EFFECT OF HYDROPHILIC POLYMER ON DESIGN EXPERT ASSISTED ORO-DISPERSIBLE STRIP (ODS) OF ISOSORBIDE MONONITRATE

ABSTRACT

Oral conventional formulations like tablets, capsules and liquids have many limitations. Due to this and patient incompliance, there is a need to develop new formulations with better efficiency and stability. The aim of the present study was to develop and optimize fast dissolving Oro-dispersible strips (ODS) of isosorbide mononitrate by 3^2-full factorial design. HPMC E15 (X_1) concentration and glycerin (X_2) concentration were selected as the independent variables, whereas, *in vitro* disintegration time (Y_1), percent drug release (Y_2) and tensile strength (Y_3) were selected as dependent variables. Fast dissolving Oro-dispersible strips of isosorbide mononitrate were prepared by the solvent casting method.Tensile strength, disintegration time and *in vitro* dissolution of ODS of the strip were found to be within accepted range for optimized formulation. Statistical validity of the polynomials was established by ANOVA using Design-Expert software. The study suggests isosorbide mononitrate fast dissolving Oro-dispersible strip as potential alternative dosage form in management of angina pectoris.

Keywords:Oro-dispersible strips, Full factorial design, Solvent casting method, Isosorbide mononitrate

INTRODUCTION

The origin of Fast Dissolving Drug Delivery Systems (FDDDS) can be traced back to the late 1970's as a potential substitute for other oral dosage forms like tablets, capsules, syrups and other formulations. Their major benefit is for pediatric and geriatric patients suffering from dysphasia problems. The FDDDS possesses the advantages of conventional tablets and liquid formulation[1,2]. The ease of administration and better patient compliance makes FDDDS a formulation of choice for pediatric, geriatric and mentally challenged persons[3].

Delivery of the drug to the site of action successfully is the prime moto of any drug delivery system. The drug delivery system should be safe, effective, convenient and economical with highest patient compliance[4,5]. In FDDDS, the drug gets disintegrated, dissolved or swallowed and then reaches into the systemic circulation to show desired therapeutic effect[6,7].

Oro-dispersible strips (ODS) is one of the convenient novel drug delivery systems for the delivery of the drugs. It is based upon the technology of trans-dermal patch and consists of a very thin oral strip, to be placed on the patient's tongue or any oral mucosal tissue. This film then gets instantly wet by saliva and the strip rapidly hydrates and adheres onto the site of application[8].

Ease of administration, dosing accuracy, self-medication and patient compliance are the advantages offered by ODS over the other dosage forms[9]. For ODS administration, there is no need of water and can administered anytime, anywhere. These strips provide better disintegration and dissolution in the oral cavity due to its large surface area[10].

Isosorbide mononitrate is the long-acting metabolite of isosorbide dinitrate utilized as the vasodilator's specialist in the administration of angina pectoris by expanding the vessels. It brings down the circulatory strain and decreases the left ventricular pre-load and after-load, in this manner prompts a decrease of myocardial oxygen necessity. Usual dose of isosorbide mononitrate is 10-60 mg. The limit of absolute oral bioavailability of isosorbide mononitrate is about 90-95% and absorption is about 100%. Oral fast dissolving Oro-dispersible strips of isosorbidemononitrate will be convenient for geriatric patients and adults with swallowing difficulty[11].

The present research work involves the formulation and optimization of Oro-dispersible strips of isosorbide mononitrate by applying 3^2-factorial designs to understand the effect of formulation variables likes concentration of polymer (HPMC E15) and concentration of plasticizer (glycerin) on *in vitro* evaluation parameter.

METHODS

Isosorbide mononitrate was procured from Piramal Laboratories Ltd. Mumbai, India. HPMC E15 was obtained from Loba Chemie, Mumbai, India. Glycerin, citric acid and mannitol were procured from SD Fine Chem Ltd., Mumbai, India. All the materials used in this study were of analytical grade. Double distilled water was used throughout the study. The drug and all materials

were analyzed for FT-IR and DSC to check compatibility among the selected materials[12,13].

Formulation of Oro-dispersible strips (ODS)

The Solvent Casting Method was used to prepare quickly dissolving Oro-dispersible strips of isosorbide mononitrate[14]. The polymer HPMC E15 and plasticizer (glycerin) were dissolved in purified water and permitted to swirl for 4 h and held for 1 h to eliminate any trapped air bubbles; this solution was referred to as 'aqueous solution-I'. Drug and other excipients, such as mannitol and saliva stimulating agent (citric acid) were allowed to dissolve in distilled water, referring to as 'Aqueous 'solution-II'. Then 'solution-I' and 'solution-II' were mixed and agitated for 1 h. The resultant mixture was eventually permitted to spill into the glass petri dish and was dried overnight. The dried strips were carefully removed from the petri dish, checked for any imperfections, and cut in squares of 6 cm^2. For further analyses, samples were placed in airtight containers.

Experimental design

For the optimization of ODS, the 3^2-full factorial design was used. All the batches designed as per the 3^2-full- factorial are shown in Table I.The mechanical property of ODS was studied using two factors at 3 levels and the identification and performance of nine possible combinations of experimental trials. Independent variables selected for this analysis were concentration of HPMC E15 (X_1) and concentration of glycerin (X_2), whereas *in vitro* disintegration time; (DT), percentage of drug release (% DR) and tensile strength (TS) were selected as dependent variables at three levels low, medium and high. The corresponding factor levels were marked as -1, 0 and +1. In Design-Expert 8.0.7.1 software, the data were subjected to a contour and linear correlation plot to determine the effect of polymers on the dependent variables. A statistical model incorporating interactive and polynomial terms was used to calculate the responses as follows:

$$Y=b_0+ b_1X_1 + b_2 X_2+ b_{12} X_1 X_2+ b_{11} X^2_1 + b_{22} X^2_2 \quad \ldots (1)$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_1 is the estimated coefficient for the corresponding factor X_i, which represent the average result of changing one factor at a time from its low to high value. The term interaction (X_1, X_2) indicates how the response varies as two factors shift at the same time. To investigate the nonlinearity, the polynomial terms (X_1X_1 and X_2 X_2) are included.

Evaluation of Oro-dispersible strips

The assessment parameters for the Oro-dispersible strips of isosorbide mononitrate were weight, surface pH strength, width, product quality, folding endurance, content uniformity, disintegration time and *in vitro* dissolution[15–19].

The percentage moisture loss was calculated as follows[20].The experiments were performed in triplicate and recorded mean values are reported.

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Strip thickness} \times \text{Strip width}} \times 100 \quad \ldots (2)$$

In vitro dissolution studies

The *in vitro* dissolution studies for strips were performed using USP Type II dissolution apparatus at 37±0.5 °C and 50 rpm speed in 900 mL of phosphate buffer (pH 6.8). 5 mL aliquots were withdrawn at the time interval of every 60 seconds and was replaced with equal volume of fresh dissolution medium and analyzed by spectrophotometer at 221 nm. The cumulative amount of drug release at various time intervals was calculated.

Stability study

Stability study on the optimized formulation of Oro-dispersible strip was carried out as per ICH Q1A (R2) guidelines to determine the effect of temperature and humidity on the stability of the formulation. The optimized formulation was stored in stability chamber at 40±2 °C /75±5% RH and 25 °C/40% RH for duration of 90 days. The sample, were withdrawn at 15, 30, 60- and 90-days intervals; evaluated for physical and chemical parameters[21].

Data analysis

Statistical validation of the polynomial equation was developed by the Design-Expert, based on ANOVA provision in the software. It produced a total of nine runs (F1-F9) with a triplicate center point. The findings of the resulting experimental response properties were correlated with those of the forecasted values.

Polynomial equations:

$$Y_1=28.44 + 8.17X_1 + 0.50X_2 + 2.50X_1X_2 + 4.83X^2_1+ 2.83X^2_2 \quad \ldots (3)$$

$$Y_2= 94.36 - 2.95X_1 + 0.25X_2 \quad \ldots (4)$$

Table I: Evaluation of physical parameters of prepared oro-dispersible film

Formulation code	*Drug content (%)	*Thickness (mm)	*Weight variation (mg)	*Surface pH	*Folding endurance	*Percent moisture loss
F1	96.45±0.4	0.26±0.01	54.00±0.52	6.73±0.28	356±1.52	6.10±0.22
F2	97.91±0.2	0.29±0.01	53.89±0.37	6.80±0.33	392±3.89	3.81±0.43
F3	96.76±0.3	0.25±0.01	53.33±0.49	6.83±0.29	248±2.76	6.10±0.15
F4	97.12±0.5	0.33±0.01	55.11±0.41	6.81±0.33	402±4.01	3.78±0.32
F5	97.82±0.5	0.27±0.01	53.69±0.37	6.83±0.29	247±1.52	6.96±0.19
F6	98.17±0.2	0.23±0.01	52.48±0.34	6.97±0.35	216±2.00	5.98±0.29
F7	98.02±0.5	0.24±0.01	53.95±0.52	6.96±0.32	270±3.05	2.80±0.24
F8	96.88±0.3	0.21±0.01	50.00±0.36	7.10±0.26	202±2.08	6.25±0.28
F9	96.50±0.6	0.26±0.01	50.70±0.51	6.90±0.30	215±3.20	3.41±0.35

Evaluation of physical and chemical stability of optimized batch (F6) at 40±2°C/75±5% RH as per ICH Q1A (R2) guidelines of stability study

Time (days)	Physical change		Chemical change	
	Appearance	*Weight variation (mg)	*Percent drug content	*Surface pH
1	No Change (Film appears transparent, uniform and clear)	53.69±0.22	97.80±1.25	6.83±0.12
15		53.30±0.15	97.45±2.35	6.76±0.25
30		53.18±0.11	96.90±1.44	6.69±0.14
60		53.00±0.32	96.61±2.25	6.66±0.25
90		52.30±0.22	96.55±1.84	6.59±0.55

All the observations were taken in triplicate as ±SD, (n=3)

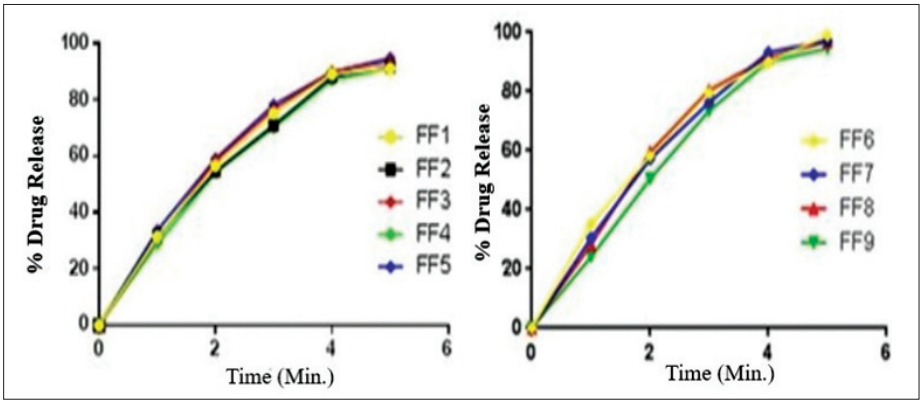

Fig. 1: *In vitro* drug release profile of fast dissolving strips

$$Y_3 = 0.20 + 5.333X_1 + 9.833X_2 + 2.250\ X_1X_2 - 1.000\ X^2_1 - 4.500\ X^2_2 \quad \ldots (5)$$

RESULTS AND DISCUSSION

Optimized Oro-dispersible strips (ODS) were evaluated for parameters like weight of strips, thickness, surface pH, folding endurance, drug content, tensile strength, percent moisture loss, *in vitro* disintegration time and *in vitro* dissolution. All the results of these parameters are presented in Table I and drug release study of all the batches according to 3^2-full factorial design is shown in Fig. 1.

Fitting model to the data

Full factorial statistical experimental design needs 9 runs, as provided by the Response Surface Methodology (RSM). The Y_1, Y_2 and Y_3 ranges are 30.00-47.00 seconds, 91.2-97.8% and 0.18-0.21 N m^{-2}, respectively. Simultaneously fitted to first order, second order, linear and quadratic models using Design-Expert for all response observed for 9 formulations were prepared. It is clear that both of the two independent variables, namely polymer concentration (X_1) and plasticizer concentration (X2), have interactive effects on the three responses Y_1, Y_2 and Y_3, respectively. A positive value reflects an influence that supports optimization, while a negative value implies an inverse factor-response relationship.

Contour plot and response surface analysis

Two-dimensional contour plots for all three responses are for response Y_1, Y_2 and Y_3. These plots are known to study the interaction effect (studying the effects of two factors at one time) of the factor on the response properties were drawn. Linear correlation plot showed high R-squared values for all three responses taken between the predicted values and the experimental ones. The R-squared values of Y_1, Y_2 and Y_3 were found to be in the range of 0.9958-0.9984, 0.9837-0.9877 and 0.9856-0.9946, respectively.

Response 1 (Y1): Effect on disintegration time

The following polynomial equation prevailed from the model for disintegration time,

$$Y_1=28.44 + 8.17X_1 + 0.50X_2 + 2.50X_1X_2 + 4.83X^2_1 + 2.83X^2_2 \quad \text{... (6)}$$

where Y_1 is disintegration time. All the formulations have shown response of Y_1<60s. The model F-value is 0.0002. There is only a 0.02% chance that a "Model F-value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case X_1, X_2, X_1X_2, X^2_1, X^2_2 are significant model terms. When the values surpass 0.1, the model terms are insignificant. A positive correlation was found between the concentrations of the two independent variables (X_1 and X_2) and the consequent dependent variable (As amount of polymer and plasticizer is directly proportional to the disintegration time).

Response 2 (Y_2): Effect on drug release

The model proposes the following polynomial equation for drug release,

$$Y_2= 94.36 - 2.95X_1 + 0.25X_2 \quad \text{... (7)}$$

where Y_2 is drug release, X_1 is the polymer concentration and X_2 is the concentration of plasticizer.

The model F-value of 241.90 implies the model significant $p < 0.0001$. Thus, this model can be used to explore the design space. The contour diagram shows the impact of different independent variables on the percentage release of drugs (Y_2). The percentage of drug release declines as the quantity of polymer rises, since the drug persists inside the matrix of polymer and vice versa. The pattern of drug release in Oro-dispersible strips (ODS) is often influenced by plasticizer concentration (X_2) and maintaines a direct relationship as plasticizer quantity decreases. A positive value for the coefficient (hereinafter referred to as equation) is an indicator of the favorable effect while a negative value for the coefficient implies an unfavorable effect. Because of noise, there is just a 0.01 percent probability that a model F-value this high will occur. Value of prob > F less than 0.0500 indicates that the model terms are significant. In this case X_1 are significant model terms and value greater than 0.1000 indicate that the model terms are not significant.

Response 3 (Y3): Effect on tensile strength

The polynomial equation for tensile strength is as follows:

$$Y_3= 0.20 + 5.333X_1 + 9.833X_2 + 2.250\ X_1X_2 - 1.000\ X_1^2 - 4.500\ X^2_2 \quad \text{... (8)}$$

where the tensile force is Y_3. All the formulations showed the Y_3 response, 0.181-0.210. The model F-value of 110.52 implies that the model is important. Owing to noise, there is only 0.13 percent chance that a model F-value this huge could occur. Values of "Prob F" that are lower than 0.0500 suggest that the model terms are significant. In this case X_1, X_2, X_1X_2, X^2_1 and X^2_2 are significant model terms and response showed a positive response due to increases in impart flexibility to the strip i.e., as the amount of polymer and plasticizer increases the tensile strength also increases. Values greater than 0.1000 indicate that the model terms are not significant.

Optimization model validation

In the Design-Expert software, statistical validity of the polynomials has been developed on the basis of ANOVA provision. The feasibility and grid analysis were subsequently performed to find the composition of optimal formulations. After developing the polynomial equation for the responses Y_1, Y_2 and Y_3 with the independent variables X_1 and X_2, the contour plots were constructed using the output files generated by the Design-Experts software, and the formulation was optimized. Optimization was carried out to evaluate the level of the independent variable (X_1 and X_2) which would give a maximum value of F6. The R-squared values were 0.9984, 0.9877 and 0.9946.

Stability studies

No remarkable physical change in appearance and weight variation of Oro-dispersible strips (ODS) was observed in stability studies.

CONCLUSION

The present work is an attempt to develop fast dissolving strip of isosorbide mononitrate using water

soluble polymers. Use of HPMC E15 and glycerin played significant role in design of Oro-dispersible strip. Optimization approach favors in the modification of the disintegration time and release which could be helpful in better utilization of drug. The findings suggest that isosorbide mononitrate fast dissolving Oro-dispersible strip has the potential as an alternative dosage form in treating acute disease like angina pectoris.

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Prakash N. Kendre[a]*, Akash R. Aher[b], Somnath K. Vibhute[a], Ajinkya K. Pote[a], Subhash V. Deshmane[a] and Shirish P. Jain[c]

[a] Department of Pharmaceutics, Rajarshi Shahu College of Pharmacy, Buldana - 443 001, Maharashtra, India

[b] Department of Pharmaceutics, Sanjivani College of Pharmaceutical Education and Research, Kopargaon - 423 601, Maharashtra, India

[c] Department of Pharmacology, Rajarshi Shahu College of Pharmacy, Buldana - 443 001, Maharashtra, India

***For Correspondence: E-mail: prakashkendre@gmail.com**

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