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Formulation, Design and Optimization of Orodispersible Tablets of Atenolol

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ABSTRACT: The purpose of this research was to develop orodispersible tablets of atenolol. Tablets containing atenolol, camphor, kyron-T 314, and lactose were prepared by direct compression technique. Camphor was sublimed by exposure of tablet to vacuum. The tablets were evaluated for percentage friability, wetting time, and disintegration time. In the investigation, a 3^2 full factorial design was used to investigate the joint influence of two formulation variables: amount of camphor and kyron-T314 (superdisintegrant). The results of multiple linear regression analysis revealed that for obtaining a rapidly disintegrating dosage form, tablets should be prepared using an optimum concentration of camphor and a higher percentage of kyron-T 314. A Response Surface Plot is presented graphically to represent the effect of the independent variables on the disintegration time and percentage friability. A checkpoint batch was also prepared to prove the validity of the evolved mathematical model. The systematic formulation approach helped in understanding the effect of formulation processing variables.

KEYWORDS: Orodispersible Tablet, 3^2 Full Factorial Design, Atenolol, Kyron-T 314, Camphor, Response Surface Methodology.

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed innovative drug delivery systems known as orally disintegrating tablets (ODTs). These are novel types of tablets disintegrate/dissolve/disperse in saliva. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market (1,2).

The basic approach used in the development of the ODTs is the use of superdisintegrants. Another approach used in developing ODTs is maximizing pore structure of the tablets. Freeze-drying (3,4) and vacuum-drying (5,6) techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and it yields a fragile and hygroscopic product. Therefore, it was decided to adopt the vacuum-drying technique in the present investigation. Vacuum drying was adopted after addition of a subliming agent to increase porosity of the tablets. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly.

Atenolol, a β1-blocker, is prescribed widely in diverse cardiovascular diseases, eg, hypertension, angina pectoris, arrhythmias, and myocardial infarction. The drug is also frequently indicated in the prophylactic treatment of migraine (7). Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor site (8,9).

An attempt was made in the present investigation to prepare ODTs of atenolol using superdisintegrant and sublimable materials.

MATERIALS

Atenolol was obtained from Yarrow chem (Mumbai), Kyron T-314 was obtained as gift sample from Corel Pharmaceutical, Ahmedabad. Croscarmellose was gifted from Zydus Cadila Health care Ltd. (Ahmedabad). Sodium starch glycolate, camphor, menthol, magnesium stearate, talc, sodium saccharin and lactose were purchased from Shraddha chemicals (Vadodara).

PREPARATION OF ATENOLOL TABLETS

Atenolol, lactose, camphor and sodium saccharin were triturated in a glass mortar and passed through # 60 sieve. Kyron T-314 was incorporated in the powder mixture and finally magnesium stearate and talc were added as lubricant. This uniformly mixed blend was compressed in to tablets containing 50 mg drug using 10 mm flat face surface punches on a Rimek-I rotary tablet machine (Karnavati Eng. Pvt. Ltd, Ahmedabad) by direct compression method. Total weight of tablet was kept 300 mg. After compression sublimation was performed at 60□C in selected batches for 24 hours. The composition of various tablet batches and the factorial design batches are as shown in Table – 1 & 2 respectively.

EVALUATION OF TABLET PROPERTIES

Hardness Determination : The crushing strength of the tablets was measured using a Monsanto hardness tester.

Friability : The friability of a sample of whole tablet corresponding to about 6.5 gm. was measured using a Roche Friabilator**.** Preweighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fines & dusts from it. The percentage of weight loss was calculated (10).

Wetting time : The wetting time of the tablets (n=5) was measured using a simple procedure. Five circular tissue papers were placed in a petri dish which covered the entire surface area of petri dish. 10 ml of water at 37□ ± 0.5□C, containing eosin, a water-soluble dye, was added to the petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time (11).

Disintegration time : Disintegration time was measured using a modified disintegration method (n = 5). For this purpose, a petri dish was filled with 10 ml of water at 37□ ± 0.5□C. The tablet was carefully put in the center of the petri dish and the time for the tablet to completely disintegrate into fine particles was noted (11).

Full Factorial Design

A 3^2 randomized full factorial design was used in the present study. In this design two factors are evaluated, each at three levels, and experimental trials are performed at all nine possible combinations (12,13). The amount of superdisintegrant, Kyron T-314 (X_1) and the amount of subliming agent, camphor (X_2) was selected as independent variables. The disintegration time (DT) and percentage friability (% F) were selected as dependent variables.

RESULTS AND DISCUSSION

Water insoluble diluents such as microcrystalline cellulose and dicalcium phosphate were omitted from the study as they are expected to cause an unacceptable feeling of grittiness in the mouth. Among the soluble diluents, lactose was selected as a model soluble diluent considering its advantages in terms of easy availability, cost-effectiveness, and relative moisture insensitivity (14).

The preliminary trials were conducted by using 2% superdisintegrants (croscarmellose sodium, sodium starch glycolate, and Kyron T-314). Three batches were prepared using a single superdisintegrant. On the basis of the results obtained in the preliminary screening studies, the batch containing Kyron T-314 showed the fastest disintegration. Hence, it was selected for further studies.

The crushing strength of the tablets was adjusted to 4 kilopond (kp). Subliming agents such as menthol and camphor were used to increase porosity of the tablets in the preliminary tablet formulations. Camphor-containing tablets exhibited faster disintegration as compared with tablets containing menthol. Hence, it was selected for further studies. Tablet formulation and the results of preliminary batches are shown in table 3 and 4 respectively.

The porous structure is responsible for faster water uptake; hence it facilitates wicking action of Kyron T-314 in bringing about faster disintegration.

The use of a sublimation agent resulted in increased friability probably due to increased porosity. The results of preliminary batches reveal that sublimation of camphor from tablets resulted in faster disintegration. The compaction process might have caused breakage of porous packing and subsequent reduction in porosity. The tablets required about 20 hours of drying. The longer drying time was required in the tablets probably because of the decreased surface area and porosity. In order to investigate the factors systematically, a factorial design was employed in the present investigation.

Factorial Design

The amount of superdisintegrant (Kyron T-314, X_1) and subliming agent (camphor, X_2) were chosen as independent variables in a 3^2 full factorial design. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses (15).

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (1)$$

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 factor X_1. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity.

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis using Microsoft Excel. The results depicted in Table 5 clearly indicate that all the dependent variables are strongly

dependent on the selected independent variables, as shown by the wide variation among the 9 batches (F_1-F_9). The fitted equations (full and reduced) relating the responses disintegration time and percentage friability to the transformed factor are shown in Table- 5. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (ie, positive or negative). Table 6 shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors.

The high values of correlation coefficient for disintegration time and percentage friability (Table 6) indicate a good fit i.e. good agreement between the dependent and independent variables. The significance test for regression coefficients was performed by applying the Student *t* test. A coefficient is significant if the calculated *t* value is greater than the critical value of *t*.

Full and Reduced Model for Disintegration Time

The significance level of coefficient b_{22} was found to be $P = 0.4883$, hence it was omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 5. The coefficients b_1, b_2, b_{11}, and b_{12} were found to be significant at $P < 0.05$, hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficient b_{22} contributes significant information for the prediction of disintegration time or not (16). The results for testing the model in portions are shown in Table 6. The critical value of *F* for $\alpha = 0.05$ is equal to 10.13 (df = 1, 3). Since the calculated value ($F = 0.2280$) is less than the critical value ($F = 10.13$), it may be concluded that the interaction term b_{22} does not contribute significantly to the prediction of disintegration time and therefore can be omitted from the full model.

The results of multiple linear regression analysis (reduced model) reveal that, on increasing the concentration of either Kyron T-314 or camphor, a decrease in disintegration time is observed; both the coefficients b1 and b2 bear a negative sign. When higher percentage of camphor is used, higher porosity is expected in the tablets. The water uptake and subsequent disintegration are thus facilitated. It is obvious that in the presence of higher percentage of superdisintegrant Kyron T-314, wicking is facilitated. The fitted equation used for full and reduced model relating the response was $Y_{DT} = 74 - 41.33X_1 - 10.167\ X_2 - 6\ X_1X_1 + 0.5\ X_2X_2 + 1.75\ X_1X_2$ and $Y_{DT} = 74 - 41.33X_1 - 10.167\ X_2 - 6\ X_1X_1 + 1.75\ X_1X_2$, respectively.

Full and Reduced Model for Percentage Friability

The significance level of coefficients b_{11}, b_{22}, and b_{12} were found to be $P = 0.1821$, 0.6799 and 0.7250 respectively, hence they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 5. The coefficients b_1 and b_2 were found to be significant at $P < 0.05$, hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_{11}, b_{22}, and b_{12} contribute significant information for the prediction of % friabilility or not (16).

The results for testing the model in portions are depicted in Table 6. The critical value of *F* for $\alpha = 0.05$ is equal to 9.28 (df = 3, 3). Since the calculated value ($F = 1.5467$) is less than the critical value ($F = 9.28$), it may be concluded that the interaction term and polynomial terms do not contribute significantly to the prediction of friability.

Hence, conclusions can be drawn considering the magnitude of the coefficient and the mathematical sign (positive or negative) it carries.

An increase in the concentration of camphor leads to an increase in friability because the coefficient b_1 bears a positive sign. When a higher percentage of camphor is used, more porous tablets are produced, which are mechanically weak. The increase in the concentration of kyron T-314 also results in increased friability values. The fitted equation used for full and reduced model relating the response was $Y_{\%F} = 0.4255 + 0.1517X_1 + 0.0583X_2 + 0.0317X_1X_1 - 0.0083X_2X_2 + 0.005X_1X_2$ and $Y_{\%F} = 0.4411 + 0.1517X_1 + 0.0583X_2$, respectively.

Fig. 1 & 2 show response surface plot for DT and % F respectively. The plots were drawn using Sigma Plot 10.0 software. The plots demonstrate that the both X_1 & X_2 affect the DT and % F. It was arbitrarily decided to select a batch of tablets that disintegrate in less than 70 seconds. Batches F6 (0,1), F7 (1,-1), F8 (1,0), F9 (1,1) fall in acceptable criteria. The final selection is done after considering ease of manufacturing, cost, etc. In industry, the total time required for manufacturing a dosage form is of prime concern. When the variable X_2 goes beyond "0" level (5%), drying time for complete sublimation increases (5%: 5 hours; 10%: 20 hours). A checkpoint batch F10 was prepared at $X_1 = 0.3$ level and $X_2 = 0.8$. From the reduced model, it is expected that the friability value of the checkpoint batch should be 0.53% and the value of disintegration time should be 53 seconds. Table 2 indicates that the results are as expected. Thus, we can conclude that the statistical model is valid.

CONCLUSION

The results of a 3^2 full factorial design revealed that the amount of Kyron T-314 and camphor significantly affect the dependent variables, disintegration time, and percentage friability. It is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts. Sublimation technique would be an effective alternative approach compared with the use of more expensive adjuvants in the formulation of Orodispersible tablets.

Table - 1: Tablet formulation

Formulation Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Atenolol	50	50	50	50	50	50	50	50	50
Sodium saccharin	6	6	6	6	6	6	6	6	6
Kyron T-314	1.5	1.5	1.5	3	3	3	4.5	4.5	4.5
Camphor	0	15	30	0	15	30	0	15	30
Talc	3	3	3	3	3	3	3	3	3
Magnesium stearate	6	6	6	6	6	6	6	6	6
Lactose (q.s. to)	300	300	300	300	300	300	300	300	300

Table – 2 : 3^2 Full Factorial Design Layout

Batch code	X_1 (mg)	X_2 (mg)	DT ± SD	% friability ± SD
F_1	-1	-1	122 ± 3.36	0.26 ± 0.021
F_2	-1	0	109 ± 4.03	0.28 ± 0.026
F_3	-1	1	98 ± 2.73	0.36 ± 0.02
F_4	0	-1	84 ± 3.36	0.34 ± 0.026
F_5	0	0	75 ± 3.36	0.45 ± 0.025
F_6	0	1	64 ± 2.7	0.47 ± 0.03
F_7	1	-1	36 ± 3.49	0.54 ± 0.04
F_8	1	0	26 ± 3.42	0.61 ± 0.01
F_9	1	1	19 ± 1.58	0.66 ± 0.036
Check point	0.3	0.8	51 ± 2	0.49 ± 0.01

Coded Values	Actual Values	
	X_1	X_2
-1	1.5 mg (0.5 %)	0
0	3 mg (1 %)	15 mg (5 %)
1	4.5 mg (1.5 %)	30 mg (10 %)

Table 3 : Tablet formulation for preliminary batches

Formulation Ingredients (mg)	A_1	A_2	A_3	C_1	C_2
Atenolol	50	50	50	50	50
Sodium saccharin	6	6	6	6	6
Kyron T-314	6	-	-	-	-
Sodium starch glycolate	-	6	-	-	-
Cross carmalose	-	-	6	-	-
Camphor	-	-	-	45	-
Menthol	-	-	-	-	45
Talc	3	3	3	3	3
Magnesium stearate	6	6	6	6	6
Lactose (q.s. to)	300	300	300	300	300

Table 4 : Results of preliminary screening studies

Batch	DT ± SD (Seconds)	% F ± SD
A_1	42 ± 1.87	0.41 ± 0.012
A_2	76 ± 1.14	0.26 ± 0.013
A_3	65 ± 1.14	0.31 ± 0.014
C_1	68 ± 1.92	0.45 ± 0.015
C_2	76 ± 1.58	0.3 ± 0.017

Table – 5 : Summary and Results of Regression Analysis*

For Disintegration Time (DT)						
Response (DT)	**bo**	**b_1**	**b_2**	**b_{11}**	**b_{22}**	**b_{12}**
FM	74	-41.33	-10.17	-6	0.5	1.75
RM	74.33	-41.33	-10.17	-6	-	1.75
For Percentage Friability (% F)						
Response (% F)	**bo**	**b_1**	**b_2**	**b_{11}**	**b_{22}**	**b_{12}**
FM	0.4255	0.1516	0.0583	0.0316	-0.0083	0.0050
RM	0.4411	0.1516	0.0583	-	-	-

*FM indicates Full Model; and RM, Reduced Model

Table – 6 : Calculations for testing the model in portions*

For Disintegration time (DT)						
	DF	**SS**	**MS**	**F**	**R^2**	**Significance F**
Regression						
FM	5	10955.58	2191.11	2720.00	0.9998	1.112E-05
RM	4	10955.08	2738.77	3756.02	0.9997	2.125E-07
For Percentage Friability (% F)						
	DF	**SS**	**MS**	**F**	**R^2**	**Significance F**
Regression						
FM	5	0.1607	0.0321	47.937	0.9876	0.0046
RM	2	0.1584	0.0792	111.68	0.9738	1.789E-05

*DF indicates Degree of Freedom; SS, Sum of Squares; MS, Mean of Squares; F, Fischer's Ratio; R^2 Regression coefficient; FM, Full Model; RM, Reduced Model

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