An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

FORMULATION DEVELOPMENT AND STATISTICAL OPTIMIZATION OF A BILAYER TABLET OF ORLISTAT

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ARTICLE INFO

Key Words
Orlistat, HPMCK100M, Sodium alginate, Design expert

Access this article online Website: https://www.jgtps.com/
Quick Response Code:

ABSTRACT

The objectives of present investigation were to achieve immediate release and sustained release of orlistat from bi-layer tablets. **Methods**: A 2^3 full factorial design was adopted using the amount of sodium alginate, HPMCK100 M and ethyl cellulose as independent variables for formulation of orlistat bi-layered tablets. **Results:** The results of analysis of variance showed that the hardness of the tablet was distinctly influenced by the formulation variables. **Conclusion:** The effect of the independent variables on hardness cannot be judged from the main effects as two-way interaction term (AC) is also significant. Grid search technique or contour plot may be used for evaluating the effect of independent variables on hardness.

INTRODUCTION

Experimental design is a concept used to organize, conduct, and interpret results of experiments in an efficient way, making sure that as much useful information as possible is obtained by performing a small number of trials. Variables which are independent if varied by chance, pharmaceutical scientists apply experimental design in their product/process development to demonstrate their knowledge of it. This knowledge of product/process is defined by so-called design space, a multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters, which have been demonstrated to provide assurance of quality. Design space is done by applying concepts of design of experiments (DoE).With the introduction of user-friendly software tools, and encouraged by regulatory guidelines and Advices, DoE is surely finding its way to becoming an everyday tool in the pharmaceutical industry. Proper organization of experiments is a foundation of every thoughtful research. The number of experiments conducted is not always a direct measurement of the amount of information gained about the problem being studied. If multiple independent factors are being varied in an unorganized manner, then it is impossible to determine what affected the outcome. If factors are varied in an unreasonable range, optimization strategies can become difficult to manage. These, among others, are some of problems that can easily be anticipated by DoE. There are many purposes of DoE application: screening studies to determine the most influential factors affecting the product/process being studied; full or

fractional designs to quantify factorial effects; in-depth response surface studies particularly useful for optimization; mixture designs, etc. The selection of a particular experimental design depends upon the nature of the problem being studied and the desired level of information to be gained. It is proposed that, in the case of pharmaceutical product development, screening designs are used at the beginning of the experimental procedure for investigation of a large numbers of factors, with the aim of revealing the most important ones. Optimization is used for finding a factor combination corresponding to an optimal response profile, and robustness testing is used as a last test before the release of a product, to ensure that it stays within the specifications [1]. The main goal of any experimental study is to find the relationships between independent variables (factors) and dependent variables (results, outcomes) within the experimental framework [2]. Even though it sounds easy to accomplish, this task can be cumbersome when it is not organized correctly. In the field of pharmaceutical technology, independent variables are usually formulation factors (ingredients amount, materials attributes, etc.) or processing parameters, whereas dependent variables are product properties or parameters indicating process performance. Experimental design is, in general, used to simultaneously study the effects of multiple independent variables (factors) on response variable(s); therefore, it is a multivariate analysis technique [3]. DoE requires definition of levels (values) of analyzed factors and often this phase uses knowledge from previous experience about the problem being studied. In the simplest screening experimental design, a relatively large number of factors can be studied in a small number of experiments. In this way, the most influential factors are identified and further examined in more detail using full factorial or response surface designs. The screening design usually varies the factors on two levels and only a few of all possible combinations of different factors on different levels are used [4]. Response surface design enables optimization of the most influential factors. In this design, factors are varied on at least three levels, and many more combinations of factors on different levels are used (in comparison to screening designs) [5]. A mixture design is used for studies where examined factors are mixture related, such as in the amounts of formulation ingredients. There is a constraint that the total sum of ingredient masses must remain the same and the factors represent a fraction of the given ingredients in the formulation [6]. Orlistat is a lipase inhibitor for obesity management that acts by inhibiting absorption of dietary fats. It has short half-life (< 2hours) and requires administration three times a day. Hence it is considered as formulation of CR and IR formulations. The half-life of Orlistat is 1-2 hours, as it has been released immediately. By using controlled release dosage form the therapeutically effective concentration can be maintained for longer time than the conventional dosage form. Bilayer tablets are preferred when the release profile of the drugs is different from one another and has to be released in an immediate and controlled manner, so that therapeutic concentration can be maintained [7]. Moreover Orlistat release should be less in stomach and further release should be increased in the intestine and completed within eight hours. Hence an attempt was made to develop a bilayer tablet comprising of Orlistat controlled release and immediate release layers [8].

MATERIALS AND METHODS

Calculation of dose for bilayered tablet [9]

The immediate release part of bilayered tablet was calculated using the following equation

$$DIR = Cp \times Vd/F$$

Where is target serum level, Vd is volume of distribution and F is bioavailability factor.

The total dose of orlistat to deliver a once daily-controlled released formulation was calculated by the following equation using available pharmacokinetic data:

$$DSR = DIR\ (1 + 0.693 \times t/t_{1/2})$$

Where DSR is a total dose of drug for sustained released layer, DIR is dose of the immediate release part; *t* is the time (hours) duration for which the sustained release of the drug is desired and $t_{1/2}$ is half-life of the drug.

Formulation of the immediate release layer

The IR layer was prepared by passing the accurately weighed drug, sodium starch glycolate and 5% PVP as a dry binder through # 40 (420 μm ASTM) as per the formulae given

in Table 1. The sieved blend was transferred to a poly bag and mixed for 5 minutes. The obtained blend was lubricated for 2 minutes with magnesium stearate and amaranth passed thorough # 60 (250 μmASTM) and # 100 (150 μm ASTM) respectively. Amaranth was added to differentiate the IR layer from the CR layer as shown in Table1.

Formulation of the controlled release layer

The CR layer was prepared by blending the drug and the controlled release polymer (sodium alginate, ethyl cellulose, HPMC K 55M) individually, uniformly along with diluent and PVP K30 as a dry binder in a ploy bag as per the formulae given in Table 2 after sifting them through # 40 (420 μm). The resulting blend was lubricated with talc and magnesium stearate passed through # 60 (250 μm).

Compression of the bilayer tablet:

Initially the die was filled with CR blend and precompressed using 16 station, single rotary tablet compression machine (Cadmach Machinery Co.Pvt. Ltd., India) equipped with 6 mm round concave punches. Upon this precompressed CR layer, weighed quantity of IR blend was transferred manually followed by compression obtaining a bilayered tablet having hardness in the range of 6-8 $kgcm^{-2}$.

Evaluation of bilayered tablets

The prepared bilayered tablets were subjected to quality control tests such as weight variation, friability test, hardness or crushing strength and disintegration time. Crushing strength of the tablets was measured using Monsanto tablet hardness tester (after 24 h of compression (time for stress relaxation). Percentage friability was measured using Roche friabilator. Twenty tablets were tumbled for 4 min at 25 rpm. The tablets were then dedusted and the loss in weight caused by fracture or abrasion was recorded. Disintegration test of six orlistat bi-layered tablets was carried out by disintegrating testing apparatus.

Weight Variation

According to Indian Pharmacopoeia (I.P.) [10], 20 tablets were selected at random, weighed together and then individually. The mean and the standard deviation were determined. Prepared tablets complies the test if not more than two of the individual weights deviate from the average weight (>250 mg) by more than the percentage (5%) and none deviate more than twice that percentage.

Friability

The friability test [11] was carried out in dual chamber friabilator (Electrolab, India). Tablets equivalent to 6.5 g were weighed (W0) initially and put in a rotating drum. Then, they were subjected to 100 falls of 6 inches height (25 rpm for four min). After completion of rotations, the tablets were dedusted by using camel hair brush and weighed (W).

Hardness

Tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing. Five tablets were randomly selected and the hardness of each tablet was measured using Monsanto hardness tester [12]. The mean hardness was determined and expressed in kg cm^{-2}.

Formulation of orlistat sustained release component using 2^3 factorial design

A 2^3 full factorial design was adopted using the amount of sodium alginate, HPMCK100 M and ethyl cellulose as independent variables for formulation of orlistat bi-layered tablets as shown in Table 3. In ANOVA, the experimental error (residual) was estimated from the interactions (two or three way). The Fisher's variance ratio (F) was compared with the tabulated value ($F_{critical}$) for grading the factor as significant or non-significant. Multiple linear regression was carried out and refined model was evolved ($p<0.05$). Further conclusions were drawn using contour plot.

RESULTS AND DISCUSSION

Evaluation of bilayered tablets:

The physical attributes of the tablet were found to be satisfactory. Typical tablet defects, such as capping, chipping, and picking, were not observed. Tablet properties like weight variation, hardness, and friability and disintegration test of each batch were evaluated.

Table 1: Formula of immediate release layer of Orlistat

Ingredients	Quantity (mg)
Orlistat	8
Sodium starch glycolate	8
Sodium saccharin	81
Magnesium stearate	1.5
Talc	1.5
Amaranth	1

Table 2: Formula of controlled release layer of Orlistat

Ingredients	F1	F2	F3	F4	F5	F6	F7
Orlistat(mg)	32	32	32	32	32	32	32
Sodium alginate(mg)	20	-	20	-	40	-	40
HPMC K100M(mg)	-	20	20	-	-	40	40
Ethyl cellulose(mg)	20	20	-	40	-	-	40
Microcrystalline cellulose(mg)	124	124	124	124	124	124	64
Magnesium stearate(mg)	2	2	2	2	2	2	2
Talc (mg)	2	2	2	2	2	2	2

Table 3: Variables and their concentrations

	Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3	Response 4
Run	A:Sodium alginate	B:HPMC K100M	C:Ethyl Cellulose	Disintegration time	Hardness	Weight Variation	Friability
				secs	Kg/cm2	mg	%
1	0	1.68179	0	1.5	4.3	290	0.75
2	0	0	0	1.9	4.2	300	0.81
3	1	-1	-1	2	4.5	305	0.52
4	1	-1	1	1.3	6.2	305	0.62
5	-1	1	1	1.6	4.3	306	0.63
6	-1	-1	1	2.4	5.7	308	0.81
7	-1	-1	-1	2.6	5.8	310	0.7
8	0	-1.68179	0	1.5	5.7	301	0.52
9	0	0	-1.68179	2.3	5.8	296	0.68
10	-1	1	-1	1.4	5.9	305	0.5
11	-1.68179	0	0	2.6	5.4	302	0.63
12	0	0	0	1.6	2.5	295	0.52
13	0	0	0	2.5	2.2	298	0.44
14	1.68179	0	0	3.3	3.6	300	0.3
15	0	0	0	1.7	2.2	300	0.29
16	0	0	0	2.6	2.2	308	0.64
17	1	1	-1	2.8	5.2	298	0.69
18	0	0	0	3.3	2.2	295	0.72
19	0	0	1.68179	2.5	5.5	303	0.63
20	1	1	1	2.8	4.6	300	0.52

Table 4: ANOVA for hardness

Source	Sum of squares	df	Mean Square	F-value	p-value	
Model	0.2009	9	0.0223	5.66	0.0061	**Significant (R^2=0.836)**
A-Sodium alginate	0.0029	1	0.0029	0.7351	0.4113	**The value is significant since R^2 is 0.836.**
B-HPMC K100M	0.0023	1	0.0023	0.5778	0.4647	
C-Ethyl Cellulose	0.0002	1	0.0002	0.0394	0.8467	
AB	0.0001	1	0.0001	0.0249	0.8779	
AC	0.0013	1	0.0013	0.3292	0.5788	
BC	0.0027	1	0.0027	0.6758	0.4302	
A^2	0.0566	1	0.0566	14.34	0.0036	
B^2	0.0755	1	0.0755	19.13	0.0014	
C^2	0.0966	1	0.0966	24.49	0.0006	

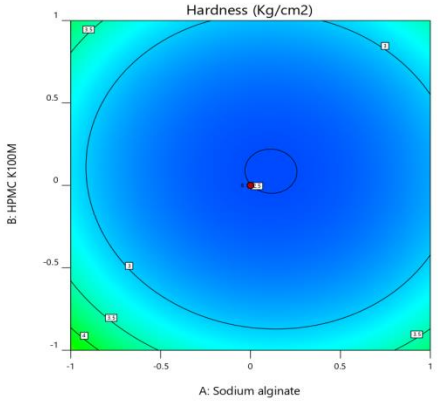

Figure 1: Response surface plots of contour plot showing the effect of sodium alginate (A) and HPMC K100M(B) on hardness

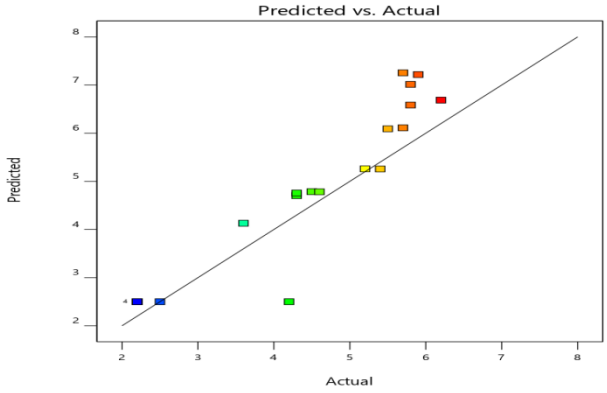

Figure 2: Response surface graph and predicted vs. actual graph for dependent response variable solubility

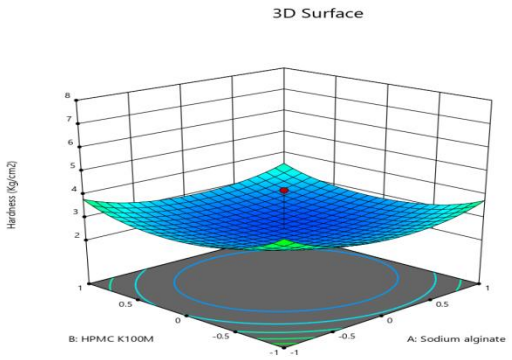

Figure 3: Contour plot for effect of independent variables on the hardness.

The average percentage of deviation of 20 tablets of each formula was less than ±5%. Friability of all batches were found less than 1% and indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed. Hardness of the tablet was found to be 2.2 to 6.2 kg/cm^2 and the disintegration time was found to be from 1.3 sec to 3.3 secs.

Factorial design:

To systematically investigate the influence of the three independent variables sodium alginate, HPMCK100 M and ethyl cellulose a 2^3 full factorial design was adopted. Table 2 represents composition and results of different batches of orlistat prepared using factorial design. The high value of independent variables was transformed to +1 and the low value to -1 to facilitate calculations. Table 2 shows that the hardness of tablet was found to be 2.2 to 6.2 kg/cm^{2}within the acceptable limits. Therefore, it can be concluded that at least one of the independent variables or interactions significantly influences hardness of the orlistat tablets. The results of ANOVA following Yates treatment, for hardness of orlistat tablets is shown in Table 4. The experimental error (residual) in ANOVA was estimated from the insignificant interactions. The mean squares relating to interactions AB, AC, BC, A^2, B^2 and C^2 were distinctly lower than the other mean squares. These interactions were combined to give residual. The results shown in Table 4 reveal that the factors sodium alginate, HPMCK100 M and ethyl cellulose and interaction between HPMCK100 M and sodium alginate are significant at $p<0.05$. The main effects A, B and C and the interaction term AB, AC, BC were retained in the model, as they were statistically significant by the following polynomial equation

Hardness=0.2009+0.0029*A+0.0023*B+0.0002*C+0.0001*AB+0.0031*AC+0.0027*BC+0.0566 A^2+0.0755 B^2+0.0966C^2. (R^2=0.836)

The effect of the independent variables on hardness cannot be judged from the main effects as two-way interaction term (AC) is also significant. Grid search technique or contour plot may be used for evaluating the effect of independent variables on hardness. In the present study, contour plot was utilized. The results of analysis of variance (ANOVA) for weight variation and disintegration time of orlistat tablets reveal that none of the factors are significant at 5% and hence multiple linear regression analysis was not carried out.

The **Model F-value** of 5.66 implies the model is significant. There is only a 0.61% chance that an F-value this large could occur due to noise. **P-values** less than 0.0500 indicate model terms are significant. In this case A^2, B^2, C^2 are significant model terms. R^2values indicate a high level of correlation between experimental and predicted responses. The closeness of the adjusted and predicted R^2 values explains the reliability of the model. The adequate precision value of greater than 4 indicates that the model is discriminating. Since coefficient of variation CV is less than 10 the model can be considered reproducible. Response surface plots allow for visual observation of significance of the regression equations by graphically depicting maxima and minima. These equations showing the influence of the independent variables on the dependent variables in the form of response surface plots (Figure 1 to Figure 3).

CONCLUSION

A bilayer tablet of orlistat containing sustained release layer and immediate release layer were successfully formulated. The above study demonstrates the use of a factorial design approach in an optimisation of bilayer tablet dosage form of orlistat. The statistical tool design expert trial version 11 was used to predict the interaction between the independent variables sodium alginate, HPMCK100 M and ethyl cellulose and dependent variables disintegration time, hardness, weight variation and friability.

Acknowledgement: The authors are thankful to Dr. Lavu Rathaiah, Chairman, Vignan group of institutions, for providing necessary facilities to carry out research work.

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