SHORT COMMUNICATION

DESIGN AND STATISTICAL OPTIMIZATION OF CONCENTRATION OF SUBLIMATING AGENTS IN FORMULATING ORODISPERSIVE TABLETS

ABSTRACT

Amlodipine is a BCS (Biopharmaceutical Classification System) class I drug with high permeability and high solubility. It has a long half-life of 30-50h. It is a suitable model drug for formulating orodispersive tablets, as the orodispersive tablets can release the drug immediately. Thus, formulation of amlodipine into orodispersible tablets will help in improved delivery of the drug at a faster rate. To achieve this, the orodispersive tablets were prepared by sublimation technique and the concentration of the sublimating agents was optimized by central composite design. Based on the results, it was concluded that camphor and thymol when used at optimum concentrations can be used in the formulation of orodispersive tablets, the drug delivery systems for drugs with long half-life. They are potential delivery systems to improve palatability also for model drugs like amlodipine.

Keywords: Amlodipine, central composite design, camphor, thymol

INTRODUCTION

Orodispersive tablets are immediate release dosage forms which can be prepared by various techniques. Sublimation technique is one of the techniques in the preparation where sublimating agents are crucial ingredients. The fear of suffocation, many pediatric, geriatric, bed ridden, nausea and intolerance may not favour taking oral dosage forms. Difficulty in swallowing conventional dosage forms is seen in patients traveling without access to water and in various physiological and neurological conditions such as dysphagia and motion sickness. This leads to non-compliance and ineffective therapy, where the use of orodispersive tablets will be of great use. In orodispersive tablets, the drugs go into solution faster. As the saliva enters the stomach, the drug goes into the solution quickly. In such cases, the drug bioavailability is significantly higher than the conventional dosage form[1-4].

Amlodipine is a BCS (Biopharmaceutical Classification System) class. I drug with high permeability and high solubility. It has a long half-life of 30-50h[5,6]. It is a suitable model drug for formulating orodispersive tablets as such tablets can release the drug immediately. Thus, formulation of amlodipine into orodispersible tablets will improve delivery of the drug at a faster rate. To achieve this, the orodispersive tablets were prepared by sublimation technique and the concentration of the sublimating agents was optimized. The present study aims to optimize the concentration of sublimating agents in the formulation of orodispersive agents of the model drug, amlodipine. The objectives of the present work are statistical optimization of sublimating agent and formulation by central composite design, formulation of amlodipine loaded orodispersive tablets by sublimation technique, precompression evaluation studies of amlodipine orodispersive tablets, preparation of optimized orodispersive tablet and *in vitro* evaluation of the optimized formulation.

RESULTS AND DISCUSSION

Construction of calibration curve in pH 6.8 phosphate buffer was done. The regression equation was found to be y = 0.0142 x +0.0229, where y is absorbance, x is concentration, 0.0142±0.008 is slope and 0.0229±0.009 is intercept. Correlation coefficient was found to be 0.9997. From the slope and intercept values, it is observed that the curve has a positive slope and positive intercept. The coefficient of correlation value of 0.9997 is good. From the data, it is evident that the concentration ranges from 1µg mL^{-1} to 50 µg mL^{-1} is within the linearity range as per the Beer-Lambert law.

A face centered central composite design was used for the design and development of amlodipine loaded orodispersive tablets by formulation parameter optimization[7-9]. The formulations obtained from the Design Expert® software were prepared. By varying the amount of camphor (0 to 37.5 mg) and thymol various formulations (0 to 37.5 mg) from F1 to F13 were prepared. Composition of formulations are amlodipine (5mg), mannitol (30mg), lactose (as a diluent and its amount varies with camphor and thymol), CCS (25mg), sodium CMC (25mg), camphor, thymol, magnesium stearate (2.5mg) and talc (2.5mg).

The total weight of the unit dosage form is 250mg. Precompression mixture was evaluated and the tablets after compression were also evaluated. The formulations were characterized for the responses wetting time and disintegration time.

The powder mixture was evaluated[8-13] for the precompression flow properties, and the results are presented in Table I. The Carr's index, angle of repose and Hausner's ratio were found to be in the range of 7.07 to 22.09, 17.7 to 29.24 and 1.03 to 1.37, respectively.

The formulations were evaluated for physical appearance (pre-and post-sublimation), disintegration time, drug content, hardness, friability, weight variation and wetting time. The disintegration time and wetting time were used as the responses in the statistical evaluation. For physical appearance, the tablets were subjected to microscopic inspection pre-and post-sublimation. Slight formation of pores, though not clear, was observed indicating sublimation process. For friability, the tablets passed the friability test with percentage weight loss < 0.5% for all the tablets. For weight variation, the results are found to be within the limits of ± 5 % as per I.P. The tablet's hardness was found to be within the limits of 2-4 kg cm^{-2}. The drug content of the formulations, disintegration time and wetting time were found to be in the range of 95.06 to 99.92%, 33 to 98 sec and 15 to 63 sec, respectively. The results of drug content, disintegration time and wetting time are presented in Table I.

The statistical analysis was performed after the input of the results obtained in characterization process into DOE software and the suggested models and fitted model and the analysis of variance (ANOVA) for the responses was done.

In this central composite design experiment, two numeric factors, camphor (X1 or A) and thymol (X2 or B), are studied at five levels ($-\alpha$, -1, 0, +1, $+\alpha$,), By using this data, for statistical optimization and fitted to linear, interactive, and quadratic models, two responses, disintegration time and wetting time, were selected. The comparative adjusted and predicted R^2 values, S.d, F and P values were calculated using the Design Expert® Software. Based on coefficient of determination R^2, for describing the data, a suitable polynomial model was selected. Disintegration time and wetting time followed quadratic model and interactive model respectively. Hence, these models were selected for further optimization. These models show higher R^2 and F-values and lower P-values. The model indicates that, it is significant that the F value of the model for response, disintegration time, was observed to be 33.72 for the oro dispersive tablets. The significance of the model and variables A, B, AB, A2 and B2 were indicated by the values of p less than 0.05 for

Table I: Precompression and post compression parameter values for all formulations

Formulation code	Pre compression parameter			Post compression parameter		
	Hausner's ratio	Angle of repose	Carr's index	Drug content (%)	Disintegration time (S)	Wetting time (S)
F1	1.22 ± 0.0361	28.22 ± 0.958	8.33 ± 0.622	97.25 ± 1.96	85 ± 2.69	27 ± 2.65
F2	1.37 ± 0.092	20.8 ± 1.06	22.09 ± 0.482	95.06 ± 0.65	87 ± 3.5	50 ± 1.60
F3	1.21 ± 0.044	22.29 ± 0.523	13.08 ± 0.400	99.92 ± 0.61	70 ± 1.32	26 ± 1.00
F4	1.20 ± 0.053	28.36 ± 0.464	13.07 ± 0.104	97.12 ± 0.63	98 ± 2.64	63 ± 1.11
F5	1.13 ± 0.046	23.26± 0.612	9.11 ± 0.806	97.09 ± 1.12	83 ± 1.93	34 ± 1.15
F6	1.15 ± 0.087	26.21 ± 0.702	16.22 ± 1.281	96.18 ± 1.14	61 ± 2.00	22 ± 1.45
F7	1.10 ± 0.096	22.29 ± 0.726	13.07 ± 0.450	95.07 ± 0.64	85 ± 1.36	29 ± 1.77
F8	1.07 ± 0.087	26.1 ± 1.509	11.42 ± 0.613	98.55 ± 0.69	51 ± 2.59	20 ± 2.67
F9	1.17 ± 0.017	17.7 ± 0.626	7.07 ± 0.898	98.77 ± 0.84	58 ± 2.78	22 ± 0.92
F10	1.08 ± 0.04	29.24 ± 0.914	12.22 ± 0.776	97.13 ± 0.57	90 ± 2.83	28 ± 1.00
F11	1.08 ± 0.036	17.74± 0.826	12.38 ± 0.919	97.25 ± 1.18	33 ± 2.78	15 ± 1.73
F12	1.03 ± 0.061	23.55 ± 0.989	15.28 ± 0.824	97.79 ± 1.06	87 ± 1.75	31 ± 1.49
F13	1.17 ± 0.020	24.22 ± 0.096	20.3± 0.986	95.46 ± 0.77	77 ± 2.17	46 ± 2.29
Values are expressed as mean ± SD (n=3)						

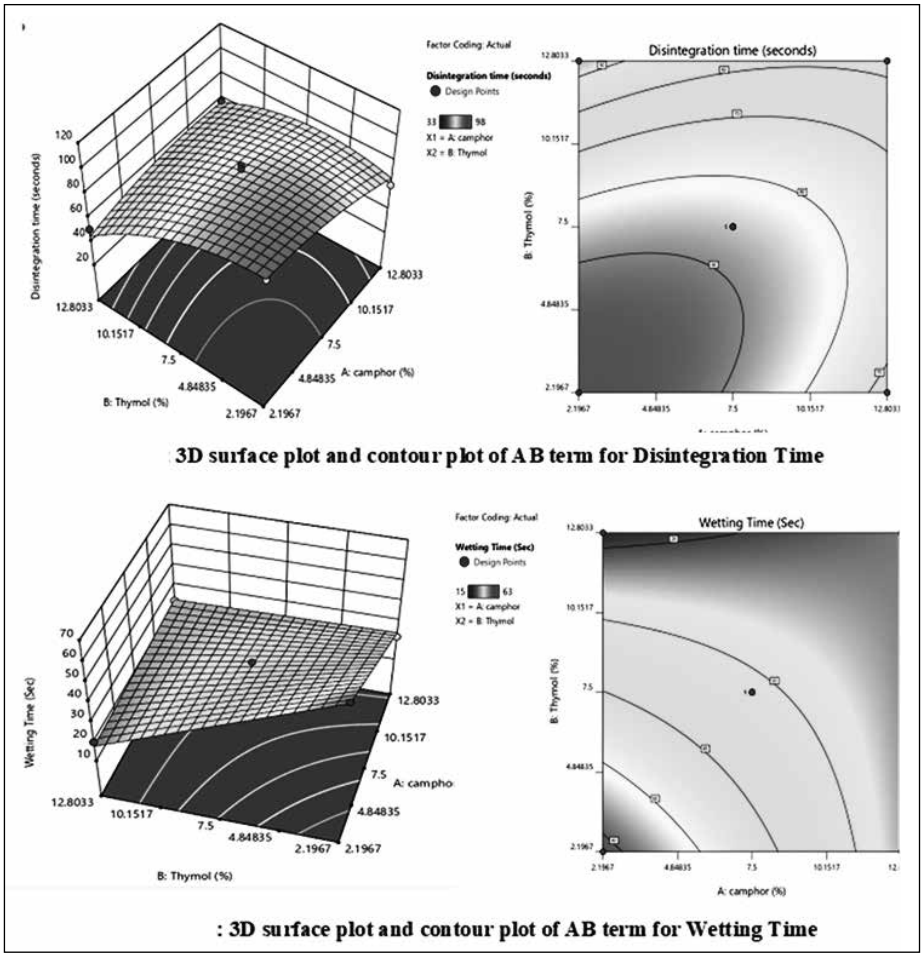

Fig. 1: 3D surface plot and contour plots

all the responses. The F value for wetting time 58.98 for orodispersive tablets indicated the significance of the models.

The regression equation final equation in terms of coded factors and the actual terms

Disintegration time (coded values) = 86 - 4.9874 * A - 15.7959 * B + 11 * AB - 6.1875 * A^2 - 12.938 * B^2.

Disintegration time (actual values) = 99.1421 - 0.573773 * Camphor + 0.988155 * Thymol + 0.391111 * Camphor * Thymol - 0.22 * $Camphor^2$ + -0.46 * $Thymol^2$

Wetting time (Coded values) = 31.7692 - 8.41053 * A - 11.5622 * B + 10.75 * AB

Wetting time (Actual values) = 81.5149 - 4.45257 * Camphor - 5.04685 * Thymol + 0.382222 * Camphor * Thymol.

From the equations, it can be analyzed that coefficient with one factor describe its effect specific factor, while those with more than one factor and those with second order terms represent the interactions between those factors and the quadratic character of the phenomena, respectively. A positive sign of the term implies that the factor has a positive (additive) effect on the reaction, whereas, a negative sign indicates the negative (antagonistic) effect on the response. Camphor, thymol, A2 and the term B2 have negative impact on the disintegration time while other terms have positive impact. The terms camphor and thymol have negative impact on wetting time while interactive term show positive impact. Plots showing the effect of variables on responses for disintegration time and wetting time were presented in Fig. 1.

The relationship between the factors and their impact in defining the responses can be studied through the contour plots and response surface plots. Here, the plots were constructed with camphor (A) and thymol (B) as factors while disintegration time (Y1) and wetting time (Y2) are the responses. With increase in the concentration of camphor and thymol, both wetting time and disintegration time decreased. It can be understood, from the perturbation plots that the term A and term B show a significant impact on responses.

In this experimental design, this optimization was done in numerical and graphical ways. The prior method involves, the selection of the desired range of constraints. Then from generated solutions, the formulation that has desirability close to or equal to 1 is selected. The second method uses desirability and overlay plots for optimization. Graphical optimization was done by desirability plot and overlay plot, with optimal values of independent variables. The higher the desirability, the more suitable is the formulation. Two formulations with predicted values of responses and having desirability of 1 were given by the software. The optimized percentage concentrations of factors (camphor and thymol) for preparing optimized amlodipine oro dispersive tablets were prepared based on the results of DOE. As per this, camphor (%) and

thymol (%) were 2.290 and 12.490 for OF1 and 3.593 and 12.784 for OF2, respectively. The optimized formulations were characterized by disintegration time and wetting time. Disintegration time for OF1 and OF2 was found to be 49 ±1.36 and 54 ± 2.00, respectively. Wetting time for OF1 and OF2 was found to be 20 ± 0.95 and 21 ± 1.34, respectively. The relative error was calculated to finalize the final formulation. Relative error (%) for disintegration time and wetting time was found to be -1.15 and -8.17 for OF1 and -8.73 and -9.29 for OF2, respectively. The formulation OF_1 was selected, it had lesser percentage relative error when compared to the other formulations. Comparing the observed values with predicted values, the prediction error was calculated according to the equation. Low values of relative error indicate a close agreement of experimental values with predicted values. This proved the predictability and validity of model and confirmed the effects of concentration of camphor and thymol.

CONCLUSION

Optimization of the sublimating agent and evaluating its influence on the process of oro- dispersion or oro-disintegration was the main aim of the present research. The present work focused on the development of amlodipine loaded orodispersive tablets, which serves the purpose of immediate release of model drug with large half-life due to effective disintegration in mouth. Camphor and thymol are the important excipients in the formulation of orodispersive tablets. Using Design Expert® Software, various proportions of the camphor and thymol for the preparation were decided. Amlodipine orodispersive tablets were formulated and evaluated. They were evaluated for precompression properties like Carr's index, angle of repose and Hausner's ratio. The post compression parameters were also performed of which disintegration time and wetting time were considered as responses and analyzed by Design Expert® Software. Thus, by this work, we could conclude that camphor and thymol, when used at optimum concentrations, can be used in the formulation of orodispersive tablets, the drug delivery systems for drugs with long half-life. They are potential delivery systems to improve palatability and for model drugs like amlodipine.

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Harani Avasarala[a,b]*, Rasi Nokku[a], Ratnam B. Pabbineedi[a], Mahalaxmi K. Palepu[a], Chandana S. Polimera[a], Niranjini Pragada[a] and Mahima Puliga[a]

[a] Department of Pharmaceutics, Aditya College of Pharmacy, Surampalem – 533 437, Andhra Pradesh, India

[b] Department of Pharmacy, Jawaharlal Nehru Technological University, Kakinada – 533 005, Andhra Pradesh, India

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

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