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Research Article

DESIGN AND CHARACTERIZATION OF COMPRESSION COATED CHRONOMODULATED SYSTEM OF NIFEDIPINE

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ABSTRACT
The main objective of the study was to formulate and evaluate compression coated chronomodulated system of Nifedipine for pulsatile release of the drug. The compression coated systems were prepared by direct compression technique using solid dispersion of nifedipine as core materials and viscoelastic polymers like PEG, HPMC K4M, HPMC K15M and HPMC K100M as coating material. The composition of polymers was varied to obtain different formulations of compression coated tablets with suitable lag time. Pre formulation and micromeritic properties were studied which were in compliance with the literatures limits. All the tablets (core and compression coated) were found uniform with respect to hardness (4.3-6.2 kg/cm^2), thickness (3.9-4.44 mm), friability (0.32-0.66 %), weight variation (0.84-1.56 %) and the drug content 90.02 - 94.60 %. Swelling studies revealed that compression coated tablets formulated with HPMC K4M swelled more than that of HPMC K15M and HPMC K100M. The mechanism of the drug release was Higuchi's model release kinetics with r^2 value between 0.983-0.997. A graph devoid of any chemical interaction was observed between pure nifedipine and optimized formulation in FTIR and DSC studies. The present study concluded with the approach that can provide a useful means for programmable release of the drug with required lag time by employing different grades of HPMC polymers and direct compression technique.
Keyword: Nifedipine, HPMC, direct compression, Lag time, pulsatile release

INTRODUCTION

Chrono therapeutics refers to a treatment method in which the *in vivo* drug availability is timed to match circardian rhythms of disease in order to optimize therapeutic outcomes and minimize side effects[1]. A number of common diseases are affected by chrono biology. Such diseases include angina, rheumatoid arthritis, allergic rhinitis, hypertension and cancer[2]. The main goal of drug delivery research in chrono therapy is to develop formulations that fulfill the therapeutic needs related to particular pathological condition. In most of ambulatory individuals possessing hypertension, B.P rises early in the morning. The morning B.P surge was reported be associated with high risk of cardiac death, ischaemic and haemmoraghic stroke. These conditions demand a release of drug at B.P surge after a lag time. The short biological half-life and high frequency of administration of the conventional antihypertensive drugs initiated a need to develop a quaque in die time controlled formulations[3]. Various technologies such as time-controlled, pulsed, triggered and programmed drug delivery devices have been developed and extensively studied in recent years for chronopharmaceutical drug delivery[4]. Several time- release technologies have been described. These include use of a rupturable coating that surrounds multiple pellets loaded with the drug[5]; a compression-coated soluble barrier that erodes, surrounding a single unit-core tablet containing the drug[6,7] and a swellable hydrogel plug which dislodges when swollen, set into a water-insoluble capsule body filled with the drug[8]; of these formulations, compression-coated tablets are among the simplest to manufacture[9]. The gellable compression coated system deliver drug after sufficient swelling which accounts for its on lag period. The objective of present study on nifedipine, a dihydropyridine L-type calcium channel channel blocker, is to formulate a pulsatile release tablet by employing different grades of HPMC polymer by direct compression technique effective for the management of hypertension.

MATERIALS AND METHOD

Nifedipine (Gift sample, Cipla Pvt. Ltd, Kurkumbh, Daund); HPMC (K4M, K15M, K100M) (Gift sample, Yasham Bio-Science Pvt. Ltd, Mumbai, India), PEG (S.D. Fine Chemicals Pvt. Ltd, Mumbai, India), Microcrystalline cellulose (S.D. Fine Chemicals Pvt. Ltd, Mumbai, India) Indion 414 (N.R. Chem. Pvt. Ltd, Mumbai, India), Magnesium stearate (S.D. Fine Chemicals Pvt. Ltd, Mumbai, India) Talc (S.D. Fine Chemicals Pvt. Ltd, Mumbai, India). All other chemicals and reagents used were of "analytical reagents" (AR) grade.

Preparation of core tablet

Core tablet were prepared by using solid dispersion of Nifedipine; solid dispersion of Nifedipine were prepared due to its low solubility and light sensitive nature. Solid dispersion containing Nifedipine: mannitol (1:2) ratio was prepared by hot melt method. The obtained physical mixture was heated at 175^{0}C until they melted. Solidification was done by cooling to room temperature under ambient conditions. Afterwards, the mixture was pulverised, sieved and the fraction ≤160 µm was selected. The selected powder mixture, microcrystalline cellulose (MCC, Avicel PH-102) and Indion 414 ingredients were dry blended for 20 minutes, followed by addition of magnesium stearate as lubricant. The mixtures were then further blended for 10 minutes. 100 mg of resultant powder blend was directly compressed on 10 station rotary tablet machine (RIMEK Mini Tablet Compression) using 7 mm flat punch to obtain the core tablets. The composition of core tablets is given in Table 1.[10,11]

Preparation of coat layer

The coat layer consists of PEG 6000, different grades of HPMC (K4M, K15M, and K100M) in different ratio as shown in Table 1. HPMC powders of different grade, PEG 6000, were passed through a sieve #80 and then thoroughly mixed in a bottle using tumbling method for a period of 10

minutes, 150 mg of resulting mixture of powder was used for the outer coat.

Preparation of compression-coated tablets

The coat layer (powder mixture) of 150 mg for different formulations was divided into two fractions, each 75 mg to act as upper and lower coat. The compression coating of tablets was performed using a rotary tablet machine. A half amount of the powder (lower coat) was filled into the die to make a powder bed, in the center of which core tablet was placed manually. Then, the remaining half of the coating material filled in the die (upper coat), and the contents were compressed under a sufficient compression force, using a flat punch 8 mm in diameter. The composition of coat layer is given in Table 1.

Characterization

Pre formulation and pre compression studies

Flow ability of pure drug, solid dispersion and pre compression mixture of core tablet was performed by measuring the angle of repose by funnel method. The loose bulk density (LBD) and tapped density (TBD) of pure drug Nifedipine, solid dispersion and pre compression mixture were determined using bulk density apparatus (Electro lab, India) from 3 independent analyses. Carr's index and Hausner's ratio were calculated using LBD and TBD value.

Post compression studies of core and compression-coated tablets

Hardness

Monsanto hardness tester was used for the determination of the hardness. The tablet to be tested was held between a fixed and a moving jaw and reading of the indicator adjusted to zero. The force applied to the edge of the tablet was gradually increased by moving the screwknob forward until the tablet breaks. The reading was noted from the scale which indicates the compressionure required in kg or lb to break tablets[12].

Uniformity of thickness

The crown-to-crown thicknesses of 10 tablets from each batch were determined using vernier calipers. The thickness variation limits allowed was ± 5 % of the size of the tablet.

Friability

Friability of the tablets was determined using Roche friabilator (Electro lab, Mumbai, India). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) was calculated using formula:

$$F = (1- W_0 / W) \times 100$$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test[13]

Weight variation

Ten tablets were randomly selected from each batch and weighed individually. The average weight and standard deviation was calculated[14].

Uniformity of drug content

For determination of drug content five tablets from each formulation were weighed individually, crushed and diluted to 100 ml with sufficient amount of phosphate buffer of pH 7.2. Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 341 nm against blank[15].

Dissolution studies

The dissolution study of core and coated tablet was carried out in acid buffer pH 1.2 and pH 7.2 phosphate buffer in presence of 2 % SLS, as dissolution enhancer. In both cases 8 station USP dissolution apparatus (Electro Lab, TDT-O8L, Mumbai, India) was used. The dissolution studies of compression coated tablets was carried out in acid buffer of pH 1.2 with 2 % sodium lauryl sulphate for 2 h and in phosphate buffer of pH 7.2 with 2 % sodium lauryl sulphate for next 10 h at 37 ± 0.5^0 C at 75 rpm. At regular time interval, 5 ml of sample was withdrawn from the dissolution medium and replaced with equal volume of fresh medium. After filtration and appropriate dilution, the samples were analyzed at 341 nm for nifedipine against blank using UV-Visible spectrophotometer. The amount of drug present in the samples was calculated using standard curve. During the dissolution study the whole apparatus was shielded from light to prevent degradation of nifedipine.

FT-IR Study

The compatibility between drug and polymer was detected by IR spectra obtained on (Shimadzu 8400, Japan). The pellets were prepared on KBr-compression. The spectra were recorded over the wave number range of 4000 to 500 cm^{-1}.

DSC Study

Characterization of formulation is essential for establishing stability of the formulation. Several techniques are used for characterization of formulation in addition to IR spectroscopy. DSC thermo gram study is another technique employed for establishing characterization of the formulation. In present study DSC thermo grams for pure drug and its optimized formulation are taken. Thermo gram were obtained by using a differential scanning calorimeter (DSC Q20 V24.4 Build 116, Japan) at a heating rate of 10^0C/min over a temperature range of 35-300^0C. The sample was hermetically sealed in an aluminum crucible. Nitrogen gas was purged at the rate of 10 ml/min for maintaining inert atmosphere.

Stability studies

The stability study of the selected formulations was carried out at 40 ± 2^oC/75 ± 5 % RH for one month by storing the samples in stability chamber (Lab-care, Mumbai)[16].

RESULTS AND DISCUSSION

Pre formulation studies

Pure Nifedipine exhibited angle of repose (52.16 ± 0.28^0) indicating extremely poor flow property. It was further supported by high Carr's index value (23.54 ± 0.25 %) and Hausner's ratio (1.42 ± 0.02). In case of Nifedipine solid dispersion, angle of repose (38.98 ± 0.84^0) indicated the need of glidant to improve the flow property. It was further ascertained by Carr's index value (21.32 ± 0.15 %) and Hausner's ratio (1.07 ± 0.01). Hence lubricant and glidant were added to improve the flow properties of the solid dispersion. As a result of addition of glidants the angle of repose of core tablet powder was 30.15 ± 0.12^0, Carr's index 16.29 ± 0.12 % and Hausner's ratio of 1.14 ± 0.03 indicating good flow properties to obtain a compact mass. The results are shown in Table 2.

Table 1: Composition of Compression-Coated Nifedipine Tablets

Formulation code	Core Part (100 mg)				Coat Layer (150 mg)			
	Nifedipine solid dispersion (mg)	Mcc (mg)	Indion 414 (mg)	Mg. stearate (mg)	PEG 6000 (mg)	HPMC K4M (mg)	HPMC K15M (mg)	HPMC K100M (mg)
F-1	88	10	1	1	135	15	-	-
F-2	88	10	1	1	120	30	-	-
F-3	88	10	1	1	105	45	-	-
F-4	88	10	1	1	90	60	-	-
F-5	88	10	1	1	135	-	15	-
F-6	88	10	1	1	120	-	30	-
F-7	88	10	1	1	105	-	45	-
F-8	88	10	1	1	90	-	60	-
F-9	88	10	1	1	135	-	-	15
F-10	88	10	1	1	120	-	-	30
F-11	88	10	1	1	105	-	-	45
F-12	88	10	1	1	90	-	-	60

Table 2: Pre formulation Studies

	Angle of repose* (θ)	Carr's Index* (%)	Hausner's ratio*(%)
Nifedipine	52.16 ± 0.28	23.54 ± 0.25	1.42 ± 0.02
Nifedipine solid dispersion	38.98 ± 0.84	21.32 ± 0.15	1.07 ± 0.01
Core tablet	30.15 ± 0.12	16.29 ± 0.12	1.14 ± 0.03

*Average of 3 determinations

Table 3: Post compression Characterization of Core and Compression-Coated Tablets

Code	Hardness^{+} (kg/cm^2)	Thickness† (mm)	Friability† (%)	Weight variation* (%)	Drug content** (%)
Core tablet	2.5 ± 0.33	1.15 ± 0.02	0.87 ± 0.12	0.89 ± .15	95.65 ± 0.13
F1	4.5 ± 0.33	4.07 ± 0.02	0.46 ± 0.01	1.08 ± 0.34	92.75 ± 0.33
F2	4.4 ± 0.25	3.93 ± 0.03	0.50 ± 0.02	1.07 ± 0.19	91.09 ± 0.65
F3	4.5 ± 0.64	4.19 ± 0.02	0.45 ± 0.01	1.05 ± 0.37	90.82 ± 0.42
F4	4.7 ± 0.30	4.08 ± 0.01	0.55 ± 0.03	1.37 ± 0.48	93.17 ± 0.21
F5	4.7 ± 0.40	4.08 ± 0.03	0.47 ± 0.04	1.56 ± 0.75	91.02 ± 0.49
F6	4.7 ± 0.46	4.25 ± 0.07	0.48 ± 0.02	0.94 ± 0.35	92.50 ± 0.67
F7	4.5 ± 0.24	3.92 ± 0.04	0.32 ± 0.03	0.94 ± 0.29	90.08 ± 0.52
F8	4.5 ± 0.33	4.03 ± 0.01	0.58 ± 0.01	0.87 ± 0.34	94.6 ± 0.33
F9	4.6 ± 0.30	3.92 ± 0.04	0.60 ± 0.03	1.10 ± 0.48	92.55 ± 0.21
F10	4.9 ± 0.28	4.03 ± 0.02	0.43 ± 0.06	1.28 ± 0.65	94.23 ± 0.16
F11	4.3 ± 0.35	4.07 ± 0.03	0.41 ± 0.01	0.84 ± 0.16	92.93 ± 0.38
F12	4.6 ± 0.40	4.34 ± 0.03	0.46 ± 0.04	1.15 ± 0.75	91.17 ± 0.49

All values are expressed as mean SD± $^{+}$n = 6, †n = 10, *n = 20, **n = 3

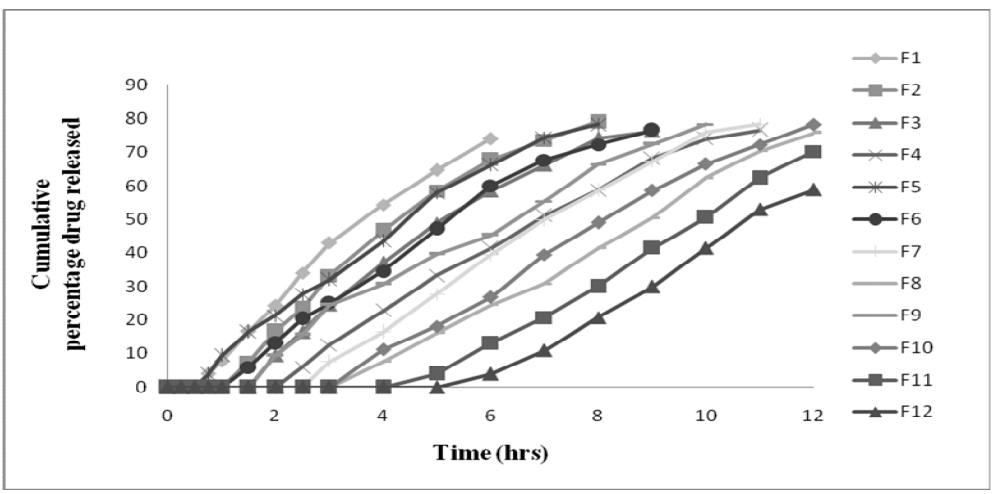

Figure 1: Dissolution studies of compression coated nifedipine tablets

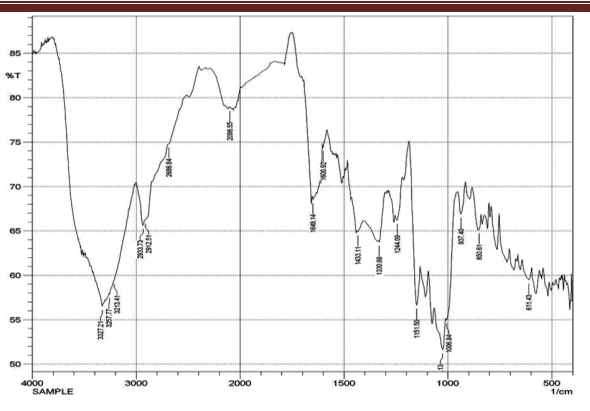

Figure 2: FTIR spectra of pure drug nifedipine

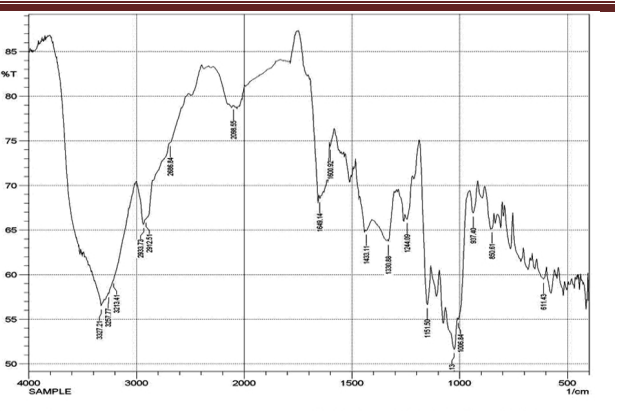

Figure 3: FTIR spectra of compression-coated optimized tablet of nifedipine (F10)

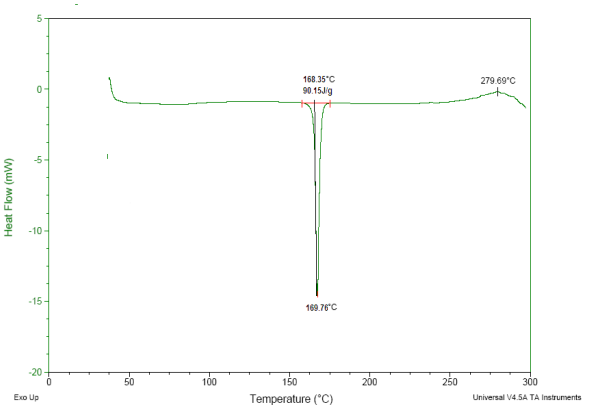

Figure 4: DSC Thermo gram of nifedipine pure drug

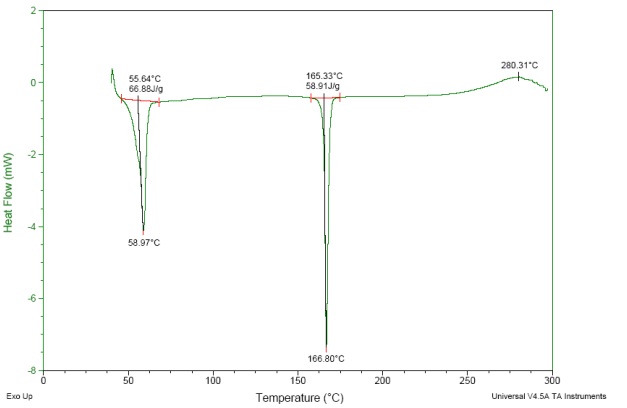

Figure 5: DSC thermo gram of compression-coated optimized tablet of nifedipine (F10)

Post Compression studies

In order to avoid the effect of tablet hardness and thickness on *in vitro* drug release, these two parameters have been maintained at specific values i.e. hardness at about 2-3 kg/cm^2 and thickness at about 1.15 ± 0.02 mm for core tablet to maintain its physical strength while placing core tablet manually on centre of lower bed. The compression-coated tablets of different batches of HPMC were found uniform with respect to hardness (4.3 to 6.2 kg/cm^2) and thickness (3.90 to 4.44 mm). The hardness of the tablets with different polymer was adjusted accordingly. The friability (0.32 to 0.66 %) and weight variation (0.84 to 1.56 %) of different batch of tablets were found within prescribed limits. Drug content for core tablet was found to be 95.65 % and it ranged from 90.02 to 94.6 % for coated tablets. Some loss in drug content of compression-coated tablets than in core tablet is due to very light sensitive nature of drug molecule. Hence compression coated tablets of nifedipine could be prepared satisfactorily by direct compression method. The results of Post compression studies are given in Table 3.

Dissolution studies

The dissolution studies of the prepared compression coated tablets of nifedipine were performed. The % drug released was in range of 58 % (F12) to 79.046 % (F2) and lag time range from 30 minutes (F1, F5) to 5 h (F12). The compression coated tablets containing HPMC K4M grade provided a lag time of 0.5 h (F1) to 2 h (F4) with polymer concentration varying from 15 mg to 60 mg. The % drug release was in range 74.094 % to 79.046 % (F1-F4). The compression coated tablets with HPMC K15M grade provided a lag time of 0.5 h to 3 h with polymer concentration varying from 15 mg to 60 mg. The % drug release was from 75.901 % (F8) to 78.344 % (F5) in 12 h. Similarly for HPMC grade K100M the lag time obtained was 1.5 h (F13) to 5 h (F12) with polymer concentration varying from 15 mg to 60 mg. The % drug release was 58.86 % (F12) to 78.38 % (F9). During dissolution study, gel formation on core tablet by barrier layer was observed macroscopically in all formulations which controlled the release of drugs through coat layer. The highest retardation effect was observed with F12 containing 60 mg of HPMC K100M. The release rate was decreased with decrease in PEG 6000 concentration. Among above formulation F5 and F6 containing HPMC K15 released maximum drug in short period i.e. 78.34 % in 8 h and 76.63 % in 9 h respectively. The formulation F10 is considered the optimized one with 3 h lag time and 78.288 % release. The results are shown in Figure 1.

FT-IR Study

The FTIR study of pure drug nifedipine and optimized formulation F10, revealed the characteristic peaks in IR region as shown in Figure 2 and 3. The characteristic peaks indicated that the IR spectra of pure drug nifedipine and formulation have got lot of similarity. Further it is also clear from the spectra that the change in position of characteristic

bands of the drug molecule is negligible and is within limit of the absorption range. Hence it may be viewed that no appreciable change has taken place in characteristics of the pure drug in its formulation. It may be concluded from IR spectrum study that there is no interaction of the drug with polymer and other excipients.

DSC Study

The DSC thermo gram of pure drug showed an endothermic peak at 168°C that corresponds to melting point of drug. The literature survey of drug profile indicates that the drug has melting range between 168 to 174^{0}C. The DSC thermo gram of formulation F10 has endothermic peak at 167.29^{0}C which is almost equal to thermo gram peak of pure drug. Thus it indicates that drug does not interact with polymer and other excipients. The results are given in Figure 4 and 5.

Stability studies

Stability studies were carried out for selected formulation F10 at 40 ± 2°C/75 ± % 5 RH for a period of one month. At the end of one month the drug content was found to be 93.86 ± 0.46 % and *in-vitro* dissolution study showed 75.85 % drug release. The nifedipine compression coated tablets were found to be stable with respect to drug content, friability, hardness, weight variation and release profile during the stability study period.

CONCLUSION

Thus, for the chrono therapeutic management of hypertension, compression coated time release tablets of Nifedipine were obtained using direct compression technique. Solid dispersion of Nifedipine using mannitol (1:2) improved the solubility of Nifedipine. HPMC different grades and PEG 6000 mixture provide sufficient lag time for time release of Nifedipine. Pre formulation studies on Nifedipine pure drug fairly corroborate with the reported literature limits. FT-IR and DSC studies of selected formulation revealed the absence of chemical interaction between drug and polymers used. Hardness, friability, weight variation, drug content, swelling index and *in-vitro* release were uniform and reproducible. Lag time was found to be influenced by type of polymer, grade of polymer and amount of polymer. Appropriate lag time of 3 to 4 h was obtained from different grades of HPMC varying their concentration. The drug released slowly from the swollen polymer by diffusion after specified lag time. The release was inversely proportional to the polymer concentration. F10 was chosen best formulation among selected formulation. HPMC polymer with different grades is suitable for use to achieve a lag time of 30 minutes to 5 h. Amounts and viscosity grade of the polymer are particularly important to achieve the main aim of the studies. Hence, compression-coated tablets of Nifedipine prepared with hydrophilic polymers showed promising results to be chosen for chrono therapeutic treatment of hypertension and there exist a prominent scope for *in-vivo* evaluation using suitable animal models.

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