Open Access Contents
Int. J. Drug Dev. & Res.
| July-September 2013 | Vol. 5 | Issue 3 | ISSN 0975-9344 |
www.ijddr.in

Full Length Original Research Paper

Development and Optimization of Elementary osmotic pump tablet of Nicardipine Hydrochloride using central composite experimental Design

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Abstract: Elementary Osmotic Pumps (EOP) consists of osmotic core (coated with a semipermeable membrane (SPM) and a small orifice is created in the membrane. The objective of the present study was to develop an optimized EOP tablets containing inclusion complex of Nicardipine Hydrochloride (NH) using central composite design. Amount of osmotic agent (X_1) and size of delivery orifice (X_2) were selected as independent variables. Formulations were prepared by direct compression method and evaluated for % Cumulative Drug Release (% CDR) at 540min. as dependent variables. Amount of osmotic agent and size of delivery orifice had a significant effect on % CDR. The results of multiple linear regression analysis revealed that EOP tablets should be prepared using an optimum concentration of osmotic agent and size of delivery orifice to achieve a zero order drug release. Contour plots as well as response surface plots were constructed to show the effects of X_1 and X_2 on % CDR. A model was validated for accurate prediction of % CDR by performing checkpoint analysis. The computer optimization process, contour plots and response surface plots predicted at the concentration of independent variables X_1 and X_2 (50mg and 0.8mm respectively), for maximized response. The drug release from the developed formulation was found independent of pH and agitational intensity. The above optimized batch was also evaluated by different pharmacokinetic models. Stability study of optimized batch was conducted at accelerated conditions for six month and it was found to be stable.

Keywords: Elementary osmotic pump, β-Cyclodextrin, Cellulose acetate, Delivery orifice, Zero-order drug release

Introduction

Conventional drug delivery systems have little control over the drug release and so it is difficult to achieve and maintain the concentration of the administered drug within the therapeutic range, leading to fluctuations in the plasma drug levels. However, significant advances have been made in the development of drug delivery devices that can precisely control the rate of drug release for an extended period of time. In the recent years, pharmaceutical research has led to the development of several novel controlled drug delivery systems of which oral controlled release (CR) systems hold the major market share. This is due to advantages of controlled drug delivery system like improved patient convenience and compliance, reduction in fluctuation in steady state plasma level so decrease intensity of local or systematic side effects and increase safety margin of high potency drugs. There is maximum utilization of drug in CR systems so it enables reduction in total amount of dose administered and possibility of delivering drugs having short biological half-life[1,2].

Many designs are available to control or modulate the drug release from a dosage forms. These dosage forms fall in the category of matrix, reservoir or osmotic systems. The orally administered drugs, in the form of conventional matrix or reservoir type formulations, poses problems of bioavailability fluctuations due to gastric pH variations. Moreover, the release of drugs from these systems is affected by the hydrodynamic conditions of the body. A one of the novel drug delivery system named as Osmotically controlled drug delivery systems (OCDDS) utilize osmotic pressure as the energy source for controlled delivery of drugs[3,4].

Various approaches like controlled porosity osmotic pump (CPOP), elementary osmotic pump (EOP) and push pull osmotic pump (PPOP)[5,6] are widely used. EOP tablets consist of an osmotic core consisting of drug with or without an osmogent. These tablets are coated by a semi-permeable membrane with a small orifice through which a solution or suspension of the drug will be released. However, EOP is only suitable for delivering moderately water-soluble drugs. To overcome this problem, a push pull osmotic tablets was developed in the 1980s to control delivery of water-insoluble drugs successfully[7-9]. However, PPOP system has some limitations for example laser drilling technology should be required to drill the orifice[10] and long lag time of drug release from osmotic pumps after coming in contact with the aqueous media[11]. In contrast to push-pull osmotic system, EOP tablets are prepared with a simple technology without any lag time for drug release and economical from industrial point of view but it requires enhancement of solubility to improve the dissolution rate of poorly water-soluble drugs. Different methods are available to improve the solubility and dissolution rate of poorly water-soluble drugs such as Nicardipine Hydrochloride. Amongst them, the solid dispersion technique and the complexation are most frequently used techniques[12,13].

Nicardipine Hydrochloride (NH), a calcium channel-blocking agent, is an effective drug in the management of mild to moderate hypertension, angina pectoris and cerebral disease. It was used as model drug since its bioavailability is very limited (15–40%) and like other dihydropyridine derivatives, its standard formulation undergoes rapid absorption and extensive biotransformation in the liver, with a short elimination half-life (about 1 h), which often results in significant fluctuations in plasma concentrations. To attain a prolonged therapeutic effect and a reduced incidence of side effects, sustained release formulations of NH have been developed to maintain a suitable plasma level for a long period of time with minimal frequency of daily administration[14-15].

The objective of the study was to develop osmotically controlled release two times a day tablets of NH. The tablets were coated with cellulose acetate as the semipermeable membrane containing plasticizer like polyethylene glycol. Prepared tablets were also evaluated for thickness, hardness, friability, drug content, *in-vitro* drug release, effect of osmotic agent, size of delivery orifice, pH and agitational intensity.

Materials and Methods

NH was obtained as a gift sample from Zydus-Cadila Healthcare limited, Gujarat, India. β-Cyclodextrin (Gangwal Pharmaceuticals, Mumbai) and Spray dried lactose (Foremost Farm, USA) were used for solubility enhancement

and direct compression respectively. Fructose was purchased from the S. D. Fine chemicals, Mumbai. Cellulose acetate (320 S) was obtained from Sun Pharmaceutical Ltd, Vadodara used as a semipermeable membrane. Poly ethylene oxide-200K (PEO-200K, WSR N80) was obtained from Dow Chemicals and Polyethyleneglycol 400 was purchased from Finar Chemicals Limited, Ahmedabad used as plasticizer.

Drug–Excipient Compatibility Studies by DSC

Differential Scanning Calorimetry (DSC) was performed using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter. The instrument comprised of calorimeter (DSC 60), flow controller (FCL 60), thermal analyzer (TA 60) and operating software (TA 60). The samples (drug alone or mixture of drug and excipients) were heated in sealed aluminum pans at a scanning rate of 5°C/min from 24±1 to 350°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the drug and drug-excipient mixture. The physical mixtures of drug with different excipients for compatibility studies were prepared by triturating drug and additives in a dried mortar for 5 min.[16].

Drug–Excipient Compatibility Studies by FTIR

The infrared spectra were obtained using an FTIR spectrophotometer. FTIR spectra of the samples were taken in the range of 400-4000 cm^{-1} by using Perking Elmer spectrum GX FTIR. A pellet of NH, drug with other excipients and dry potassium bromide was prepared using hydraulic pellet press at a pressure of 7 to 10 tones. A FTIR spectra of drug and excipient mixture was compared with FTIR spectra of pure drug.

Formulation of EOP Tablets using Central Composite Design (CCD)[17]

Optimization of Variables Using Central Composite Design

A CCD with a = 1 was employed as per the standard protocol. The amount of Osmotic agent i.e. Fructose (X_1), and size of delivery orifice (X_2), were selected as the factors (Table 1), studied at three levels each. The central point (0, 0) was studied in quintuplicate. All other formulation and processing variables were kept invariant throughout the study. Table 2 summarizes an account of the 13 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study. % Cumulative drug release at 540min. was taken as the response variables.

The general form of the multiple linear regression analysis model is represented as equation:

$$Y = \beta o + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1 X_2^2 + \beta_7 X_1^2 X_2$$

where βo is the intercept representing the arithmetic average of all quantitative outcomes of 13 runs; β_1 to β_7 are the coefficients computed from the observed experimental values of Y; and X_1 and X_2 are the coded levels of the independent variable(s).

Selection of Factors, Levels and Responses for Central Composite Design

In the present work, a CCD was adopted to find out the optimum combination of independent variables to obtain desired values of %CDR.

Table 1: Variables and Their Levels in Central Composite Design

Independent Variables	Levels		
	Low	Medium	High
X_1 = Amount of Osmotic Agent (Fructose) (mg)	25	50	75
X_2 = Size of Delivery Orifice (mm)	0.6	0.8	1
Transformed Value	-1	0	1
Dependent Variable	Y_{540} = % Cumulative Drug Release at 540min.		

Table 2: Variable Level in Coded Form

Batch Code	Amount of Osmotic Agent (X_1)	Size of Delivery Orifice (X_2)
E1	-1	-1
E2	1	-1
E3	-1	1
E4	1	1
E5	-1	0
E6	1	0
E7	0	-1
E8	0	1
E9	0	0
E10	0	0
E11	0	0
E12	0	0
E13	0	0

Data Transformation

The data transformation simplifies the calculations for model development. The data generated by the experimental design was utilized for drawing contour plot, to obtain an optimized region within the factorial space, and thereby produce an optimized formulation.

Table 3: Composition of EOP tablets

Ingredients	Quantity per tablet (mg)												
	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E13
NH + β-CD inclusion complex	96	96	96	96	96	96	96	96	96	96	96	96	96
Fructose	25	75	25	75	25	75	50	50	50	50	50	50	50
PEO-200K (WSR N80)	50	50	50	50	50	50	50	50	50	50	50	50	50
Spray dried lactose	109	59	109	59	109	59	84	84	84	84	84	84	84
SLS	10	10	10	10	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5
Total	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**
Delivery Orifice (mm)	0.6	0.6	1	1	0.8	0.8	0.6	1	0.8	0.8	0.8	0.8	0.8

Preparation of Core Tablets

Inclusion complex of NH with β-CD was used in preparation of EOP tablets due to poorly solubility of drug. Inclusion complex was prepared using kneading method and equivalent weight of drug was taken in core tablets. Core tablets of NH were prepared by direct compression technique. Accurately weighed quantity of each ingredient was passed through sieve #85. All the ingredients were manually blended homogeneously in mortar through geometric dilution and lubricated using talc and magnesium stearate. The resultant mixture was compressed into round tablets with concave punches (9mm) using a Minipress-I rotary tablet machine (Karnavati Engineering, Ahmedabad).

Coating of Tablets

Cellulose acetate (CA, 3%w/v) in a mixture of Acetone and Methanol (9:1) containing known levels of plasticizer (Polyethylene glycol-400) was used as coating solution. The coating was carried out by spray pan coating machine with hot air blower. Pan was made up of stainless steel, having diameter of 22 cm and was rotating at a speed of 36 rpm. The spray rate was fixed at 3 ml/min. Inlet and outlet temperatures were 45°C and 35°C. Coated tablets were dried in hot air oven at 50°C for 12 hr. All the formulations were drilled by a microdrill in the center of each tablet[18].

Characterization of EOP tablets

Weight Variation Test

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of twenty tablets was calculated[19].

Thickness and Diameter

Thickness and diameter of the core tablets were measured by using screw gauge. Ten tablets from each batch were randomly selected and used. Thickness and diameter is expressed in millimeters[19].

Hardness and Friability

Hardness of randomly selected tablets was tested using hardness tester (Monsanto hardness tester). Friability of core tablets was carried out on a Roche friabilator for twenty accurately weight tablets[19].

Content Uniformity

Five tablets were weighed individually and powdered. An amount equivalent to 10 mg of NH was accurately weighed and placed in a 10 ml volumetric flask to prepare a 1 mg/ml solution in methanol. Fifty microliters of NH solution from 1 mg/ml solution was added to 5 ml distilled water to yield a theoretical concentration of 10 mg/ml. The sample was measured at λmax 239 nm using a Shimadzu UV/Vis double-beam spectrophotometer (Japan) and NH concentration was calculated from the standard curve prepared simultaneously[20].

In-vitro Drug Release Study

The release rate of NH from EOP tablets was determined according to the USP using rotating paddle method. The dissolution test was performed using 900 ml of acidic buffer (pH 1.2) for first 2 hrs and phosphate buffer (pH 6.8) for subsequent 3 to 12 hrs. The stirring speed of the paddle was 100 rpm, and the temperature was maintained at 37°C ± 0.5°C. A 5ml samples were withdrawn at various time intervals and filtered through 0.45µm membrane filter. Absorbance of these solutions was analyzed at λmax 239 using a Shimadzu UV/Vis double-beam spectrophotometer (Japan). Cumulative drug release was calculated using the equation generated from Beer Lambert's calibration curve[20].

Statistical Analysis

Statistical analysis of the batches prepared according to CCD was performed by multiple regression analysis using Microsoft Excel. Two-way analysis of variance (ANOVA) was performed using the Design Expert 8.0.5.2 version software to evaluate the contribution of each factor with different levels to the response. To graphically demonstrate the influence of each factor on the response, the response surface plots were generated using the Design Expert 8.0.5.2 version software, State Ease.

Checkpoint Analysis

A checkpoint analysis was performed to confirm the role of the derived polynomial equation and contour plots in predicting the responses. Values of independent variables were taken at 3 points, 1 from each contour plot, and the theoretical values of % CDR were calculated by substituting the values in the polynomial equation. EOP tablets were prepared experimentally at 3 checkpoints and evaluated for the responses.

Optimization Data Analysis

The optimized formulation was obtained by applying constraints (goals) on dependent (response) and independent variables (factors). Constraints for responses and factors are shown in Table 1.

The models were evaluated in terms of statistically significant coefficients and R^2 values.

Various feasibility and grid searches were conducted to find the optimum parameters. Various 3D response surface graphs were provided by the design expert software. The optimized checkpoint formulation factors were evaluated for various response properties. The resultant experimental values of the responses were quantitatively compared with the predicted values to calculate the percentage prediction error.

Characterization of Optimized Formulation

Effect of pH

An osmotically controlled release system delivers its contents independent of external variables. The *in-vitro* drug release of optimized formulation was carried out in simulated gastric fluid (SGF, pH 1.2), phosphate buffer (pH 4.6) and phosphate buffer (pH 6.8).

Effect of Agitation Intensity

In order to study the effect of agitational intensity of the release media, release studies of the optimized formulation was carried out at various rotational speeds i.e. 50, 75, and 100 rpm in USP type-II dissolution apparatus.

Kinetics of Drug Release

In general, the release of drug from an osmotic system depends on many factors like osmotic pressure, pore size, coating thickness etc. In order to describe the kinetics of drug release from controlled release formulation, various mathematical equations have been proposed namely, Zero order rate, First order equation, Higuchi model and Hixson–Crowell cube root law. To authenticate the release model, dissolution data can further be analyzed by Korsmeyer Peppas equation. The selection criteria for the best model were based on goodness of fit, Akaike Information Criteria (AIC) and residual Sum of Squares (SSR).

Stability Studies

The formulations which gave the desired zero order release profile were strip packed and subjected to stability studies at 40◦C/75% RH as per ICH guidelines. Samples were evaluated for appearance, hardness, friability, drug content and *in-vitro* drug release.

Result and Discussion

Drug-Excipient Compatibility Study by DSC

The drug exhibited a sharp melting endotherm at 170.00^{0}C. The DSC thermograms of NH, mixture of NH with fructose, PEO-200K and spray dried lactose is depicted in Figure 1. No change in the endotherm of the drug was observed in the mixture of drug with all other excipients. From this it was concluded that there was no interaction between the drug and excipients.

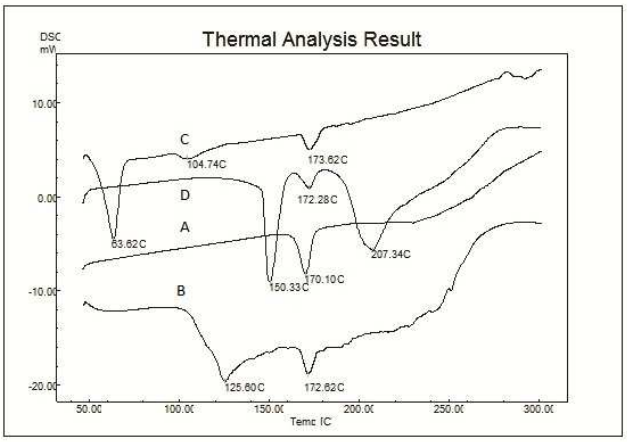


Figure 1: DSC thermograms of (a) NH (b) Mixture of NH and Fructose (C) Mixture of NH and PEO-200K (D) Mixture of NH and Spray dried lactose

Drug Excipient Compatibility Study by FTIR

The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. It does not show any major changes in peaks which indicate no well-defined interaction in between NH and excipients. This indicates that the drug is compatible with the formulation

components. The spectra for pure drug and excipients are shown in Figure 2 and interpretation of spectra is reported in Table 4.

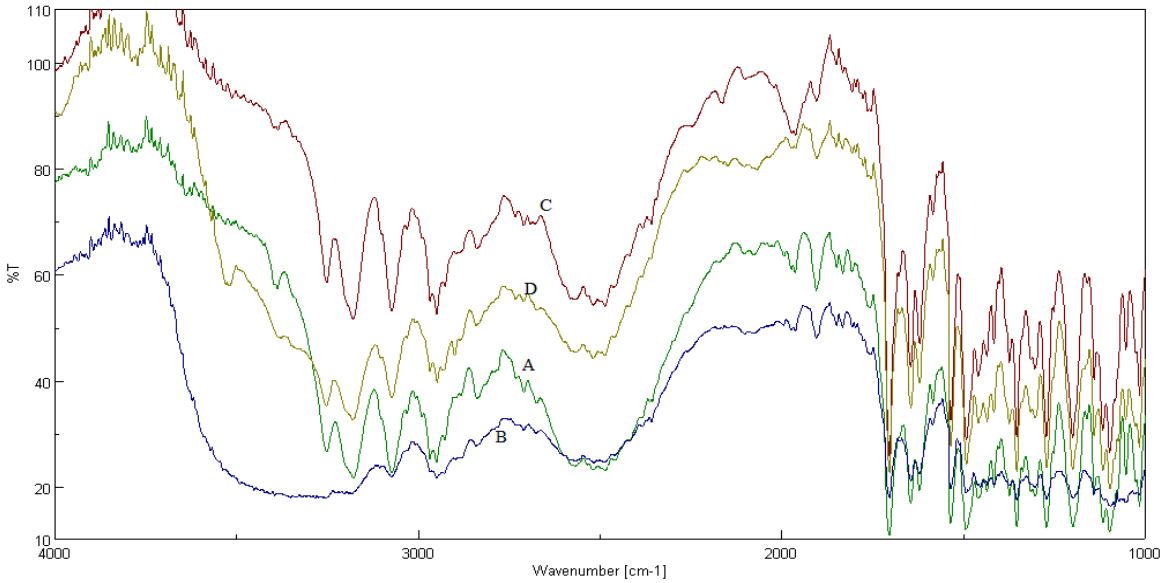


Figure 2: FTIR Spectra of (A) NH (B) Mixture of NH and Fructose (C) Mixture of NH and PEO-200K (D) Mixture of NH and Spray dried lactose

Table 4: Interpretation of FT-IR of Drug with all Excipients

Sr. No	Drug/Drug + Excipient Mixture	Functional Group Wave number (cm^{-1})							
		N-H stretching	C-H aromatic stretching	C-H aliphatic stretching	C=O stretching (in Ester Group)	N-O stretching		C-C stretching (in Ring)	C-O stretching (in Ester Group)
A	NH	3179.08	3070.51	2937.74	1703.08	1490.7	1536.02	1645.95	1270.86
B	NH and Fructose	3179.50	3070.54	2937.62	1702.97	1491.13	1536.15	1645.45	1270.59
C	NH and PEO-200K	3178.99	3070.25	2937.10	1702.75	1490.52	1536.56	1645.32	1270.31
D	NH and Spray dried lactose	3179.02	3069.91	2936.82	1702.82	1490.24	1535.95	1645.10	1270.13

Characterization of EOP Tablets

Weight Uniformity

Weight variation of the prepared tablets indicated no significant difference in the weight of individual tablet from the average value.

Thickness and Diameter

Thickness and diameter of all the tablets were found in the range of 6.290 ± 0.043 to 6.325 ± 0.027 mm and 8.98 ± 0.12 to 9.09 ± 0.06 mm respectively.

Hardness and Friability

Hardness of the prepared tablets was observed within the range of 6.34 ± 0.82 to 6.61 ± 0.49 kg/cm^2. Friability of all the tablets was found below 1%.

Drug Content

The drug content in all the batches of NH tablets was in the range of 98.63% to 100.67% as shown in Table 5. This ensured the uniformity of the drug content in the tablets.

Table 5: Evaluation of Core tablets

Batch	Tablet Weight (mg, n=20)	Thickness (mm, n=10)	Diameter (mm, n=10)	Hardness (kg/cm², n=10)	Friability (%, n=20)	Drug Content, (%, n=5)
E1	300.70 ± 0.08	6.304 ± 0.071	9.05 ± 0.04	6.34 ± 0.82	0.47 ± 0.02	98.95%
E2	299.46 ± 0.71	6.290 ± 0.043	9.00 ± 0.05	6.61 ± 0.49	0.37 ± 0.05	99.03%
E3	299.62 ± 0.83	6.299 ± 0.018	9.02 ± 0.03	6.50 ± 0.73	0.39 ± 0.03	100.33%
E4	300.81 ± 0.95	6.325 ± 0.027	9.07 ± 0.07	6.53 ± 0.54	0.44 ± 0.07	98.87%
E5	300.12 ± 0.33	6.290 ± 0.055	8.99 ± 0.09	6.47 ± 0.66	0.51 ± 0.06	99.59%
E6	299.34 ± 0.57	6.314 ± 0.091	9.09 ± 0.06	6.60 ± 0.29	0.29 ± 0.05	100.09%
E7	301.46 ± 0.88	6.315 ± 0.049	9.00 ± 0.05	6.44 ± 0.82	0.41 ± 0.04	98.63%
E8	299.99 ± 0.01	6.300 ± 0.066	9.03 ± 0.04	6.39 ± 0.75	0.42 ± 0.03	99.41%
E9	299.56 ± 0.24	6.293 ± 0.099	8.98 ± 0.12	6.41 ± 0.59	0.51 ± 0.08	99.89%
E10	298.99 ± 1.03	6.298 ± 0.052	9.00 ± 0.01	6.57 ± 0.65	0.29 ± 0.09	100.56%
E11	300.22 ± 0.80	6.301 ± 0.088	9.05 ± 0.08	6.50 ± 0.37	0.46 ± 0.03	99.90%
E12	299.55 ± 0.05	6.297 ± 0.061	9.01 ± 0.02	6.60 ± 0.95	0.36 ± 0.02	100.67%
E13	299.22 ± 0.45	6.311 ± 0.077	8.99 ± 0.03	6.57 ± 0.63	0.41 ± 0.05	99.17%

***In vitro* Drug Release Study**

All batches were prepared using different concentrations of osmotic agent. In that Batch E1, E3 and E5 contained 25mg, batch E7 to E13 contained 50mg while batch E2, E4 and E6 contained 75mg of osmotic agent. From the *in vitro* drug release study of all batches (Figure 3,4,5), it was observed that as the concentration of osmotic agent increased amount of drug release increased. Batch E2, E4 and E6 having 75mg of osmotic agent has shown complete drug release within 10hrs. Batch E1, E3 and E5 having 25mg of osmotic agent has shown 85 to 90% drug release. While batch E7 to E13 having 50mg of osmotic agent has shown better drug release compared to other batches. From *in vitro* drug release study of all batches, it was also observed that as the size of the delivery orifice increased amount of drug release increased.

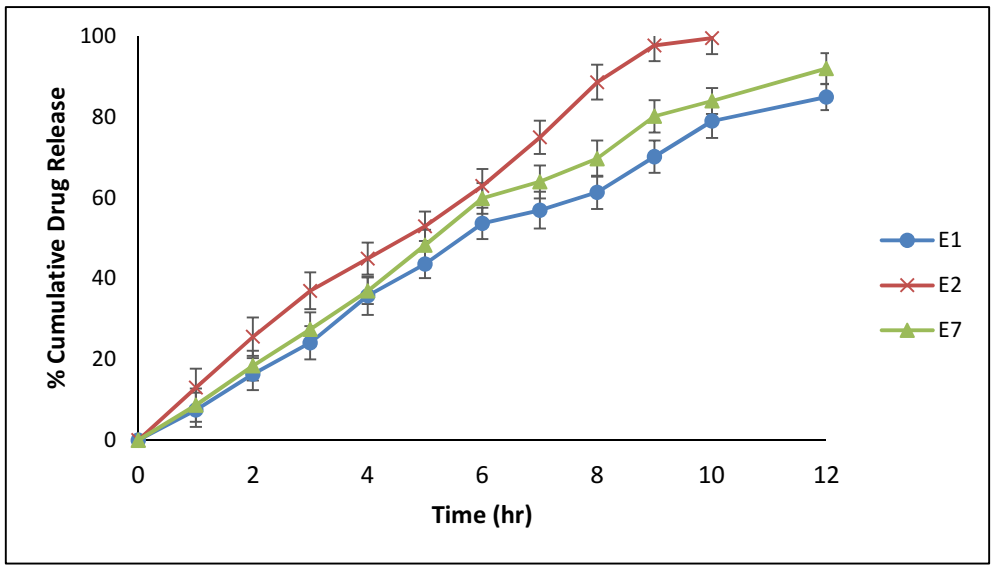


Figure 3: *In vitro* Drug Release of batch E1, E2 and E7

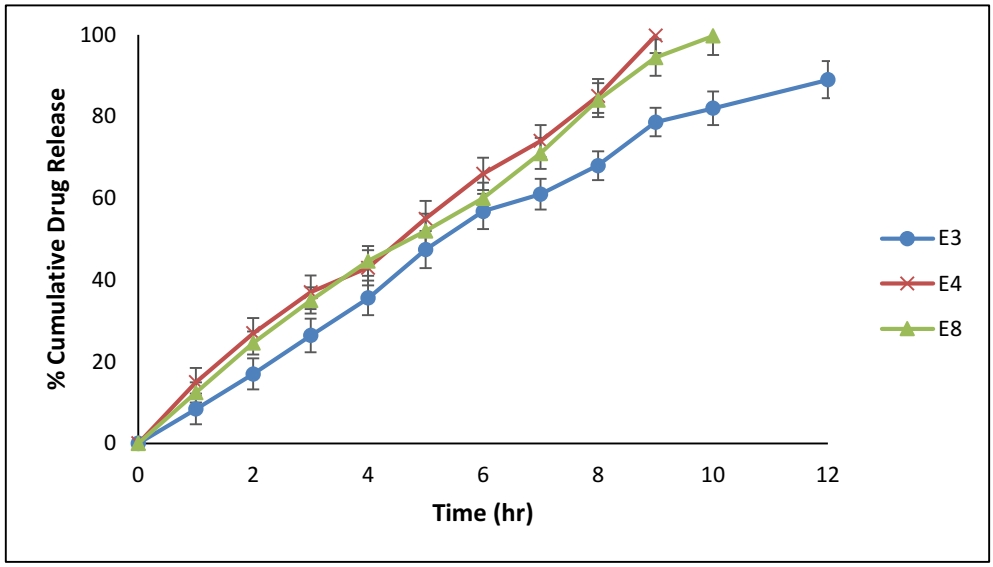


Figure 4: *In vitro* Drug Release of batch E3, E4 and E8

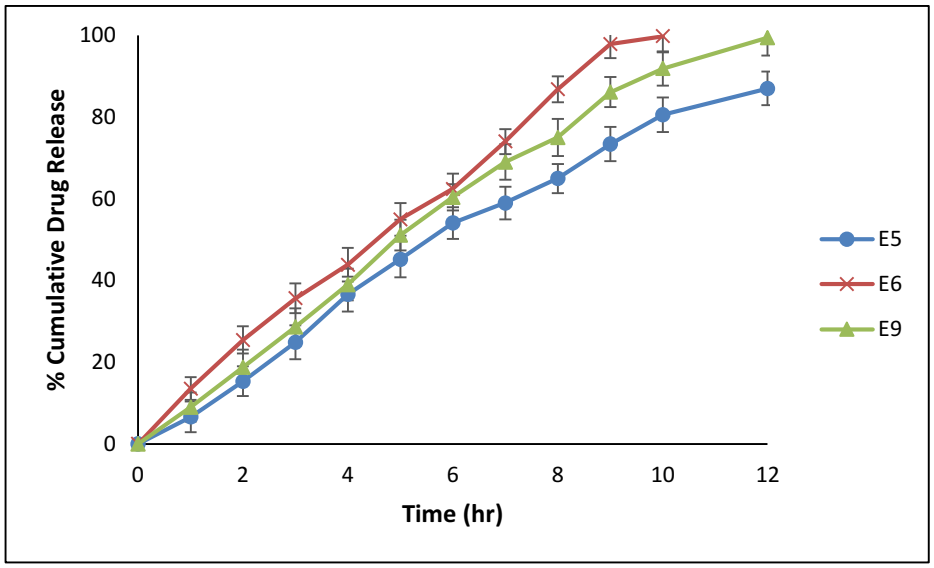


Figure 5: *In vitro* Drug Release of batch E5, E6 and E9

Statistical Analysis

CCD for two factors at three levels with a = 1 was chosen as the experimental design. This is an effective second-order experimental design associated with a minimum number of experiments to estimate the influence of individual variables (main effects) and their second-order effects. Further, this design has an added advantage of determining the quadratic response surface, not estimable using a factorial design at two levels (15).

To investigate the factors systematically, a central composite design was employed. As shown in equation, a statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

Analysis of variance (ANOVA) of the responses indicated that response surface models developed for % drug release was significant and adequate, without significant lack of fit. It was observed that %CDR indicates a high degree of correlation between the experimental and predicted responses. In addition, the predicted R^2

value was in good agreement with the adjusted R^2 value, resulting in reliable models.

Mathematical relationships generated for the studied response variables are expressed as equation:

$$Y = 86.00 + 12.23X_1 + 7.1X_2 - 1.35X_1X_2 - 0.61X_1^2 + 1.07X_2^2 - 4.25X_1^2X_2 - 0.30X_1X_2^2$$

Polynomial equation was found to be statistically significant ($P<0.0001$), as determined using ANOVA, as per the provision of design expert software. The polynomial equations comprise the coefficients for intercept, first-order main effects, interaction terms, and higher order effects. The sign and magnitude of the main effects signify the relative influence of each factor on the response. At a given set of factor levels, however, these higher order polynomials yield results as the net effect of all the coefficient terms contained in the polynomial.

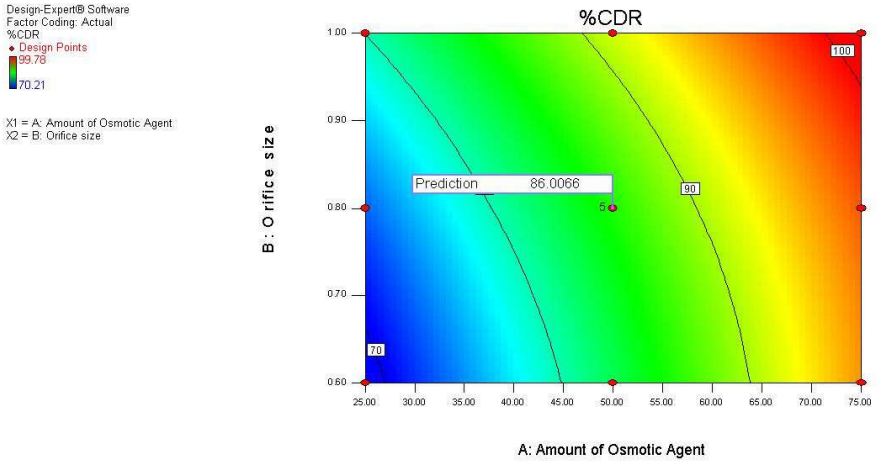
The second- order polynomial model generated revealed that the levels of osmotic agent and orifice size had a significant synergistic influence on the % CDR at 540min.. Osmotic agent and size of delivery orifice have a positive and more pronounced influence on % CDR. The response surface plot and the contour plot (Figure 6) illustrate that the % CDR increased as the amount of osmotic agent increased. This is attributed to its osmotic property, leading to increase pressure. An increase in drug release can also be attributed to increase in orifice size.

Table 6: Results of ANOVA of Full and Reduced Models for % CDR of EOP tablets

ANOVA	Df	SS	MS	F value	P value
Regression					
Full model	7	1013.25	144.75	1092.03	1.18×10^{-7}
Reduced model	6	1013.13	168.85	1297.62	4.56×10^{-9}
Residuals					
Full model	5	0.66	0.13		
Reduced model	6	0.78	0.13		

*ANOVA indicates analysis of variance; % CDR, cumulative percentage drug release; Df, degrees of freedom; SS, sum of squares; MS, mean of squares; F, Fischer's ratio.

To demonstrate graphically the effect of concentration of osmotic agent and size of delivery orifice, the contour and response surface plots were generated for the dependent variables % CDR at 540min.



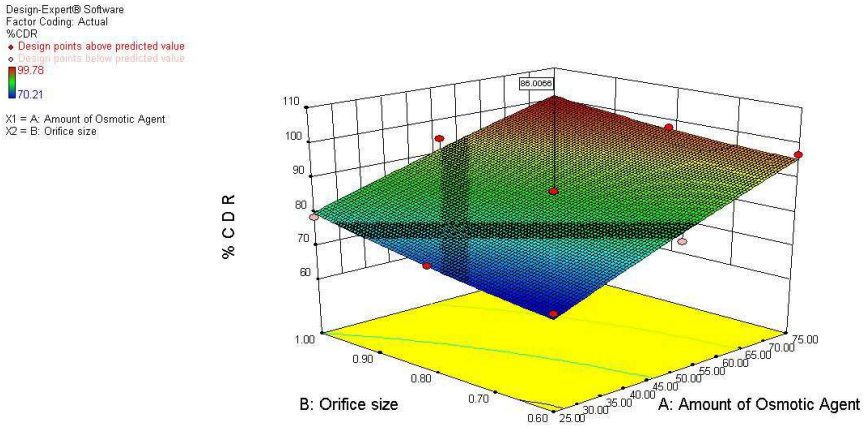


Figure 6: Contour plot and response surface plot showing the effect of Osmotic agent (Fructose, X_1) and Size of delivery orifice (X_2) on the % CDR

Check Point Analysis

Three checkpoint batches were prepared and evaluated for % CDR at 540min., as shown in Table 7. Results indicated that the measured % CDR values matches well with expected %CDR. When measured % CDR values were compared with predicted % CDR values using student's t-test, the differences were found to be not significant. Thus, it can be concluded that the obtained mathematical equation is valid for predicting % CDR at 540min.

Table 7: Checkpoint batches with predicted and measured % CDR at 540min

Batch code	X1	X2	% CDR at 540 min.	
			Measured	Predicted
E14	0	1	94.41	94.17
E15	0.5	0	90.10	91.96
E16	-0.5	-1	75.48	74.24

Formulation Optimization

For the optimization of EOP tablets of NH, constraints were fixed for all factors and response. In the present study, objective was to obtain the release upto 12hrs so that more than 80% drug should be release in 9 hrs. In optimization (Figure 7) desirability 1 indicated optimum formulation was achieved at 50mg of X_1, and 0.8mm of X_2 (Batch E17). For confirmation, a fresh formulation was prepared at the optimum values of the independent variables, and the resultant tablets were evaluated for the % CDR. The observed values of % CDR were found to be 86.007%, which were in close agreement with the theoretical values.

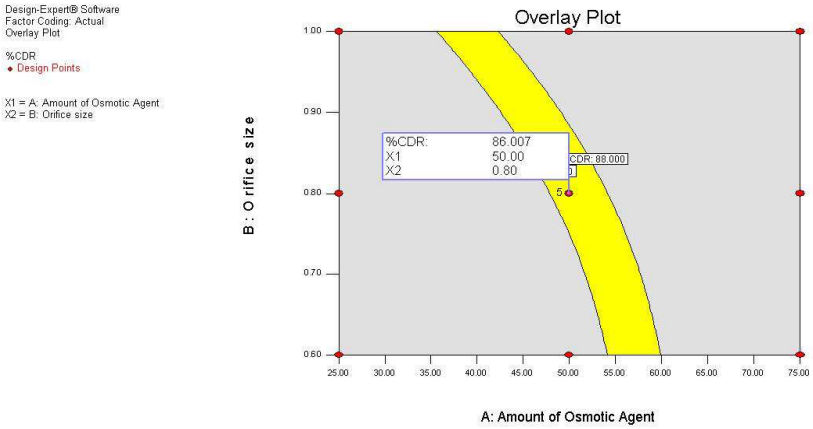


Figure 7: Overlay plot of response variables

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Table 8: Composition of Optimized Batch E17

Ingredients	Quantity (mg/tablet)
NH + β-CD inclusion complex	96
Fructose	50
PEO-200K (WSR N80)	50
Spray dried lactose	84
SLS	10
Talc	5
Magnesium stearate	5
Total	**300**
Delivery Orifice (mm)	0.8

Characterization of Optimized Formulation

Effect of pH on Optimized Formulation

Release studies of the optimized formulation were conducted according to pH change method to study the effect of pH on drug release. The release media was simulated gastric fluid (SGF, pH 1.2), Phosphate buffer (pH 4.6) and Phosphate buffer (pH 6.8). Figure 8 shows release of NH from optimized formulation and it is clearly evident that the release profile is similar in all the media, demonstrating that the developed formulation is having pH independent release.

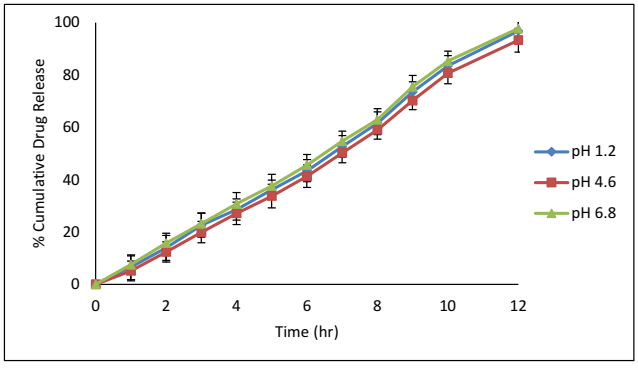

Figure 8: Effect of pH on drug release from optimized batch E17

Effect of Agitation Intensity on Optimized Formulation

Figure 9 shows that the release profile of NH from the developed formulation is fairly independent of the agitational intensity of the release media and hence, it can be expected that the release from the developed formulation will be independent of the hydrodynamic conditions of the body.

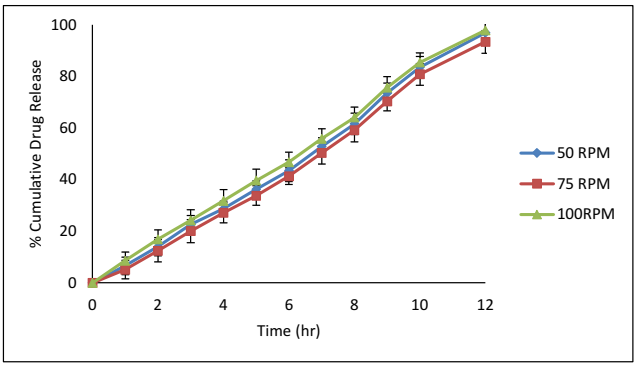

Figure 9: Effect of agitation intensity on drug release from optimized batch E17

Kinetics of Drug Release

Dissolution data of the optimized formulation E17 was fitted to various mathematical models (zero-order, first-order, Higuchi, Korsmeyer Peppas and Hixson Crowell Model) in order to describe the kinetics of drug release. Smallest value of sum of squared residuals (SSR), Akaike information criterion (AIC) and best goodness-of-fit test (R^2) were taken as criteria for selecting the most appropriate model. It is evident from the data that Zero Order Kinetic and Korsmeyer-Peppas model were the best fit model for batch E17. The value of n is indicative of release mechanism. Here $0.5 < n < 1$ so, anamolous (non-fickian) diffusion was seen. The values of diffusional exponent (n) of all batches are between 0.5-1.0, so all batches showed diffusion control release mechanism.

Table 9: Fitting of Dissolution data of the optimized formulation to kinetic Models

Batch	Model	Parameters Used				
		R^2	r	k	SSR	AIC
E17	Zero-order	0.9949	0.9980	8.108	54.64	50.011
	First-order	0.9071	0.9687	0.127	1002.45	84.92
	Higuchi	0.8275	0.9466	22.18	1860.86	92.34
	Korsmeyer Peppas	0.9971	0.9986	6.886 n=1.076	31.089	45.24
	Hixson Crowell model	0.9411	0.9803	0.037	635.40	79.45

R^2 - Goodness of fit
r - Correlation Coefficient
k - Release rate Constant
SSR - Sum of Squared residuals
AIC - Akaike Information Criterion

Stability Study of Optimized Batch

Stability study was done to see the effect of temperature and humidity on tablets. Tablets were evaluated periodically at 0 month, and after 6 month for appearance, hardness, friability, drug content and *in vitro* drug release. The results of the stability study for the optimized batch E17 is given in Table 10.

No significant changes were observed in any of the studied parameters during the study period, thus it can be concluded that formulation was stable.

Table 10: Stability Study of Optimized Batch (E17) at Accelerated (40 ± 2°C & 75 ± 5% RH) Condition

Test	At 0 month	After 6 month
Appearance	Light yellow colour, round shaped concave tablet	No change in appearance
Hardness (Kg/cm^2)	6.47 ± 0.68	6.49 ± 0.53
Friability %	0.36 ± 0.06	0.40 ± 0.05
Drug content (%)	99.89 ± 0.52	99.36 ± 0.79
In vitro drug release (%)	99.41 ± 0.72	99.57 ± 0.66

Conclusion

β - Cyclodextrin was effective in increasing the solubility of NH. Elementary osmotic tablets coated with cellulose acetate as a semipermeable membrane has been developed for NH. The effect of different formulation variables was studied to optimize release profile. The system was optimized for different concentration of osmogent, and size of delivery orifice to achieve desired release profile. From the *in vitro* drug release study, it was inferred that as the amount of osmotic agent and size of delivery orifice was increased amount of drug release increased. The osmotic system (batch E17) containing 50mg of osmotic agent and 0.8mm orifice diameter was found to deliver NH at a zero order rate for 12 hr. The drug release from the developed formulations was independent of pH and agitational intensity.

Acknowledgments

The authors are grateful to the Shree Swaminarayan Sanskar Pharmacy College, and Institute of Pharmacy, Nirma Univeristy, Gujarat, India for providing all the necessary facilities for my research work.

Conflict of Interest Declaration

The authors declare that they have no competing interests.

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Article History:----------

Date of Submission: 21-06-2013

Date of Acceptance: 09-07-2013

Conflict of Interest: NIL

Source of Support: NONE