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FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF NISOLDIPINE

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ABSTRACT

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. Pulsatile drug delivery system for Nisoldipine was formulated initially as core tablets followed by formulation of pulsatile tablets using press-coated technology. Core tablets were formulated using various concentrations of superdisintegrant (Sodium starch glycolate) and diluents (MCC). The core tablets were then compressed into pulsatile tablets using combinations of HPMC K 100M and HPMC K15M, Sodium alginate and ethylcellulose in various concentrations. Core tablets were evaluated and based on the dissolution studies trial F2 was optimized as it shows lower disintegration time and faster drug release. Then the pulsatile tablets were evaluated for various tests and drug release studies were conducted for pH 6.8 buffer. Pulsatile tablets were formulated utilizing press coated technology and the HPMC K100M polymer provided required lag time with satisfactory dissolutionprofile.

KEY WORDS

Nisoldipine, core tablets, natural and synthetic polymers, super disintegrant and in vitro drug release studies.

1.INTRODUCTION

Pulsatile drug delivery system offers various advantages like it provides extended activity, reduced side effects and dosage frequency, reduction in dose size, improved patient compliance, along with the main advantage of releasing the drug in required time in required quantity with satisfactory lag time.[1,2] The pulsatile drug delivery system (PDDS) is intended to deliver a rapid, or transient, and quantified medication release after a predetermined off-release period (lag time).[3] PDDS can deliver the correct amount of medication at the desired location at the optimal time for maximum effect against disease, thereby enhancing therapeutic efficacy and improving patient compliance.[4] PDDS avoids problems with degradation of drugs in the stomach or first-pass metabolism, enables the simultaneous administration of two different drugs, allows the release drugs at different sites within the gastro-intestinal tract, and can deliver a drug release burst at one or more predetermined time intervals, according to patient requirements.[5,6] The advantages of PDDS extend to drugs with chronopharmacological behaviours, where night time dosing is required, and for various diseases that are influenced by circadian rhythms.[7] Since PDDS has a unique mechanism of delivery, whereby a drug releases rapidly after a lag time, various PDDSs have appeared on the markets that replace modified-release dosage forms. The PDDS is formulated to release a drug after a predetermined lag time in a specific region of the gastrointestinal tract, or as a chronotherapeutic time-dependent release.[8] Pulsatile drug release should occur independently of the environment (e.g. pH, enzymatic activity, intestinal motility) or other stimuli, lag time prior to the release of the drug is primarily determined by the formulation's design. [9] PDDS is a type of time-controlled DDS, it may be classified as a single- unit or multiple-unit system by application of different coating

systems. Nisoldipine is a dihydropyridine derivative belongs to calcium channel blocker, primarily used to treat hypertension. Nisoldipine blocks the inward movement of calcium by binding to the L- type calcium channel in the heart and in smooth muscle of the peripheral vasculature, which prevents calcium dependent smooth muscle contraction and subsequent vasoconstriction. It also used to treat heart stroke, angina pectoris and mild diuresis.[10,11]

2. MATERIAL AND METHODS

2.1 MATERIAL

Nisoldipine was gifted by Hetero labs pvt limited, Hyderabad. HPMC K15M, HPMC K100M, Sodium alginate, ethyl cellulose, Magnesium stearate, talc gifted by A.R chemicals, chemicals.

2.2 METHODS[12,13,14]

Preparation method:

Preparation of core tablets by Direct compression method:

Different matrix embedded formulations of Nisoldipine hydrochloride were prepared by direct compression method using varying proportion of polymers either alone or in combination. The ingredients were passed through a 60-mesh sieve. Calculated amount of the drug, Various polymers and filler (MCC) was mixed thoroughly. Magnesium stearate was added as lubricant; the appropriate amount of the mixture was weighed and then compressed using a Ten station rotary press at a constant compression force equipped with a 6-mm flat-faced punches at a compression force required to produce tablets of about 7–8 kg/cm2 hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Formulation of pulsatile tablets:

Formulation of Pulsatile Tablets by Press Coated Technology. The core tablets were compressed using polymer blend which has composition of HPMC K15 M, HPMC K100 M, Ethylcellulose and sodium alginate. Half of the coating polymer material was placed in the die cavity, then the core tablet was carefully sited in the centre of the die and cavity was filled on the top with the other half of the coating polymer material. Then the tablet was compressed using Rimek tablet machine, with 8 mm punch.

Table-1: Formulation of core tablets of Nisoldipine

Ingredients(mg)	F1	F2	F3	F4
Drug	20	20	20	20
Sodium starch glycolate	40	40	40	40
Talc	2	2	2	2
Magnesium Stearate	3	3	3	3
MCC	35	35	35	35
Total wt	100	100	100	100

Table-2: Formulation of coating tablets of Nisoldipine

Ingredients(mg)	F1	F2	F3	F4
HPMC $K_{15}M$	100	-	-	-
HPMC $K_{100}M$	-	100	-	-
Sodium alginate	-	-	100	-
Ethylcellulose	-	-	-	100

EVALUATION STUDIES [15,16,17,18]

i) Pre-compression parameters

a) Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.

It is calculated using the following equation:

Bulk density = weight of sample taken /volume noted

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the cylinder was dropped at 2-second intervals onto a hard-wooden surface three times, from a height of one inch. The volume was recorded and the bulk density was calculated.

b) Tap density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the surface was carefully smoothed and the volume was measured. Tap density was calculated by measuring final volume (V_f) after 50 taps on wooden surface from 6-inch height and was expressed in g/cm^3.

Bulk density = W/V_o

Tapped density = W/V_f

c) Compressibility index

The Compressibility index and Hausner ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be

closer in value. For poorer flowing materials, there are frequently greater inte rparticle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio.

The compressibility index and Hausner ratio may be calculated using measured values for bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) as follows:

$$\text{Compressibility index} = \frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \times 100$$

$$\text{Hausner ratio} = \frac{\rho_{tapped}}{\rho_{bulk}}$$

d) Angle of repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan\theta = h/r$

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

ii) Post compression parameters

Weight variation:

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage.

Thickness

Twenty tablets were randomly selected form each batch and their thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

% F = {1-(Wo/W)} ×100

Content Uniformity

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Nisoldipine. Dissolve the weighed quantity of powder into 100 ml of phosphate buffer solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask and make up the volume with distilled water. Immediately analyze the drug by taking absorbance at 213nm using reagent blank.

Disintegration time

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electro lab USP disintegration test apparatus. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1L beaker containing Buffer solution at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

***In Vitro* Release study**

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The

dissolution medium consisted of 900 ml of Standard buffer pH 6.8 period of time. Temperature maintained at 37±5.The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask and make the volume with buffer. The diluted samples were assayed at 213 nm against reagent blank.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. The prepared tablets of Nisoldipine were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 30 days.

3. RESULTS AND DISCUSSION

Pre-compression parameters

a) **Bulk Density:** The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.398-0.412.

b) **Tapped density:** The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.501-518.

c) **Angle of repose:** The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 29 to30^0

c) **Compressibility index:** Compressibility index was carried out, it found between 10% to 22.55% indicating the powder blend have the required flow property for compression.

Table-3: Evaluation of pre-compression parameters

S. No	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose(0)
N1	0.398	0.501	20.55	1.25	27
N2	0.412	0.518	20.46	1.25	29
N3	0.409	0.510	19.80	1.24	27
N4	0.399	0.501	20.35	1.25	30

Post compression parameters

Weight variation:

All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness (n=3) were uniform in F1 to F4 formulations and were found to be in the range of 2.19 mm to 2.38 mm.

Hardness:

The measured hardness of tablets of each batch ranged between 6.5 to 7 kg/cm^2 . This ensures good handling characteristics of all batches.

Friability:

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:

The percentage of drug content for F1 to F4 was found to be between 93.54 % and 96.51% of Nisoldipine, it complies with official specifications.

Disintegration time:

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electro lab USP disintegration test apparatus. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1L beaker containing Buffer solution at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

Table-4: Evaluation parameters of core tablets of each batch

S. No.	Weight variation (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Drug content (%)	Disintegration time(min)
F1	99	2.25	3.15	0.54	95.90	2.1
F2	100	2.19	3.21	0.55	96.51	2.5
F3	98	2.38	3.30	0.49	94.76	2.4
F4	97	2.35	3.20	0.47	93.54	2.3

Table-5: Evaluation parameters of Press coated pulsatile tablets of Nisoldipine

S. No.	Weight variation (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Drugcontent (%)	Disintegration time(min)
F1	199	3.16	4.29	0.61	95.90	3.5
F2	200	3.20	4.25	0.68	96.51	3.2
F3	197	3.22	4.60	0.63	94.76	3.3
F4	198	3.37	4.41	0.65	93.54	3.6

Dissolution studies:

All the three formulation of prepared matrix tablets of Nisoldipine were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table-6: Dissolution Profile of all formulations

Time (hrs)	% Cumulative drug released			
	F1	**F2**	**F3**	**F4**
0	0	0	0	0
1	19.12	17.85	16.90	18.35
2	31.20	36.46	35.46	33.87
3	42.19	45.98	44.52	43.25
4	54.20	56.86	58.96	55.26
5	65.80	69.48	63.85	61.47
6	74.89	73.92	72.18	71.50
7	81.19	83.16	82.45	79.98
8	90.78	95.55	93.99	93.15

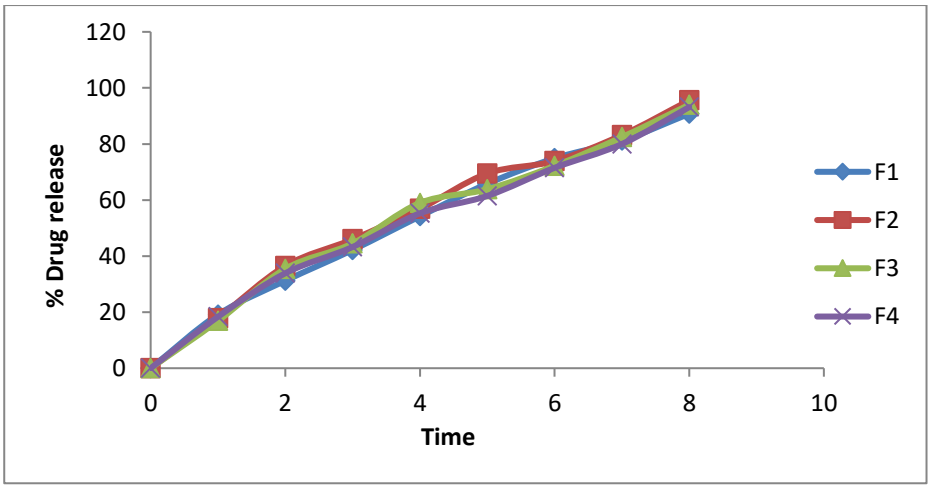

Fig-1: Percentage drug release for all formulations

Lag Time Determination by Rupture Test:

The time taken for the outer coating to rupture is defined as the lag time of the pulsatile tablet. It was determined by using the USP II paddle dissolution apparatus. initially 900 ml of 6.8 phosphate buffer was taken as media and was carried for 12 hrs at 37.0 ± 0.5°C, 50 rpm. The time at which the outer coating layer starts to rupture was noted and considered as the lag time.

Table-7: Evaluation of Lag time

Formulation	Time (min)
F1	192
F2	200
F3	199
F4	203

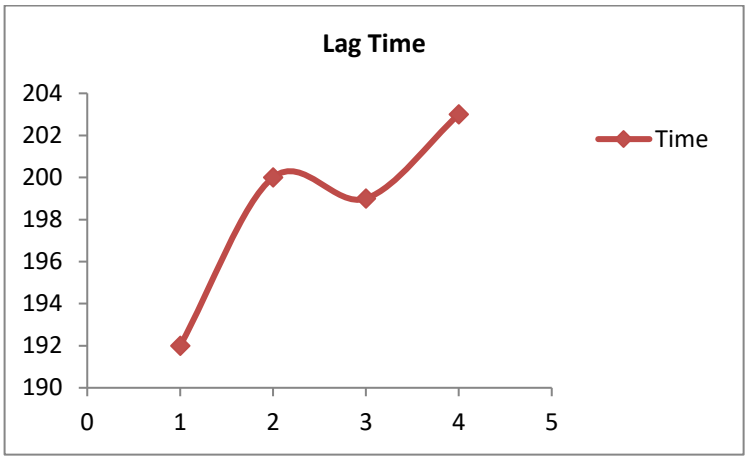

Fig-2: Evaluation of Lag time

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-2 after 30 days.

Table-8: Stability studies for optimized formulation

Formulation Code	Parameters	Initial	1st Month	Limits as per Specifications
F-2	**25^{0}C/60%RH % Release**	**95.55**	**95.50**	**Not less than 85 %**
F-2	**30^{0}C/75% RH % Release**	**95.55**	**95.49**	**Not less than 85 %**
F-2	**40^{0}C/75% RH % Release**	**95.55**	**95.45**	**Not less than 85 %**

4. CONCLUSION

In this study pulsatile tablets were prepared, which consist of two parts, the core tablet and its outer polymeric part. Core tablets of Nisoldipine were formulated by conducting different trials using sodium starch glycolate as super disintegrant along with diluents like microcrystalline cellulose, talc, magnesium stearate were used as glidant. The F2 formulation was optimized which contains sodium starch glycolate as super disintegrant, because as it shows lower disintegration time and good dissolution profile. Core tablets were press coated using various polymers like HPMC K15M, HPMC K100, Sodium alginate and ethylcellulose. The Chrono therapeutic drug delivery system of nisoldipine was prepared which provided desired lag time thus it can be taken at bedtime such that the drug will be released in the morning hours i.e. at the time of symptoms and useful for chronopharmaceutics of hypertention. The results indicated that amount of polymer in the formulation affects the drug release rate. The drug release was high-pitched and full after the lag time, which is mandatory for a pulsatile drug delivery system. Thus, the formulated pulsatile tablets will deliver the drug permitting to the need of the patient so as to give the highest therapeutic benefit of treatment. The

cumulative amount of drug released through different batches. If we observe that the, F2 formulation showed 95.55 % cumulative release within 8 hours.

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