FACTORIAL DESIGN USED IN OPTIMIZATION IMMEDIATE RELEASE SOLID DOSAGE RANITIDINE HYDROCHLORIC.

A utilização da análise fatorial na otimização da liberação imediata do Hidrocloreto de Ranitidina.

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Abstract

The aims of this study were to develop a predictive immediate release tablet formulation system for soluble drugs. Ranitidine hydrochloride, silicifiedmicrocrystallinecellulose (SMCC), polyplasdone XL and hydroxyprophylmethylcellulose (HPMC) E6 were evaluated for powder properties. The effects of binder (HPMC E6) and disintegrant (Polyplasdone XL) were investigated. A 3^2 factorial design was applied to optimize the drug release profile. The amount of binder and disintegrant were selected as independent variables. The times required for 50% (t50) and 80% (t80) drug dissolution and similarity factor (f_2) were chosen as dependent variables. The results of factorial design indicated that a high amount of binder and low amount of disintegrate favored the preparation of drug release. The difference (f_1) and similarity (f_2) factors were used to measure the relative error and the closeness (similarity) between the factorial design batches and brand name drugs. No significant difference was observed between the brand drug and ranitidine batches F1, F2, F5, F6 and F9. Ranitidine batch F2 yielded the highest value of f_2 (71%) and the lowest of f_1 (10%). This research indicates that the proper amount of binder and disintegrant can produce drug dissolution profiles comparable to their brands.

Keywords: Factorial Design; Immediate Release; Ranitidine Hydrochloride.

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Resumo

O propósito deste estudo foi desenvolver uma formulação de um comprimido com liberação imediata do medicamento Hidrocloreto de ranitidina, celulosemicrocristalina silicificada (SMCC), poliplasdona XL e hidroxipropilmetilcelulose (HPMC) E6 foram avaliados em relação a propriedades físicas dos pós. Os efeitos do ligante (HPMC E6) e do desintegrante (poliplasdona XL) foram investigados. Um desenho fatorial de 3^2 foi usado para otimizar o perfil da liberação do medicamento. A quantidade de ligante e do desintegrante foram selecionados como variáveis independentes. Os tempos requeridos para 50% (t50) e 80% (t80) da dissolução do medicamento e similaridade (f_2) foi escolhida como variáveis dependentes. Os resultados do projeto fatorial indicaram que uma quantidade elevada de ligante e uma quantidade baixa de desintegrante favoreceram a preparação da liberação do medicamento. Os fatores da diferença (f_1) e da similaridade (f_2) foram usados para medir o erro relativo e de aproximação (similaridade) entre as formulações do projeto fatorial e a medicação de marca. Nenhuma diferença significativa foi observada entre a droga do tipo e as formulações F1 de ranitidine, F2, F5, F6 e F9. A formulação de F2 de ranitidine forneceu um valor mais elevado de f_2 (71%) e do mais baixo de f_1 (10%). Os resultados indicam que a quantidade apropriada de ligante e de desintegrante pode fornecer perfis de dissolução da droga comparáveis aos medicamentos de marca.

Palavras-chave: Análise factorial; Liberação imediata; Hidrocloreto de ranitidina.

Introduction

The majority of the pharmaceutical companies use the expression “state of the art” referent a drug design. However, the design of a drug is a science. Experimental design is a planned structure interference in the natural order of events. Its strength lies in the fact that much of the substantial gain in knowledge in all sciences has come from actively or deliberately manipulating or interfering with the stream of events. A physical model must be constructed and in the basis of either empirical data or experimental values. Various mathematical formulas are investigated with the objective of obtaining a most suitable formula which will form the basis of linking the variables of the process. The formulas include dissolution profiles of all batches, which can be fitted to zero order, first order (1-2), Higuchi , Hixson Crowell, Korsemeyer and Peppas , and Weibull models to ascertain the kinetic modeling of drug release.

The aims of this study were to develop a predictive immediate release tablet formulation for soluble drugs. In this experiment, ranitidine hydrochloride was chosen as an active product due to its highly soluble in water and its low permeability (3). In order to obtain the most favorable ranitidine tablet formulation, the effect of binder and disintegrant levels were examined which may interact with each other in an experiment and have an effect on responses (t50 and t80).

Several designs are available; however, factorial design is a major interest. Factorial design has been used to establish the extent of the main effects and the extent and significance or non significance of interaction effects. Two factors (binder and disintegrant) were selected at 3 levels, low, medium, and high. In the case, there are 2 factors at 3 levels each; therefore, 3^2 experiments are required.

Material and Methods

Materials

All materials used in this experiment were obtained from TIPT. The powders were analyzed for its physical properties. Different tablets formulations were placed into 9 batches (F1 – F9) with different levels of binder and disintegrant (Table 1). The tablets contain 150 mg of ranitidine hydrochloride. HPMC-E6 and Polyplasdone XL were used as binder and disintegrant respectively. Azantac tablets, Reg. No. 12483SSR, Glaxowelkomme 532437 021437 were provided as reference tablet.

Table 1 - Composition (in %) of tablets matrices.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ranitidine Hydrochloride	40.0	40.0	40.0	40.0	40.0	40.0	40.0	40.0	40.0
SMCC	56.8	52.8	52.8	48.8	54.8	50.8	54.8	50.8	52.8
HPMC-E6	1.0	5.0	1.0	5.0	1.0	5.0	3.0	3.0	3.0
Polyplasdone XL	2.0	2.0	6.0	6.0	4.0	4.0	2.0	6.0	4.0
Magnesium Stearate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Methods

Dissolution Study

Dissolution study was carried out in Dissolution Vankel apparatus (4) and USP apparatus II (paddle) at a rotational speed of 50 rpm at 37^0 C in distilled water at pH 6.8. Samples were withdrawn at time intervals of 1, 2, 3, 5, 10, 15, 20, 25, 35, 45, 55 minutes and accelerated at the end for 10 minutes at 200 rpm. Absorbances of the samples were determined at UV 315 nm using UV-Visible detector (5). The average values and the percentage drug released of t50 and t80 were obtained from the plot of drug release versus time.

Factorial Design

Two independent variables are HPMC-E6 as binder and Polyplasdone XL as disintegrant. The three percentage levels of each variable were determined to develop tablet matrix. The levels were set as low, medium, and high. Then a 3^2 factorial design was constructed to study the effect of binder and disintegrant levels. t50 and t80 were selected as dependent variables.

A statistical model incorporating interactive and polynomial terms was developed to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{1.2} X_1 X_2 + b_{1.1} X_1^2 + b_{2.2} X_2^2$$

where:

y is dependent variable

b_0 is the arithmetic mean response of the 9 runs

b_1 is the estimated coefficient for the factor X_1

X_1 X_2 is the main effects represent the average result of changing one factor at a time from its low to high value. The interaction terms X_1 X_2 demonstrate how the response changes when 2 factors are changed simultaneously.

X_1^2 X_2^2 is used to investigate nonlinearity (6).

The statistical analysis of the factorial design was performed using 2 Stages Least Squares Regression using SYSTAT 11 (SYSTAT, Software Inc).

Comparison with Reference Tablet

The model independent acknowledged as statistical approach used is fit factor technique. FDA (7) recommends that mathematical models used to compare dissolution profile between two products are

difference factor (f_1) and similarity factor (f_2). The methods were reported by Moore and Flanner (8). f_1 was calculated to measure the relative error formula and to estimate the percentage error between the test and the reference mean dissolution profiles (9), where the standard values are 0-15. Dissolution profiles of control and samples would be considered similar when f_2 is larger than 50.

The difference factor,

$$f_1 = \{ \frac{\sum | Rt - Tt |}{\sum Rt} \} \times 100$$

The similarity factor,

$$f_2 = 50 \times \text{Log} \{ [1 + 1/n \sum (Rt - Tt)^2]^{-0.5} \times 100 \}$$

where:

Rt = % dissolution at time t of the reference batch

Tt = % dissolution at time point t of the test batch

| Rt – Tt | = modulus value

n = number of sample points

∑ = summation over all time points

f_1 is defined as the percent difference between two dissolution curves at each time point and is a measure of the relative error between the curves. On the other hand, f_2 is defined as the logarithmic reciprocal square root transformation of the sum of squared error and is a measure of the similarity in the percent dissolution between the two curves.

Content Uniformity and Friability Test

Tablets content uniformity and friability were tested to confirm their roles for the similarity of the dissolution profiles. 10 tablets for each batch were dissolved to confirm whether the dissolution amounts were within the acceptable standards. After 10 tablets were crushed, the exact weight of the powder was measured and transferred to volumetric flask 200 ml and then was filled to the mark with water. Then, after stirring for 30 minutes, 2 ml of dissolution was filtered and 1 ml dissolution was diluted into 10 ml of water to be analyzed spectrophotometrically using Beckman Coulter DU 800 UV/Visible Spectrophotometer. All tablets should be within 85 – 115% of label claim and standard deviation is less than 6% to meet the requirement (10).

Tablets friability was determined by weighing 10 tablets. After dusting, then placing them on the Roche-type friabilimeter and rotating the basket vertically at 25 rpm for 4 minutes (100 drops). Then, the total remaining weight of the tablets was recorded to calculate the friability percentage (11).

$$\text{Friability} = \frac{(\text{weight final} - \text{weight original})}{\text{weight original}} \times 100$$

Results and Discussion

Tablet Formulation and Dissolution Profiles

Tablet matrix was developed based on ratio 40% of active product ingredient (API) Ranitidine. This formula was judged to be the best formula since it provided the greater amount plasticity, excellent hardness compact and better flowability. Then, the levels of binder and disintegrant used were determined on the basis of the selected ratio. Trial tests were done at low levels and high levels composition of binder:disintegrant at 1%:2% and 5%:6% respectively. Since the results of both concentrations fell within the predetermined specification, therefore, the application of binder and disintegrant levels were justified to be within 1-5% and 2-6% respectively as shown in Table 1. t50 and t80 were derived from the plot of cumulative percentage of amount dissolved at time sampling points. As demonstrated in Table 2, t50 falls within 6.2 and 23.0 minutes where t80 are ranging from 15.5 and 35.2 minutes. Batches F1, F2, and F9 show similar values with the reference tablet, however, F2 formed the closest values to the reference tablet.

Table 2 - Responses of factorial design for the drug combination study

Formulation	Independent variables		Dependent variables (responses)	
	Binder (X_1)	Disintegrant (X_2)	t50 (min)	t80 (min)
F1	-1	-1	17.0	34.0
F2	+1	-1	16.0	23.7
F3	-1	+1	11.8	22.9
F4	+1	+1	6.2	23.0
F5	-1	0	13.5	35.2
F6	+1	0	12.5	20.2
F7	0	-1	23.0	41.8
F8	0	+1	9.5	15.5
F9	0	0	18.6	31.0
Reference tablet			16.2	27.5

A 3^2 factorial design constructed as shown in Table 2. Low levels are set as -1, medium levels are set as 0, and high levels are set as 1. From the output of statistical analysis through 2 Stages Least Squares Regression, SYSTAT 11, the fitted equations were obtained as follows:

$T50 = 17.667 – 4.750X_2$ $R^2=0.922$

Dependent variable: T50
N: 9, mean of dependent variable: 14.233333
R-squared: 0.922583
Adjusted R-squared: 0.793555, uncentered R-squared (R0-squared): 0.992241

Parameter	Estimate	S.E.	t-ratio	p-value
1 CONSTANT	17.667	1.706	10.353	0.002
2 BIN	-1.267	0.935	-1.355	0.268
3 DIS	-4.750	0.935	-5.082	0.015
4 BIN*BIN	-4.200	1.619	-2.594	0.081
5 DIS*DIS	-0.950	1.619	-0.587	0.599
6 BIN*DIS	-1.150	1.145	-1.005	0.389

The linear regression with coefficient $R^2 \geq 0.90$ is acceptable. The value indicates there are effects on the responses. 95% confidence level, $p \leq 0.05$ suggests the terms of significance. The results of statistical analysis show that the p values of constant and X_2 (DIS) are significant (0.002 and 0.015 respectively). However, the p value of X_1 (BIN) is not significant (0.268). In addition, p value of X_1X_2 (BIN*DIS) also shows no significance (0.389). Consequently, the linear regression confirms that only the main effect (disintegrant) is significant and there is no significance interaction of binder and disintegrant at t50. Since R^2 of t80 and f_2 are lower than 0.90, therefore, they are not acceptable.

Comparison with Reference Tablet

The difference factor (f_1) and the similarity factor (f_2) results from each formula are described in Table 3. f_1 is a proportional to the average difference between the two profiles. It measures the percentage error between the reference and sample mean dissolution profiles. The results in Table 3 illustrates that batches 1, 2, 5, 6 and 9 provide the acceptable percentage errors according to FDA standard. The acceptable errors are between 0 – 15 (12). Batch 2 produced the lowest error at 10%.

Table 3 - Fit factors test of predictive formulations

Batch	f_1	f_2	Similarity
F1	13	66	Yes
F2	10	71	Yes
F3	17	49	No
F4	28	36	No
F5	15	51	Yes
F6	15	51	Yes
F7	22	44	No
F8	20	39	No
F9	12	62	Yes

FDA recommends that f_2 comparison of dissolution profiles of samples and reference to investigate the profile similarity. The dissolution measurements of the two products test and reference were made under the same test conditions. The dissolution time points for both the profiles were the same at 1, 2, 3, 5, 10, 15, 20, 25, 35, 45, and 55 minutes. Since the value of f_2 are sensitive to the number of dissolution time points, therefore, only one measurement should be considered after 85% dissolution is achieved for f_2 calculation. FDA regulation states that dissolution profiles are considered to be similar when f_2 result is 50 – 100. As we show in Table 3, dissolution profiles batches 1, 2, 5, 6 and 9 fulfill the criteria set by FDA. Batch 2 produced the highest value of f_2, 70%. Figure 1 depicts the similarity between the reference and the sample tablets, whereas Figure 2 shows the dissolution profiles of tablets that are not within the acceptable range.

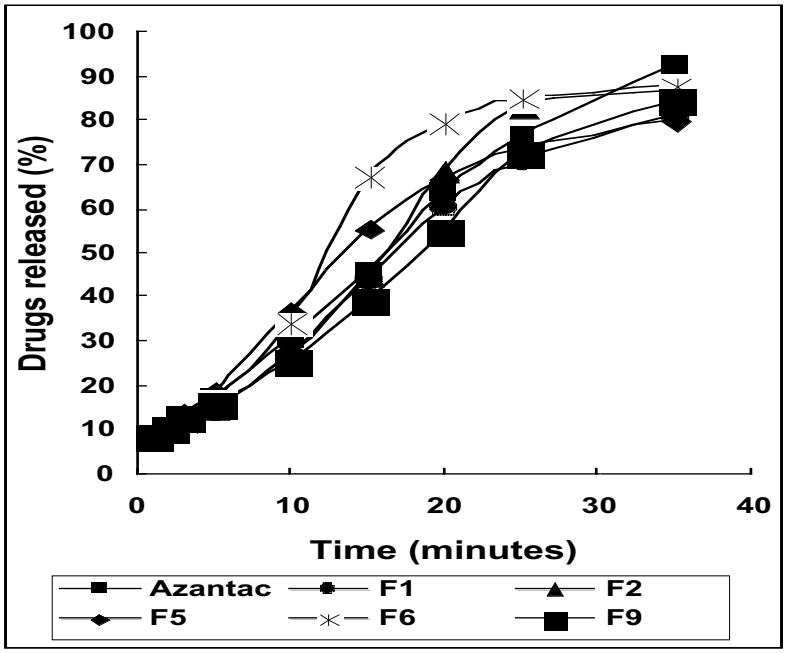

Figure 1 – Comparative observed and predicted dissolution profiles for check points which produced f_2 higher than 50.

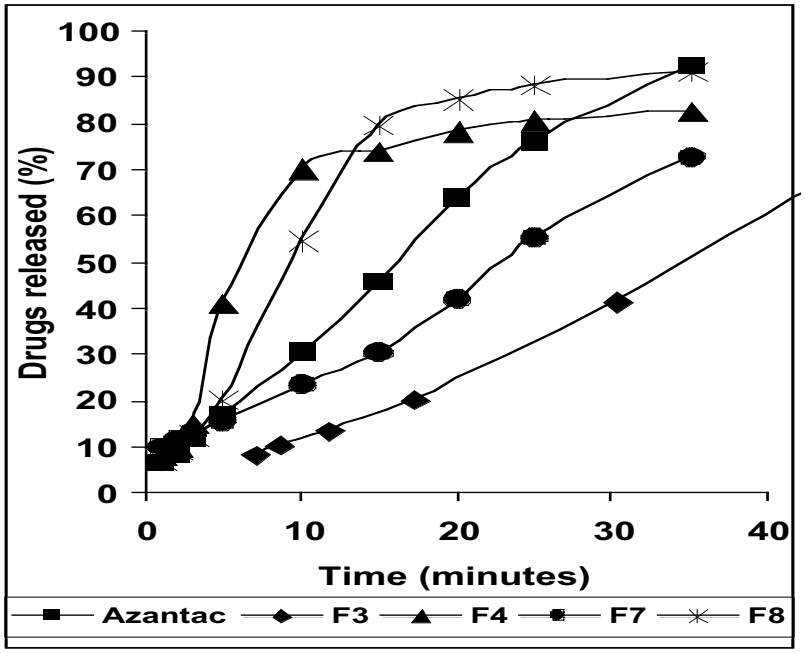

Figure 2 - Comparative observed and predicted dissolution profiles for check points which produced f2 lower than 50.

Content Uniformity and Friability Test

Table 4 demonstrates the results of content uniformity and friability test. The results from the tests lead to the conclusion that tablets content uniformity met the requirement. The friability test also revealed good results; where all batches weight loss is less than 1%.

Table 4 - Summary of content of uniformity and friability test

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Content of uniformity (mg)	140.91	145.12	142.68	138.79	142.62	145.82	140.56	149.33	149.76
Content of uniformity (%)	93.94	96.75	95.12	92.53	95.08	97.21	93.71	99.55	99.84
Friability test – weight loss (%)	0.01	0.01	0.08	0.09	0.78	0.76	0.79	0.80	0.85

Conclusion

A factorial experiment is an experiment consisting of combinations of all factors at all selected levels. The purpose is to derive the nature of a relationship between independent factors and dependent variables. High order interactions are possible in that one factor may depend on the presence or absence of two other factors, termed a second-order interaction. The study of 3^2 factorial designs represented that batch F2 provided the closest similarity to the reference drug, though, only amount of disintegrant which has significant effect to the profile. Since uniformity and friability test were also perfect, therefore, this could be caused by the influence of formulation or manufacturing techniques.

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Recebido em / *Received:* December 7, 2005.
Revisado em / *Revised:* January 31, 2006.
Aceito em / *Accepted:* February 15, 2006.