WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Volume 1, Issue 1, 120-127. Research Article ISSN 2277 – 7105

FORMULATION AND STATISTICAL OPTIMIZATION OF PROPRANOLOL MATRIX TABLET

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Article Received on
28 December 2011,
Revised on 01 February 2012,
Accepted on 23 February 2012

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ABSTRACT

Matrix system are favored because of their simplicity, patient compliance etc, than traditional drug delivery(TDS) which have many drawbacks like repeated administration, fluctuation in blood concentration level etc. Developing oral sustained release matrix tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of highly water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. The steady state half lives of propranolol and its derivative are 5 and 11 hours, respectively, necessitating the administration, two or three times daily so as to maintain adequate plasma level of drug. The objective of this study was to investigate extended release formulation of a highly water-soluble drug, propranolol using a wax matrix. Natural waxes such as bees wax and carnauba wax can offer economy. The combination was used to get desired release and physical strength for tablets. Primary studies included the use of various waxes in the formulation development of sustained release formulation out of which beeswax and carnauba wax showed good results and selected for further optimization. A 3^2 full factorial design was employed for development of sustained release formulation of propranolol tablets in which the amount of beeswax and carnauba wax were taken as formulation variables (factors) for optimizing $T_{50\%}$ and release after 12 hours. A mathematical model was generated for each response parameter. Both waxes retarded T_{50} % and release after 12 h. but bees wax

showed significant influence. The optimum formulas were selected by intensive grid search method and their predicted results were found to be in close agreement with experimental findings.

Key Words: Propranolol, Matrix tablets, Factorial Design, Sustained release

Introduction

Propranolol HCL is used as an antihypertensive drug. The compound is highly water soluble which poses processing and formulation challenges to the formulation scientists[1]. The present research endeavor was directed towards the development of a sustained release dosage form of propranolol HCL in the form of tablet to be taken once daily[2]. Different waxes viz carnauba wax and bees wax tried. Waxes have properties to retard drug release from the formulation[3]. Most of the waxes are naturally available, economical and easy to obtain[4]. Matrix system are favored because of their simplicity, patient compliance etc, than traditional drug delivery(TDS) which have many drawbacks like repeated administration[5], fluctuation in blood concentration level etc. Developing oral sustained release matrix tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist[6]. Most of highly water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration[7,8].

Purpose of present work is to use waxes as granulating agent for propranolol and formulating once daily tablet using a computer-aided optimization process. 3^2 FD was employed to investigate the effect of two independent variables (factors) i.e., amount of two waxes :carnauba wax and bees waxes. Release till 12 hr. (rel12h) and time taken to release 50% of the drug (t50%) were taken as the response variables.

Material and Methods

Materials

Propranolol HCL was a gift sample from torrent Pharmaceuticals Pvt. Ltd. (Ahmedabad, India), talc powder, sodium starch and glycol were from Cosmo chem. (Pune, India), and Lactose from M/s Loba Chemie Ltd. (Mumbai, India). All other chemicals used in the study were of analytical grade.

Methods

Preparation of wax matrix tablet

The preliminary study was done by using various waxes such as compritol, precirol, carnauba wax, bees wax and Stearic acid and result was obtained. Out of which the bees wax and carnauba wax was showed satisfactory results. Wax matrix tablet was prepared by combination of the bees wax and carnauba wax. Both waxes were melted in a porcelain dish on a water bath maintained at 85ºC. The drug (propranolol) was gradually added to the molten mass with continuous stirring. After cooling, the mass was subjected to granulation by passing through a #20 sieve screen. Then granules are lubricated with lactose and talc.

Table-1 Formulation of propranolol sustained release wax matrix tablet

Ingredients	Quantity (mg)
Propranolol HCL	30
Carnauba wax	18.75-56.25
Bees wax	18.75-56.25
Talc powder	5
Lactose	q.s.

Factorial design

A 3^2 full FD was constructed where the amounts of carnauba wax (X1) and bees wax (X2) were selected as the factors. The levels of the two factors were selected on the basis of the preliminary studies carried out before implementing the experimental design. All other formulation and processing variable were kept invariant through the study.

Factors	Levels		
X1= Carnauba wax	Coded Level	Actual Level	
X2 = Beeswax		X1	X2
	-1	0.50	0.50
	0	1.00	1.00
	1	1.50	1.50

		Experiment								
Trials		1	2	3	4	5	6	7	8	9
Variables	**X1**	-1	-1	-1	0	0	0	1	1	1
	X2	-1	0	1	-1	0	1	-1	0	1

Coded Level	**-1**	**0**	**1**
X1 = Carnauba wax (mg)	18.75	37.5	56.25
X2 = Beeswax (mg)	18.75	37.5	56.25

Tablet Evaluation

All the prepared tablet formulations are evaluated for hardness, friability, weight variation and assay. Drug release studies (n=3) were conducted for all the formulation combinations using dissolution test apparatus (DA-6D USP Standard). Distilled water (900 ml) was taken as the release medium at 100rpm and 37±1ºC employing USP II paddle method (Apparatus 2).

Data analysis

Various computations for the current optimization study using RSM were carried out, employing software Design Expert Version 7 [and] MS EXCEL. The general form of the model is represented as in equation given below.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1^2 X_2 + \beta_7 X_1 X_2^2 + \beta_8 X_1^2 X_2^2$$

Where β_0 the intercept, is the arithmetic average of all quantitative outcomes of nine runs, β_1 to β_8 are the coefficient computed from the observed experimental values of Y, and X_1 and X_2 are the coded levels of the independent variable(s). The terms X_1X_2 and X^2_i (i = 1, 2) are the interaction and polynomial terms, respectively. The statistical validity of the polynomials was established on the basis of Yate's ANOVA.

Validation of optimization model

Six optimum formulations were selected by intensive search, performed over entire experimental domain, to validate the chosen experimental design and polynomial equations.

RESULTS AND DISCUSSION

Physical Evaluation

Physical evaluation of compressed matrices shows that, all the physical parameters of the compressed matrices tablets were practically within control. Tablet weights varied between 98.5 and 102.5mg and hardness between 5.1 and 5.7 kg/cm^2. The assay content of propranolol varied between 98.0 and 99.8%, and the friability ranged between 0.3 and 0.6%. Response surface plot (Figure-1 and 2) showing the influence of Carnauba wax & Bees wax on the Release 12 Hours and $T_{50\%}$ values of sustained release tablet of propranolol. Figure 3 and 4 shows the in vitro dissolution profile of sustained release formulations.

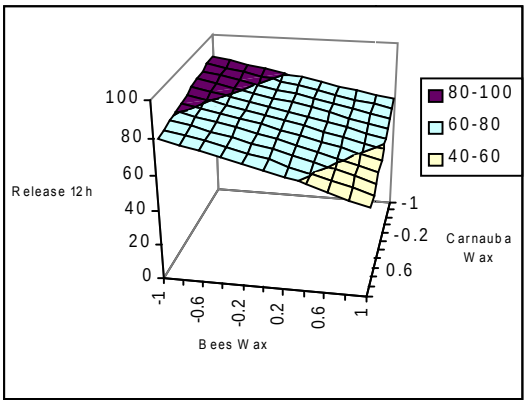

Figure 1: Influence of Carnauba wax & Bees wax on the Release 12 Hours of propranolol.

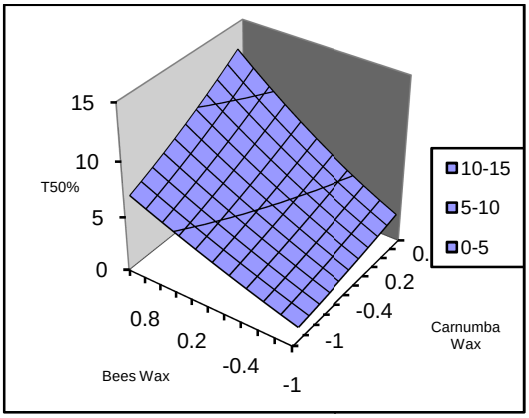

Figure 2: Influence of Carnauba wax & Bees wax on $T_{50\%}$ values of sustained release tablet of propranolol.

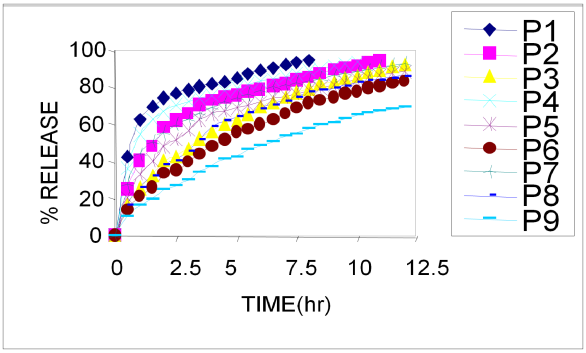

Figure 3: Dissolution profile of sustained release formulation of propranolol.

Validation of optimization model:

The mathematical relationships constructed for the studied response variables are expressed as Equation. All the polynomial equations were found to be highly statistically significant ($\rho<0.001$), as determined by ANOVA. Experimentally observed response parameter of six optimum formulation and comparison with predicted values for validation of response surface methodology were shown in Table 2.

Table 2: Experimentally observed response parameter of six optimized formulation and comparison with predicted values for validation of response surface methodology.

Formula-tion code	Formulation composition Carnauba/Beeswax	Response property	Experimental value	Predicted value	Percentage error
P1	18.75/41.71	Release 12 Hr $T_{50\%}$	77.16 4.40	76.29 4.31	1.127 0.681
P2	21.56/44.53	Release 12 Hr $T_{50\%}$	73.47 5.003	73.64 4.99	-0.231 0.259
P3	31.87/34.68	Release 12 Hr $T_{50\%}$	75.88 4.21	75.20 4.26	0.896 -1.187
P4	34.68/37.03	Release 12 Hr $T_{50\%}$	72.18 4.76	72.78 4.83	-0.831 -1.470

P5	47.81/27.65	Release 12 Hr $T_{50\%}$	74.29 4.19	74.31 4.13	-0.026 1.431
P6	52.50/29.53	Release 12 Hr $T_{50\%}$	70.42 4.80	71.64 4.87	-1.732 -1.458

Conclusion

From above study it was concluded that both waxes retarded $T_{50\%}$ and release after 12 h, but bees wax showed significant influence. It can be promisingly used to formulate sustained release tablet.

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