ORIGINAL ARTICLE

Development of Nifedipine Timed-release Spansule Dosage form by Extrusion-Spheronization Technology

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Abstract

Aims: Sustained-release formulations have been widely developed to improve the therapeutic performance of drugs, in particular, to increase pharmacological efficacy and reduce side effects. Developing spansule dosage form of nifedipine using extrusion and spheronization technique provides efficient control of delivery of drugs over the period of 8 h. Nifedipine pellets coated with hydrophilic hydroxypropyl methylcellulose polymer, hydrophobic polymer (ethyl cellulose), and semipermeable polymer (cellulose acetate) to sufficient weight gain. Desired rate of release achieved by of blend of polymers after optimization of variable. **Settings and Design:** A rotatable central composite design used with five levels and three polymers for 15 formulations. Based on rate of drug release, formulation optimized backward two-factor interaction and polynomial regression equation. **Materials and Methods:** Initially nifedipine pellets prepared by extruder and spheronizer and later coated up to desired weight gain by conventional coating pan utilizing various polymers. After coating, pilot blend was prepared with all three polymers. *In vitro* dissolution carried out to find out release rate and percent of dissolution at t95% as dependent variable. Then, optimized formulation compared with market preparation and *in vivo* animal study done using mice. **Results:** *In vitro* dissolution rate of drug indicated the drug release depends on thickness of coat. However, formulation shown considerable release even with higher level of coat thickness with ethyl cellulose because of other two polymers present in the blend dominates the release pattern. The ratio of mixing of pilot blends also a critical factor in developing spansule dosage form. Desired release pattern achieved after equal ratio of mixing polymer pilot blend and optimization of polymer level. **Conclusion:** The prototype of this formulation design can use for developing spansule dosage form of any drug.

Key words: Central composite design, nifedipine, optimization, spansules, timed-release pellets

INTRODUCTION

Drug delivery in conventional dosage forms often suffers from the drawbacks of repeated drug administration and large fluctuations in drug blood levels.[1] Sustained-release formulations have been widely developed to improve the therapeutic performance of drugs, in particular, to increase pharmacological efficacy and reduce side effects.[2] Most of all polymeric coating techniques have been widely applied in pharmaceutical industry for many reasons such as taste masking, protective barrier, stability improvement, and mostly controlled release of drugs for the preparation of various dosage forms.[3]

Pellet dosage forms and their formulation design have shown many advantages and flexibility in enhancing therapeutic safety and potency. As a result, on many occasions, formulators prefer to select pellet dosage forms as the main choice during dosage form development.[4]

Nifedipine, a systemic calcium channel blocker, is a practically water insoluble and light-sensitive drug used in angina pectoris and hypertension. As its biological half-life is about 2 h and is eliminated rapidly, repeated daily administrations

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are needed to maintain effective plasma levels.[5] Various controlled release formulations prepared and evaluated using nifedipine by Kumaravelrajan *et al.*, study.[6-8] Time-dependent variability of nifedipine reported by Grundy *et al.*[9]

Therefore, the aims of this work were: (1) To develop timed-release capsules to deliver poorly water soluble drug such as nifedipine and (2) to evaluate the influence of coated formulation (independent) variables including amount of hydroxypropyl methylcellulose (HPMC), added amount of ethyl cellulose, and added amount of cellulose acetate on the release characteristics (dependent variable). The surface morphologies using scanning electron microscope (SEM) also studied. A rotatable central composite design was proposed[10,11] to the formulation with five levels of coating thickness by three polymers to make 15 formulations. The effect of polymer blends on the release rate to be investigated.

MATERIALS AND METHODS

Nifedipine purchased from BMR Pharma and Chemicals suppliers(Hyderabad), Hydroxypropyl Methyl cellulose obtained from (E-15) Chemspure (Chennai), Eudragit RS-100 Loba chemie Pvt Ltd (Mumbai), microcrystalline cellulose S.D fine chemicals Ltd (Mumbai), cellulose acetate (CA 398-10NF) Eastman Chemicals company, kings port USA, and ethyl cellulose N-50 Chemspure (Chennai). All other chemicals used in the research work were purchased from a local supplier.

Methods

Differential scanning calorimetry (DSC)

Assessment of possible incompatibilities between an active pharmaceutical ingredient and different excipients forms an important part of the pre-formulation stage during the development of a solid dosage form. DSC allows the fast evaluation of possible incompatibilities because it shows changes in the appearance, shift, or disappearance of melting endotherms and exotherms and variations in the corresponding enthalpies of reaction.[12] The DSC thermograms of pure drug and drug with polymer were recorded. The samples were separately sealed in aluminum cells and set in NETZSCH DSC. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 50-300°C.

Formulation of nifedipine pellets

Weighed quantity of drug and excipients were mixed properly to get homogeneous powder dispersion. Wet massing was done with invasive pulmonary aspergillosis to produce a sufficient plastic mass. Then, the wet mass was placed into the extruder, where it was continuously formed into a cylindrical rod of uniform shape. After the extrudate was prepared, they were partially dried and were spheronized in a load of 100 g using a speed of 900 rpm in a spheroniser. The friction plate was broken the rod-shaped particles into smaller particles and rounded them as spheres. The pellets were dried on trays as a monolayer at room temperature.[13] The detailed formula is given in Table 1.

Design of experiment

A rotatable central composite design was employed to produce sustained-release pellets of nifedipine. The design consisted of four full factorial points (F1-F5), four axial points (A1-A5), and five center points (C1-C5).[14] The polymer levels in the coating of pellets, (cellulose acetate X1, HPMC X2, and EC X3) were the three independent variables analyzed. The dependent variables investigated were the drug release. The selected factor combinations indicating the actual and coded levels as per the design are represented in Table 2.

Coating procedure

Before coating, the pellets were preheated to 30-32°C, and at the end of the coating process, a drying procedure was applied for 5 min. Around 40 g pellet batches representing the axial points and the central point were coated. The film coating was performed in conventional coating pan (Cemach machineries, Ahmedabad, India). The pellets were coated with a 2% dispersion of HPMC (HPMC E-15 Chemspure, Chennai), 2% of ethyl cellulose (S.D fine chemicals, Chennai), and 2% of cellulose acetate (Eastman Chemicals Company, Kings Port USA) separately, to the desired weight gain. A total of 3.5% of triethyl citrate (S.D fine chemicals, Chennai) was used as a plasticizer. To ensure dissolution of triethyl citrate, the dispersion was blended by a magnetic blender for 30 min. 3% magnesium stearate (S.D fine chemicals, Chennai) was used as an antiadhesive agent. The HPMC solution was kept on an ice bath during the film coating to prevent nozzle blockage. The granules were heated to 40°C before the coating was started. The pneumatic spraying pressure used

Table 1: List of ingredients used in formulation of nifedipine pellets

Ingredients	Percentage
Nifedipine	14.64
Microcrystalline cellulose	64.36
Lactose	15.241
Eudragit RS 100	1.478
Starch	4.031
Magnesium stearate	0.25
IPA	Qs

IPA: Invasive pulmonary aspergillosis

was 5 g/min, and the inlet temperature 47°C. The coating solution was added at a rate of 5 g/min, and the coating was continued until a 4% (maximum) theoretical weight increase was achieved. The granules were dried for 5 min at 40°C in the coating chamber.

The experimental matrix and pilot blend ratio for developed formulations are presented in Tables 3 and 4.

Dissolution study

The release characteristics of coated nifedipine pellet were evaluated using United States Pharmacopeia dissolution Apparatus II (paddle method) was used for Nifedipine TRC (Timed-release capsules) release studies. A sample equivalent to 30 mg of nifedipine was added into a 900 mL of simulated gastric fluid (pH 1.2, 0.1M NaCl-HCl buffer) for 2 h followed by switching to intestinal fluid (pH 6.8, 0.2M phosphate buffer) for 8 h at 37±0.5°C. A sinker was used to prevent the flotation of the pellet (0.5% sodium dodecyl sulfate [SDS]). Periodically, a 5 ml solution withdrawn from the dissolution medium was filtered with a 0.45 mm cellulose acetate filter disk and measured by a ultraviolet (UV)-visual spectrophotometer at 236 nm. A 5 ml blank dissolution medium, 0.5% SDS solution, was replaced back into the dissolution medium after each sampling to maintain a sink condition. The dissolution test was done with 2-3 replicates. Sufficient precautionary measures were taken to prevent the photolytic degradation of nifedipine.[15]

SEM study

The external and surface morphology of nifedipine pellets was analyzed by SEM.[16] The pellets were fixed on supports with carbon-glue and coated with gold-palladium under an argon atmosphere using a gold sputter module in a high vacuum evaporator. Samples were then observed with a FEI, Quanta 200 SEM (FEI, Quanta 200 SEM, USA) at 20 kV.

In vivo studies

A comparative bioavailability studies on optimized formulation were carried out in Wistar rat weighing 150-250 g. The permission was obtained from the committee for the purpose of control and supervision of experiments on animal/Institutional Animal Ethical Committee (IAEC) proposal No IAEC/XLIX/07/CLBMCP/2016. The drug was

Table 2: Coded and actual values of variable

Independent variables	Symbol	Levels				
		(−1.41)*	(−1)*	(0)*	(+1)*	(1.41)*
Cellulose acetate	X1	0.41	1	2	3	3.41
HPMC	X2	1.69	2	3	4	4.41
Ethyl cellulose	X3	0.84	1	1.5	2	2.2

HPMC: Hydroxypropyl methylcellulose. *→% Weight gain of coating solution on pellets

Table 3: Matrix of the central composite design

Experimental code	X1	X2	X3	Experimental code	X1	X2	X3
F1	1	−1	1	F1	3	2	2
F2	0	0	1.41421	F2	2	3	2.2
F3	0	0	0	F3	2	3	1.5
F4	0	1.41421	0	F4	2	4.41	1.5
F5	0	0	0	F5	2	3	1.5
F6	−1	1	1	F6	1	4	2
F7	0	0	0	F7	2	3	1.5
F8	−1.41421	0	0	F8	0.41	3	1.5
F9	0	0	0	F9	2	3	1.5
F10	0	0	−1.41421	F10	2	3	0.84
F11	0	−1.41421	0	F11	2	1.69	1.5
F12	−1	−1	−1	F12	1	2	1
F13	0	0	0	F13	2	3	1.5
F14	1.41421	0	0	F14	3.41	3	1.5
F15	1	1	−1	F15	3	4	1

Table 4: Experimental design matrix for blending of coated pellets (percentage of nifedipine TR pellets mixed to produce 30 mg equivalent drug)

Experimental Code	X1 (%)	X2 (%)	X3 (%)
F1	25	25	50
F2	25	25	50
F3	25	25	50
F4	25	25	50
F5	25	50	25
F6	25	50	25
F7	25	50	25
F8	25	50	25
F9	50	25	25
F10	50	25	25
F11	50	25	25
F12	50	25	25
F13	33.3	33.3	33.3
F14	33.3	33.3	33.3
F15	33.3	33.3	33.3

administered at a dose of 4.1 mg/kg of animal weight. There were six animals per group. Blood samples were withdrawn at 0, 1, 2, 3, 4, 5, 6, 7, and 8 h after oral administration of each dosage form. Blood samples were centrifuged at 1500 rpm for 10 min at 4°C; plasma samples were analyzed immediately by high-performance liquid chromatography (HPLC). The plasma concentration of nifedipine was determined by a HPLC method. Plasma samples (100 ml), 4 ml of a dichloromethane: n-hexane mixture (3: 7, v/v), and 1 ml of distilled water were mixed in a light-proof test tube. The mixture was shaken for 10 min with a rotary agitator and centrifuged for 5 min at 1500 g. 3 ml of the supernatant (the organic layer) were transferred to a light-proof reaction vial (Pierce Reacti-Vial, Pierce, Rockford, IL, U.S.A.). The organic phase was evaporated under nitrogen in a dry block sample incubation system (Reacti-Therm III, Rockford, IL, U.S.A.) at 408°C for 15 min. The residue was dissolved in 200 ml of the mobile phase containing n-butyl p-aminobenzoate (butamben) as internal standard (500 mg ml). 100 µl of the solution were injected into the HPLC system. The chromatographic system was equipped with a pump (Spectra-physics, SP 8700, California, U.S.A.), an autosampler (Specta-physics, AS 1000), a UV detector (Spectra-physics, UV 100), and an integrator (Spectra-physics, SP 4270). A reverse phase column (Zorbax ODS, 4 ± 6 mm, 25 cm 64.6 mm i.d.; Dupont de Nemours, Wilmington, DE, U.S.A.) was used. The column was warmed to 558 C. The mobile phase consisted of 0.01 M disodium hydrogen phosphate buffer (pH 6.1)-methanol (50:50). The flow rate was 1.0 ml min, and the detection wavelength of nifedipine was 236 nm.

RESULTS AND DISCUSSION

Formulation development

Drug delivery by spansule dosage form always time bound and ability of formulation to reach desired release profile within the time is one of the methods of optimization. Therefore, internal specification calculated based on release rate and kept as follows, 1 h - 0 to 20%, 2 h-10 to 40%, 4 h - 40 to 60%, 6 h- not more than 85%, and 8 h- not <95%. The 8 h drug release used one of the dependant variables in design. Preparation of pellets started from the selection of suitable base to prepare pellet. The purified sugar was extruded and spheronized. Due to its rough surface and getting into powder when dried so, this method fails. The lactose, MCC, and dicalcium phosphate (DCP) were selected, and individually pellets were prepared and evaluated. MCC and DCP showed some good properties for good pellets. Then, the pellets were taken and then subjected to coating of API by powder layering technology, but this was unsuccessful method. Hence, the direct incorporation of API with the excipients was planned and the drug and excipients mixed together made into wet mass and extruded then it was spheronized. This was achieved after a many trial batch.

DSC

DSC thermograms of nifedipine with excipient depicted in Figure 1 showed no change in the endotherms when compared with the thermogram of pure nifedipine. This was confirmed by observing the sharp melting point of nifedipine (174.7°C, 175.4°C). From the DSC thermogram, it was clear that there was no specific interaction between the drug and polymer used in the formulation.

Micrometrics

The angle of repose for the formulation was determined and was found to be within the limit. The formulations (F2) had excellent flow, and other formulation showed good flow. The bulk density of the formulations was found to be in the limit of 0.4-0.6, hence, it was within the limit. The tapped density of the formulations was found to be within the limit. The Carr's index and Hausner's ratio were found to be within the limit.

Effects of cellulose acetate on drug release from nifedipine TRC formulations

The first blend was prepared with higher percentage of cellulose acetate (F1 50%, 0.41% thickness) and equal percentage of (25%) HPMC and cellulose acetate gave release of maximum 76.86% at the end of the 8 h. However, initial drug release was satisfactory. In the formulation F2 (1%

thickness), the release of nifedipine was 38.77% and 68.31% observed as the higher level and percentage of mixing of ethyl cellulose retarded the release pattern. It was noticed in the formulation F3 (3% coating thickness) also the same pattern of drug release with maximum release was 89.03%, but at the initial, it was 29.21%, the reason could be due to decreased ethyl cellulose. Similarly, the release for F4 (3% thickness of coat) attained 90% and 25% at 8 h and 1 h due to higher level of HPMC 0. 93% and 15.69 % of drug release obtained in the case of F5 (3.41%) because of HPMC in the formulation. Effect of various coating thickness with respect to release rate shown in Figure 2 linear for F5.

Effect of HPMC on nifedipine release from TRC formulations

Further, the release was moderate with F6 (1.69%) gave profile of 24% and 92.14% as level of HPMC slightly more according to the design. When the middle level of all three polymers used in the formulation F7 (0 level with 2%), but higher concentration of HPMC gave better release profile of 95.66% at the end of 8 h. As expected, the release profile declined to 86.76% in the case of F8 (3% coating thickness) on increased HPMC at middle level because of 50% contribution of lower level cellulose acetate in the formulation. Higher initial drug release was achieved with F9 (4%) (32.76%) by further increased ratio of cellulose acetate. The formulation F10 (4.41%) found to be stable but maximum 90% only at the desired time of 8 h. As shown in the Figure 3, linearity in the curve was not obtained in the above case. This was reported [17] that when higher concentration polymer used, there was the formation of gel at the surface which prevent the drug release. According to the author conclusion, the drug release is inversely proportional to the viscosity of polymer.

Effect of ethyl cellulose on nifedipine release from TRC formulations

Further, in the dissolution, F11 observed to be the satisfactory profile with maximum of 95% of drug release as middle level of cellulose acetate could lead a path of dissolution of pellet. However, effective results obtained with F12 due to lowest level of ethyl cellulose-coated pellets in the blend (27.69% and 94.61%). The release pattern was satisfactory by 30% and 98.46% because of equal percentage and level of all polymer blends for F13. When the high level of cellulose acetate and middle level of HPMC and ethyl cellulose pellets were mixed, resulted 41.53% and 97.84% for formulation F14. Finally, in formulation, F15 gave the best release characteristic of 36% and 97.84% (Figure 4) because of slightly higher level of cellulose acetate and middle level of HPMC and ethyl cellulose. Earlier report indicated[18] that 5% of ethyl cellulose in the middle layer controlled release of nifedipine in pellet dosage form. However, the author used

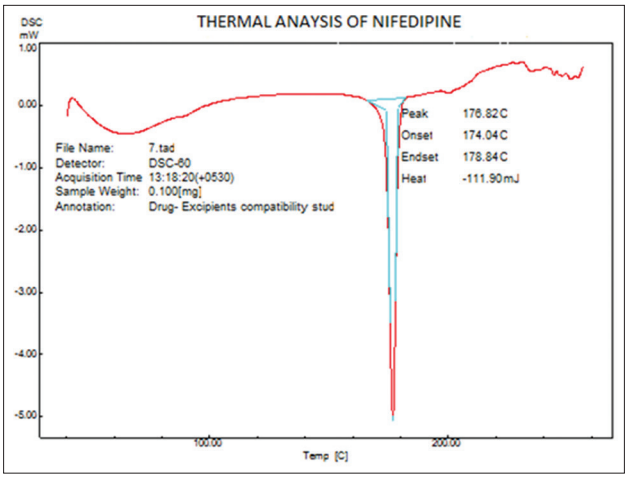

Figure 1: Differential scanning calorimeter thermogram of coated tablets nifedipine

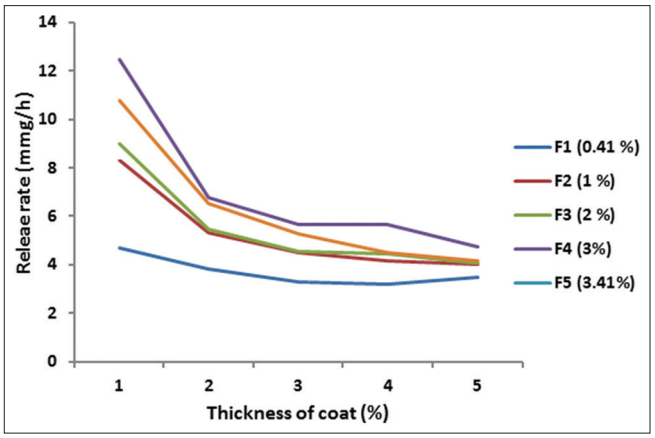

Figure 2: Effect of coating thickness of cellulose acetate on release rate of nifedipine pellets

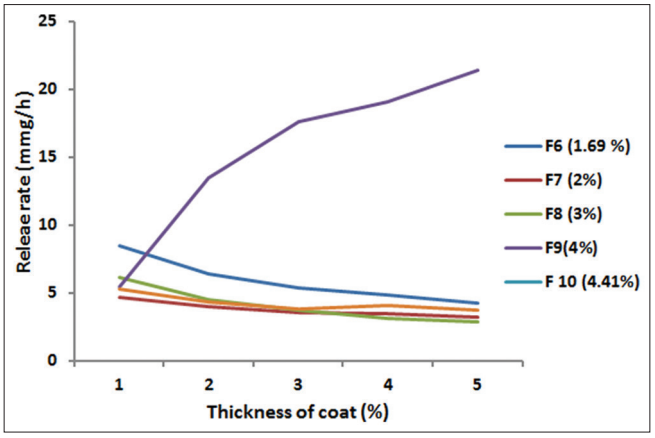

Figure 3: Effect of coating thickness of hydroxypropyl methylcellulose on release rate of nifedipine pellets

coating solution but not disclosed about the weight gain during the process. It was mentioned previously[19] when ratio between HPMC and ethyl cellulose increased by 85:15, the lag time increased up to 4.99 h, but the author used the 4.5% coating thickness in combination of two polymers.

Optimization

The results of the ANOVA indicated that these models were significant for all response parameters. The design expert 10.0 software provided suitable polynomial model equations involving individual main factors and interaction factors after fitting these data. As the model equation relating to R8 h, ANOVA study was performed, and the final equation was found to be,

Y = +151.90-25.51A-73.88B+39.54+25.47AB-10.24 AC-2.61 BC
[F = 3.82, P = 0.0425, R^2 = 0.7411]

The influences of main effects (factors) on responses investigated (R8 h, %) were further elucidated by response surface methodology. Response surface methodology is a widely proficient approach in the development and optimization of drug delivery devices. Three-dimensional response surface plots and their corresponding contour plots to estimate the effects of the independent variables (factors) on response investigated were presented in Figure 5. The three-dimensional response surface plot is very useful in learning about the main and interaction effects of the independent variables (factors), whereas two-dimensional contour plot (Figure 6) gives a visual representation of values of the response. The three-dimensional response surface plots and corresponding contour plots relating R8 h indicate (Figure 7) the deceased values of R8 h with the increment of all three independent variables. A numerical optimization technique based on the desirability approaches was adopted to achieve new optimized formulation with desired responses. The selected optimal process variable settings used for the formulation of optimized nifedipine TRC were A = 50 (1% wt. gain), B = 25 (2% wt. gain), and C = 25 (1% wt. gain).

The numerical analysis was reported[16] for their optimization, and similarly, optimization carried out to acquire the optimal values of responses based on desirability criterion with the help of Design expert 10.0 software, which led to development of optimized formulation of nifedipine spansules. The

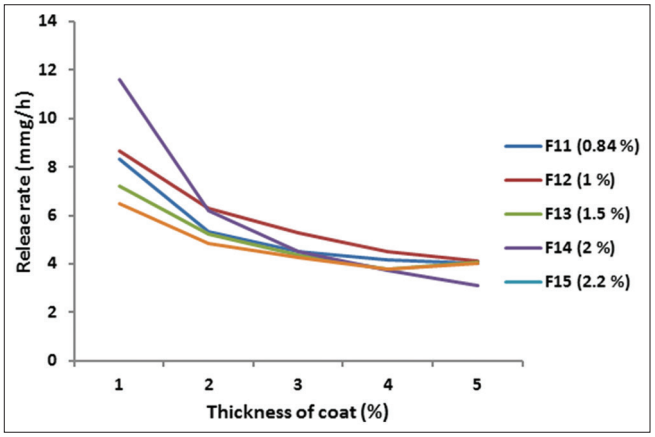

Figure 4: Effect of coating thickness of ethyl cellulose on release rate of nifedipine pellets

Optimized nifedipine TRC (F-16) showed desired release profile and complied internal specification at R8 h 97.25% with a small error values (<5), indicating that mathematical model achieved from central composite design (CCD) was suitable for this study.

Drug release kinetics

Dissolution data of the optimized formulation were fitted to various mathematical models (zero-order, and Korsmeyer-peppas) to describe the kinetics of drug release (Table 5). Regression coefficient and slope (rate) were compared in all the formulations to study their effect on drug release.[20] Further, optimized formulation fitted with selectively zero-order and peppas model to calculate the value of sum of squared residuals and Akaike information criterion, best goodness-of-fit test (R^2). High value of mean selection criterion was taken as criteria for selecting the most appropriate model.

SEM

The SEM studies were carried out on coated pellets at both lower (×270) and higher (×1000) magnifications. Views of SEM in Figure 8a-c, of HPMC, cellulose acetate, and ethyl cellulose-coated pellets at low magnification were seemed to exist as spherical discrete units while the surface morphology HPMC pellets was appeared to be visibly slightly different from that of other polymer-coated pellets as transition of macromolecules from less mobile to more mobile state (rubbery). The surface of the cellulose acetate pellets was continuous but granular compared to smooth and homogenous polymer coating of HPMC. The surface of pellets coated with ethyl cellulose was more compact, continuous, and uniform. Therefore, the diffusion length for dissolution medium to enter the drug layer and dissolved drug to diffuse out would be increased at higher coating levels that would result in slower release rate as in the case of ethyl cellulose-coated pellets.

Table 5: Kinetic parameters used for characterizing drug release curve

Zero order	No	Korsmeyer-peppas
N_observed	9	8
DF	8	6
R_obs-pre	0.9994	0.9992
Rsqr	0.9988	0.9973
Rsqr_adj	0.9973	0.9981
MSE	2.891	1.028
MSE_root	1.7003	1.0139
Weighting	1	1
SS	23.1282	6.1682
WSS	23.1282	6.1682
AIC	30.2695	18.555
MSC	5.3571	5.9476

MSE: Mean selection criterion, AIC: Akaike information criterion

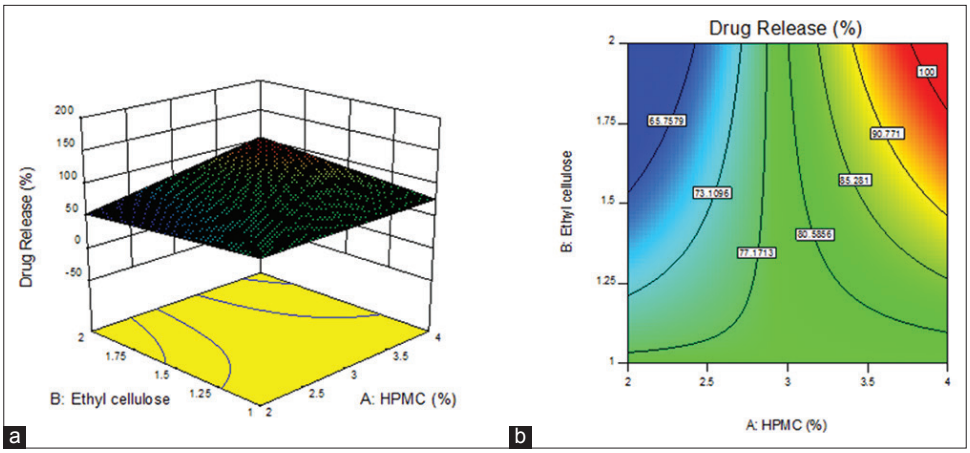

Figure 5: Effect of drug release on hydroxypropyl methylcellulose and ethyl cellulose on R8 h (%) presented by response surface plot (a) and contour plot (b)

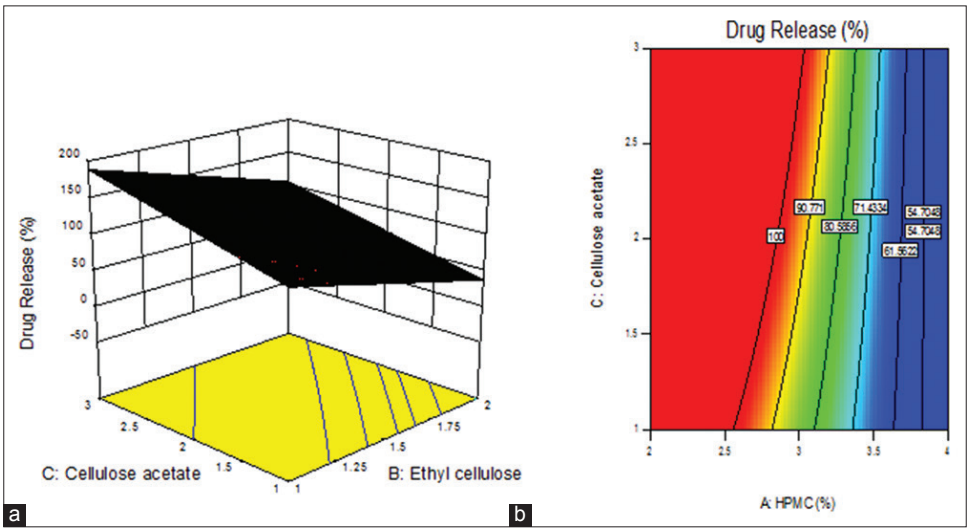

Figure 6: Effect of drug release on ethyl cellulose and cellulose acetate on R8 h (%) presented by response surface plot (a) and contour plot (b)

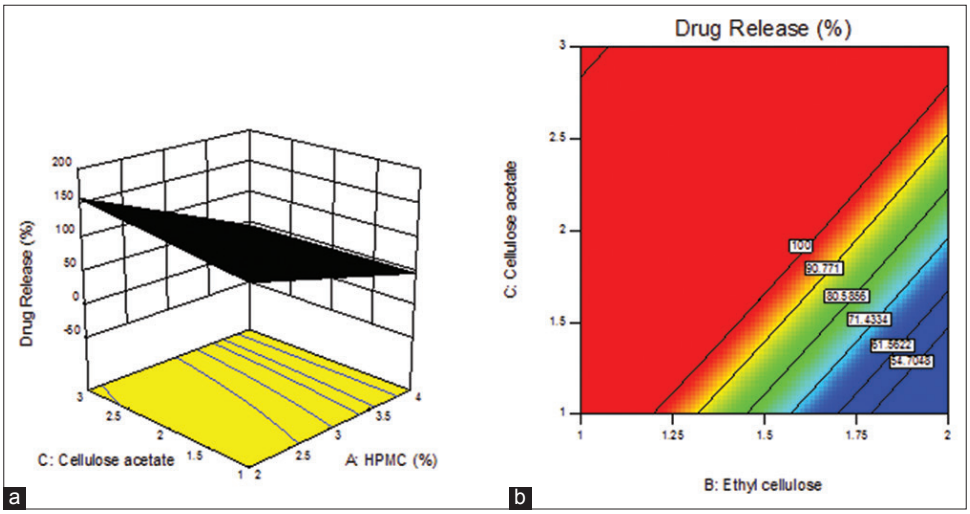

Figure 7: Effect of drug release on hydroxypropyl methylcellulose and cellulose acetate on R8 h (%) presented by response surface plot (a) and contour plot (b)

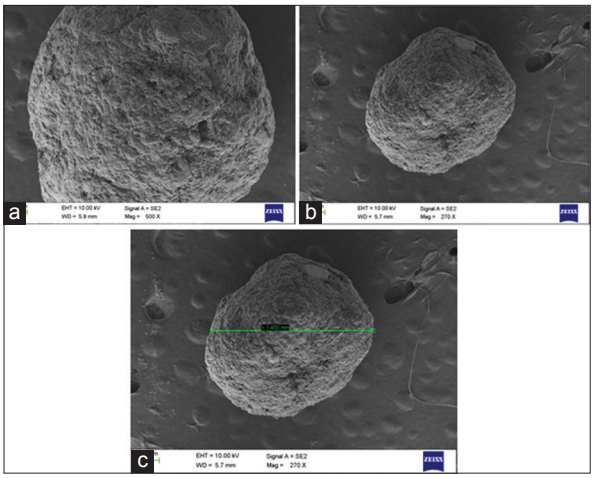

Figure 8: Surface morphology pellet coated with hydroxypropyl methylcellulose (magnification, ×500) (a), ethyl cellulose (magnification ×270) (b), and cellulos acetate (magnification ×270) (c)

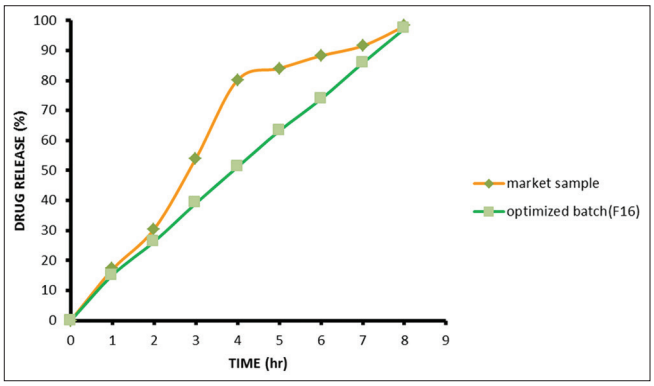

Figure 9: Comparative dissolution profile of optimized and marketed nifedipine extended release tablets

Comparison with market product

Release profiles of various formulations were compared (Figure 9) using model independent pair-wise approach, which included the calculation of "difference factor" f1 and "similarity factor" f2. The two release profiles were considered to be similar, if the f1 value was lower than 15 (between 0 and 15) and f2 value was more than 50 (between 50 and 100). For the calculation of f1 and f2 values, only one data point was taken into consideration after 85% of the drug was released. It was observed as f1 value 14 and f2 value 60.

In vivo studies

The method has been used to estimate nifedipine in plasma after a single oral dosing of 30 mg spansule formulation to rat. After administration of formulation, where as in test (optimized formulation), area under plasma concentration (AUC_{0-t}) was found to be 126 ng-h/ml, AUC (0-∞) was found to be 205 ng-h/ml, AUMC (0-t) was found to be 630 ng-h*h/ml, AUMC (0-∞) was found to be 1665 ng-h*h/ml, and its C_{max} was found to be 28 ng/ml, where as t_{max} at 4 h. However, values reported[21] were 23.2 µg/l and 9 h when nifedipine administered as fed state with 60 mg dose for the human volunteer.

CONCLUSION

Nifedipine timed-release spansules dosage form developed using extrusion-spheronization technique. Central composite design used with independent variable of HPMC, cellulose acetate, and ethyl cellulose and drug release by 95% used as dependent variable. The optimized formulation prepared with 1% coated cellulose acetate, 2% HPMC, and 1% of ethyl cellulose. Pilot blend with the ratio of 2:1:1 contains cellulose acetate, HPMC, ethyl cellulose gave desired release profile. The optimized batch F16 showed extended timed-release of nifedipine over a period of 8 hr. The *in vitro* profile of the optimized batch proves the case-II Korsmeyer peppas order with release exponent (*n*) equal to 0.833. *In vivo* pharmacokinetic studies in Wistar rats confirmed the average t_{max} 4 h value and C_{max} 28 ng/ml. The optimized formulation found to be stable under accelerated condition for 1 month with respect to the physical characteristic and drug content. The timed-release Spansule dosage form nifedipine controlled release behavior suitable to administer three times a day for hypertension and angina pectoris. However, clinical studies at different conditions are required to confirm these results.

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