsule body and the cap was sealed with a small amount of 5% Eudragit S-100 which is dissolved in acetone. Then the sealed capsules were completely coated with 5% Eudragit S-100 solution by dip coating method. Coating was repeated until 8-12% increase in total weight of capsule was obtained [7].

Table 1: Composition of different formulations of hydrogel plug

S.No.	Ingredients	Formulation code			
		P1	**P2**	**P3**	**P4**
1.	HPMC (mg)	200	100	100	100
2.	PVA (mg)	--	100	--	--
3.	Xanthan gum (mg)	--	--	100	--
4.	Gelatin (mg)	--	--	--	100
	Total weight (mg)	200	200	200	200

Table 2: Composition of pulsincap

S. No.	Ingredients	Weight taken (per capsule)
1.	Optimized microcrystal formulation (mg)	Equivalent to 120 mg of drug (w/w)
2.	Sodium starch glycolate (mg)	4% (w/w)
3.	Lactose (mg)	Quantity sufficient
Total weight (mg)		200 mg

Characterization of nateglinide pulsincaps

Fourier transforms infrared spectroscopy (FT-IR)

Fourier transforms infrared (FT-IR) spectral measurements for nateglinide, optimized nateglinide microcrystals and physical mixture of nateglinide microcrystals - SSG-lactose were recorded using Thermo-IR 200 FT-IR spectrophotometer. Potassium bromide pellet methods were employed [8].

***In vitro* release studies of pulsincap**

In vitro dissolution studies were carried out by using USP dissolution type-I apparatus (basket type), in 900 ml medium at 37^0C at a rotation speed of 50 rpm. Capsules were placed in the basket and immersed completely in dissolution media. Based on lag time the pulsincaps was tested at 0.1N HCl (simulated gastric fluid) initially for 2 hours and the rest of period dissolution was carried out in pH 6.8 (simulated intestinal fluid). At predetermined time intervals samples was withdrawn and replaced by an equal volume of fresh dissolution medium to maintain constant volume. The samples withdrawn was filtered and diluted suitably and the samples were analysed for their drug content by using UV spectrophotometer at wavelength of 210 nm [9].

3. Results & Discussion

***In vitro* release studies of microcrystals**

In vitro dissolution profiles of nateglinide microcrystals prepared by rapid solvent change method were compared with that of the pure nateglinide. The concentration of stabilizing agent of all the formulations (F1-F10) remains same at the concentration of 0.1% w/v. Solvent to anti-solvent ratio (v/v) changes for each formulation, which needs to be optimized. The formulations F1,F2,F3,F4,F6, F7, F8, F9,F10 shows drug release 54.85, 80.16, 87.88, 96.33, 50.83, 69.53, 81.96, 85.27 and 87.09% respectively at the end of 1hr, whereas F5 formulation has shown drug release of 96.21% respectively at the end of 45 min. Therefore, among ten formulations F5 was selected as the best formulation for the development of pulsincap dosage form based on its effective release where the solvent and antisolvent in the ratio of 1:10. All the formulations *viz.* F1-F10 has shown increased cumulative dissolution profiles in comparison with that of pure drug as shown in Figure No. 1.

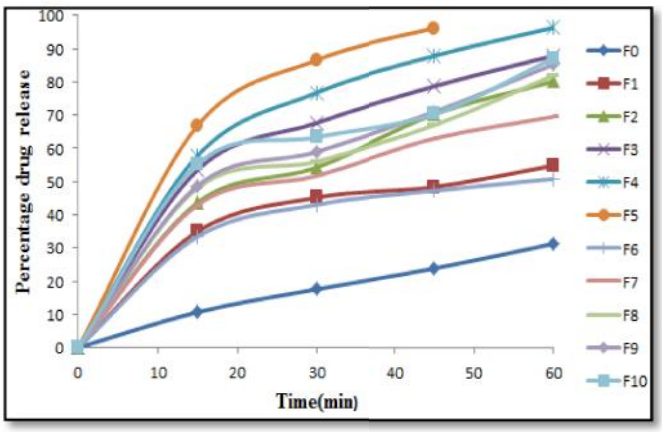

Figure 1: Dissolution profile of nateglinide microcrystals

Differential Scanning Calorimetry

The DSC curve showed that nateglinide appeared an endothermic peak at about 141^0C corresponding to its melting point. However, the microcrystals prepared with hydrophilic stabilizers like PVP K30 and Guar gum shows shift of endothermic peak towards lower temperature at 100 and 140^0C respectively. Shift of endothermic peak towards lower temperature dictates decreased melting point of drug in the formed microcrystals which indicates decrease in crystalline nature of nateglinide. The DSC thermograms of

nateglinide indicate that there is no interaction between the drug and excipients. The DSC graphs of pure drug and its microcrystals prepared using 0.1% w/v of PVP K30 and guar gum respectively were shown in the Figure No. 2

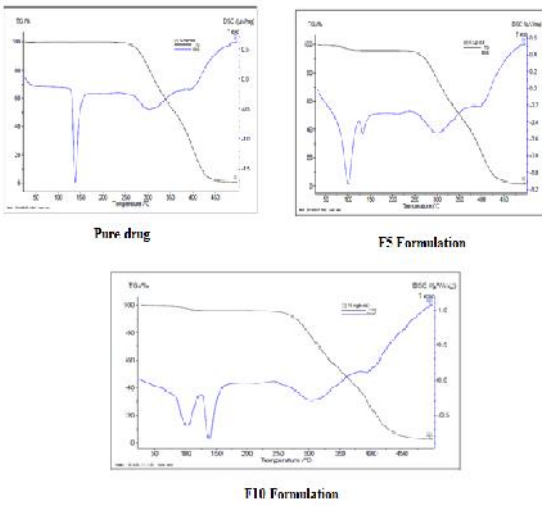

Figure 2: DSC of Nateglinide and its microcrystals

X-ray diffraction studies

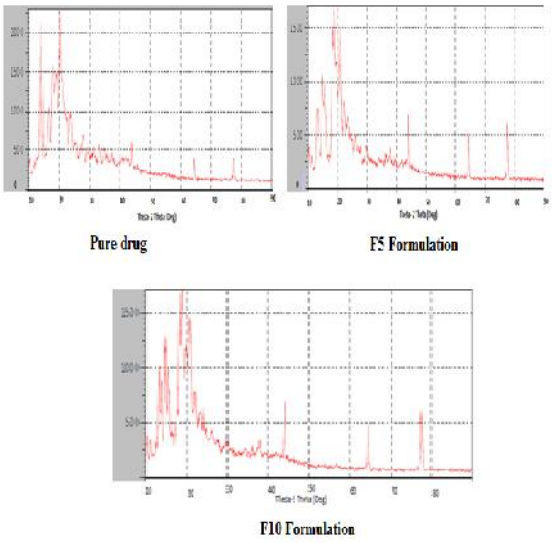

Figure 3: XRD of Nateglinide and its microcrystals

The X-ray diffraction patterns for pure nateglinide and its microcrystals containing 0.1% w/v of PVP K30 and guar gum as hydrophilic stabilizing agents were shown in figure No.3. XRD pattern of Nateglinide showed intense and sharp peaks indicating its crystalline nature.No. of peaks and peak height decreased in the nateglinide microcrystal's than the untreated nateglinide. The lack of numerous distinctive peaks of the drug in case of nateglinide microcrystals indicates the reduced crystallinity when compared to that of pure drug. This may be due to partial conversion of the drug to amorphous state from crystalline state.

Scanning electron microscopy

Scanning electron micrograph discloses the surface morphology of nateglinide and nateglinide microcrystals. SEM results of pure nateglinide and its microcrystals were shown in Figure No.4. From the results it was found that the surface morphology of crystals was changed by solvent change method. This is due to face specific adsorption of stabilizing agent alters the growth rate of the crystal faces where adsorption takes place and thus changes the morphology of the crystal. Modification of crystal habit can improve the dissolution rate by promoting the growth of more hydrophilic faces or inhibiting the growth of more hydrophobic faces.

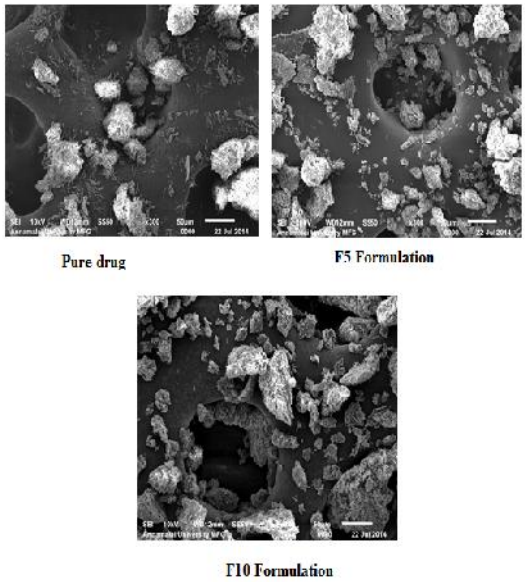

Figure 4: SEM of Nateglinide and its microcrystals

***In vitro* release studies of pulsincap**

In vitro dissolution test was done in dissolution media of 1.2 and 6.8 to simulate gastric and small intestine pH respectively. The formulations NP1, NP2, NP3 and NP4 released 95.17%, 85.72%, 70.06% and 81.69% of drug for an extended period of 8 hrs**.** Based on the lag time and *in vitro* release values NP1 (6hrs lag time) was selected for final formulation of pulsincap it indicates that all the dosage forms released the drug uniformly without any significant difference. The cumulative percentage drug release was plotted against time (Fig.5).

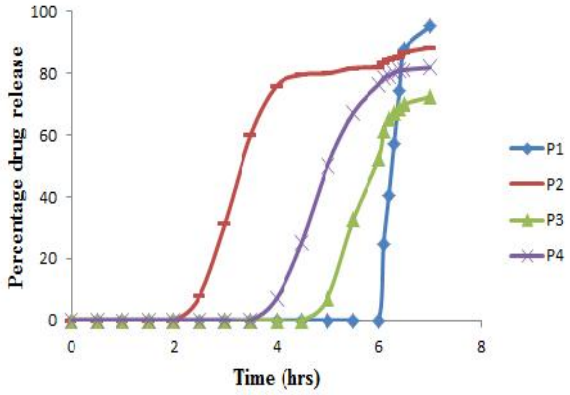

Figure 5: Dissolution profile of nateglinide pulsincap formulations

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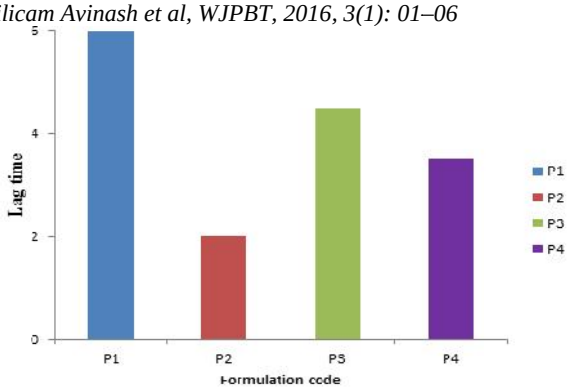

Figure 6: Lag time profile of nateglinide pulsincap formulations

Fourier Transform infra-red spectroscopy (FT-IR):

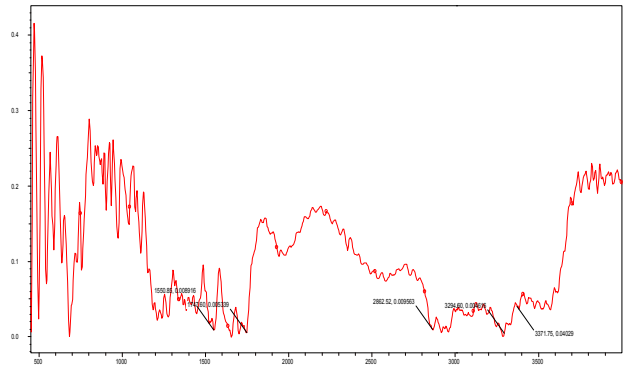

Figure 7: FT-IR spectrum of nateglinide

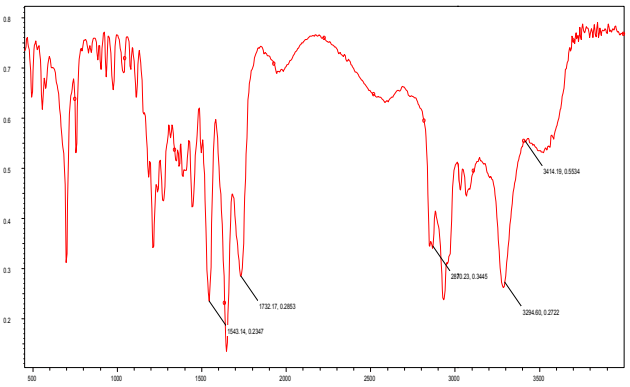

Figure 8: Optimized nateglinide microcrystal formulation (F10)

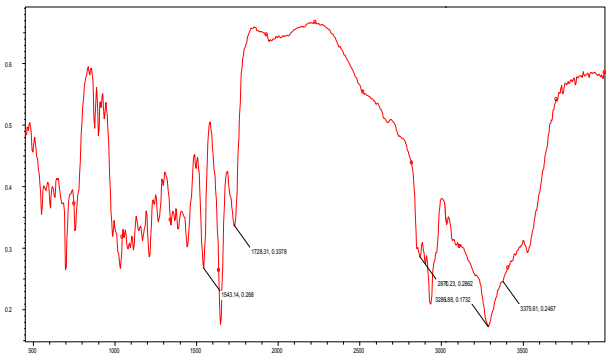

Figure 9: FT-IR spectrum of optimized nateglinide microcrystal formulation with excipients

FT-IR spectra of pure nateglinide, optimized nateglinide microcrystals and optimized microcrystal formulation containing excipients were given in Figure No.7, 8, 9. From the interpretation it is understood that there is no significant changes in the wave numbers of the drug and drug polymer combinations. Hence the drug polymers are compatible with each other.

Drug release kinetics

The results showed that the drug release patterns of all pulsincap formulations (NH1-NH4) have found to be followed the first order kinetics predominantly followed by surface erosion and hixson crowell's cube root model.

4. Conclusion

A time controlled pulsatile drug delivery of nateglinide for treatment of diabetes was successfully developed. As nateglinide is poorly water soluble drug, its solubility was enhanced by *in situ* micronization technique using hydrophilic polymers like PVP K30, guar gum. The prepared microcrystals were characterised for DSC, XRD, SEM and *in vitro* release studies. Batch F5 formulation was selected for the development of pulsincap based on its effective release. The system was found to be satisfactory in terms of release of the drug after a lag time of six hours. The dosage form can be taken at bed time and will release the contents in the early hours of morning when symptoms of disease are more prevalent. The release of drug was sharp and complete after the lag time, which is necessary for any chronomodulated drug delivery system.

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