ISSN: 2321-5674(Print)
ISSN: 2320 – 3471(Online)

OPTIMIZATION OF THIOCOLCHICOSIDE TABLET WITH PERMEATION ENHANCERS USING 3^2 FACTORIAL DESIGN

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ABSTRACT

Thiocolchicoside has a selective affinity for g-amino-butyric acid (GABA) receptors and acts on the muscular contracture by activating the GABA-nergic inhibitory pathways thereby acting as a potent muscle relaxant Thiocolchicoside (Muscoril, Myoril, Neoflax) is a muscle relaxant with anti-inflammatory and analgesic effects. It is used for the treatment of orthopedic, traumatic and rheumatologic disorders. It is currently administered by the oral, injective and topical routes. The physico-chemical properties of Thiocolchicoside are not favorable for its permeation across the skin. Thiocolchicoside has a relatively high molecular weight (563), relatively high water solubility (16.1mg/ml) and low octanol/water partition coefficient (logP=-0.34). The various Permeation enhancers were used in different ratio and its permeation enhancement is done by using Franz diffusion cell. The Data Expert software is applied for the 3^2 factorial design and the ANOVA study of the linear regression model, response surface plot as well as contour plot confirms the predicted batch with the desirability of 0.982. Result of R^2 and T-test confirmed that predicted and observed responses showed no significant difference. The optimized batch was found to be B_2 showing disintegrating agent 40 mg and binder 2.5 mg quantity with the best response.

Key words: Optimisation, Full factorial design, Contour plots, Thiocolchicoside.

INTRODUCTION

Oral administration still dominates drug therapy and more than 60 % of marketed drugs are oral products. This type of drug administration is preferred due to its convenience, high patient compliance, less stringent production conditions and lower costs. Delivering a drug by oral route is also preferred for its convenience. Tablets and capsules can be prepared in large quantity at low price (Kumar, 2011). Therefore in lead optimization step of drug discovery, oral bioavailability of a drug is important. It depends on various factors the most common being intestinal permeability, solubility during gastrointestinal transit, liberation from dosage form, liability to efflux and metabolism. Development in the field of combinatorial chemistry and high throughput screening has made it possible to generate a large number of drug candidates but it has also resulted in a number of poorly soluble and or poorly absorbable drugs. A new trend of drug development based on pharmacogenomics or development of molecular targeted drugs is also encouraging the tendency, and it does not necessarily lead to good output in terms of new drug development. Therefore it is necessary to improve the membrane permeability as well. The pharmacokinetic profile of a drug is dependent on the drugs ability to cross biological membranes. All drugs are now classified according to the biopharmaceutical classification BCS into four categories on the basis of solubility and permeability to rationalize science of drug delivery and simplify complications in the drug registration of newly evolving diverse compounds for regulatory authorities. Among the different classes of BCS the per oral delivery of class 3 and 4 drugs is partially or completely decreased due to their poor intestinal permeability. A great number of currently available drugs fall under the class III of the biopharmaceutical classification system, possess high therapeutic potential but cannot be delivered by oral route because of its poor permeation across the GIT epithelia (Amidon, 1995).

According to the BCS, Thiocolchicoside drug is classified in class III:a high solubility, low permeability compound. Thiocolchicoside is an approved drug having very low bioavailability in the solid dosage forms therefore they are also available in parenteral injections which are also not showing much difference in bioavailability. Therefore an oral dosage formulation would offer several advantages such as stability, cost effectiveness and patient compliance (Artursson P, 1990). In this paper we report the selection of optimized batch of with the best drug-permeation enhancer ratio combination using the 3^2 factorial design.

MATERIAL AND METHODS

Materials: Thiocolchicoside Drug (Saico Healthcare (P) Ltd, New Delhi) Sodium Glycolate and Sodium Caprylate (Himedia Laboratories (P) Ltd, Mumbai) EDTA (Qualikems Laboratories Reagent, New Delhi) Lactose Monohydrate (CDH Analytical Reagent, Central Drug House (P) Ltd, New Delhi) were obtained as gift samples.

Experimental Design: Experimental design is a statistical method that prescribes or advice a set of combination of variables. The number and layout of these design points within the experimental region depends on the number of effects that must be estimated. Depending on the number of factors, their levels, possible interaction and order of the model, various experimental design are chosen. Each experiment can be represented as a point, within the experimental domain, being defined by its coordinate (the value given to the variables) in the space.

Factorial design: Factorial design are used in experiments where the effects of different factors or conditions on experimental results to be elucidated. These are the design of choice for simultaneous determination of the effect of several factors and their interactions. The simplest one is the two-factorial design were two factors are considered, each at two levels, leading to four experiments, which are situated in 2-dimensional factor space at the corner of a rectangle. If there are three factors, each at two levels, eight experiments are necessary which are situated at the corners of the orthogonal cube in a 3-dimensional space. The number of experiments is given by 2^n where 'n' is the number of factors

If the number of factors and levels are large, then the number of experiments needed to complete a factorial design is large. To reduce the number of experiments, fractional factorial design can be used (i.e., ½ or ¼ of the original numbers of experiments with full factorial design) .The fitting of an empirical polynomial equation to the experimental results facilitates the optimization procedure.

The general polynomial equation is as follows: Y=B0 + B1X1 + B2X2 + B3X3 + B4X4+…+ B12X1X2 + B13X1X3 + B23X2X3 +…+ B123X1X3. Where Y is the response, X1, X2, X3 are the levels (concentration) of the 1,2,3 factors. B0, B1, B2, B3, B12, B13, B23, B123, are the polynomial coefficients. B0 is the intercept (which represents the response when the level of all factors is low).

Software for designs and optimization: Many commercial software packages are available which are either dedicated to experimental design alone or are of a more general statistical type.

Software's dedicated to experimental designs: Various softwares are available for the prediction of successful experimental design e.g.: Design Ease and Design Expert (Stat-ease).

Full Factorial Design: A 3^2 randomized full factorial design was used to optimize the variables in the present study. In the design 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. The amount (20, 40, 60 mg) of starch (X_1), and (2, 2.5, 3 mg) of gelatin(X_2), were selected as independent variables. The disintegration time and the % drug release (t_{45}) were selected as dependent variables.

***In-vitro* drug release:** The USP paddle method was adopted in this study. The release medium consisted of 900 ml of pH-7.5 buffer. A known quantity from the batches were placed in appropriate chamber of the release apparatus and agitated at 100 rpm. Timed for 45 minutes, for each 5 minutes time intervals 1ml of the release medium were withdrawn, appropriately diluted and their absorbance determined at a wavelength of 259.0 nm using UV spectrophotometer. The volume of the release medium was kept constant by replacing it with 1 ml of fresh medium after each withdrawal. The release study was repeated using pH 7.4 as a release medium and the absorbance was determined at a wavelength of 259.0 nm.

RESULT AND CONCLUSION

By the application of the Data Expert software it is confirmed that out of the 9 formulation prepared the batch B_2 is showing the best with the drug release and the disintegration time as the dependent variable, starch and gelatin as the independent variable. Thus the ANOVA study of the linear regression model, response surface plot as well as contour plot confirms the predicted batch with the desirability of 0.982. This conclude that the use of starch with 40 mg as disintegrating agent and the gelatin as binder with 2.5 mg in formulation will give the best formula for the Thiocolchicoside tablet with permeation enhancers incorporated. Result of R^2 and T-test confirmed that predicted and observed responses showed no significant difference.

ACKNOWLEDGEMENT

The author is grateful to Saico Healthcare Pvt Ltd Delhi, India, for providing the Thiocolchicoside drug.

Table 1: showing batches containing permeation enhancers with different concentration of disintegrating agent and binder

Ingredients	A 1	A 2	A 3	B 1	B 2	B 3	C 1	C 2	C 3
Thiocolchicoside	8	8	8	8	8	8	8	8	8
Sodium Caprylate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
EDTA	64	64	64	64	64	64	64	64	64
Lactose monohydrate	115.3	95.3	75.3	114.8	94.8	74.8	114.3	94.3	74.3
Starch	20	40	60	20	40	60	20	40	60
Sucrose	5	5	5	5	5	5	5	5	5
Gelatin	2	2	2	2.5	2.5	2.5	3	3	3
Talc	8	8	8	8	8	8	8	8	8
Magnesium stearate	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3

Table 2: showing *in-vitro* drug release of 9 batches

Times (min)	Batch A_1	Batch A_2	Batch A_3	Batch B_1	Batch B_2	Batch B_3	Batch C_1	Batch C_2	Batch C_3	M.F
0	0	0	0	0	0	0	0	0	0	0
5	10.31	11.31	11.13	11.89	10.53	11.11	9.41	8.31	11.51	10.33
10	16.75	19.21	19.13	22.63	24.98	21.61	19.41	20.51	18.41	17.76
15	21.51	29.31	28.43	32.69	36.42	28.43	25.41	27.21	24.32	22.61
20	26.42	37.42	35.63	41.52	45.25	35.21	32.64	33.13	31.41	26.42
25	39.81	45.12	43.31	47.61	51.43	45.32	41.41	42.52	40.51	39.12
30	45.23	51.29	49.82	54.63	59.54	54.61	51.31	51.21	51.91	44.99
35	50.37	60.43	59.39	61.51	67.56	61.43	59.12	62.49	61.43	50.32
40	56.91	65.34	61.93	66.53	74.59	69.56	68.13	71.42	68.90	56.82
45	58.13	66.21	63.23	68.17	75.31	70.23	69.12	73.14	69.31	56.92

M.F= marketed formulation

Figure.1. *In-vitro* drug release of different batches

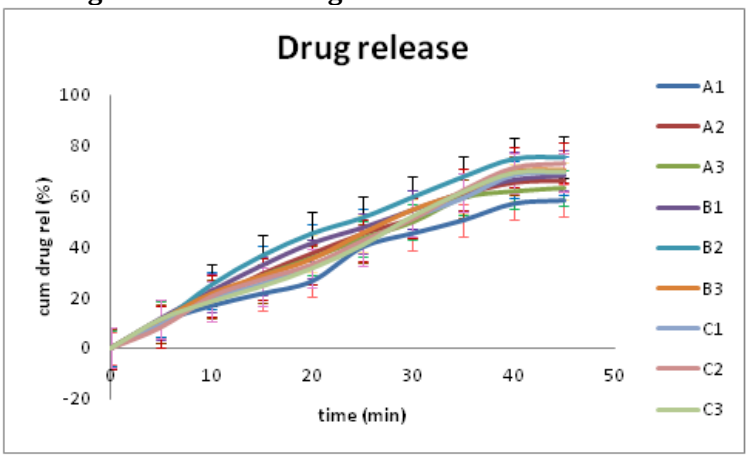


Figure.2. Comparison between drug release of marketed formulation and batch B $_2$

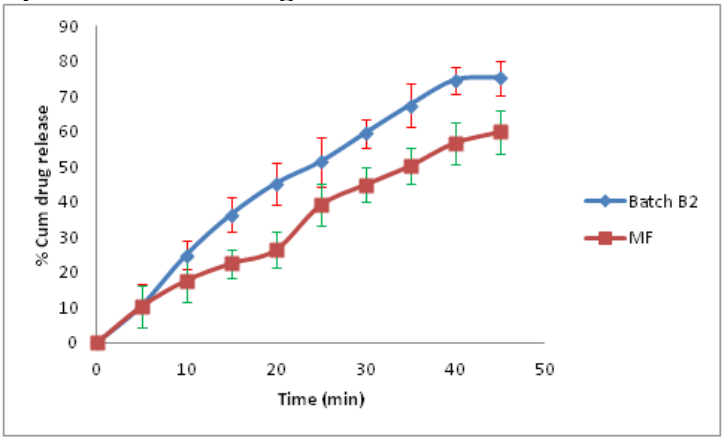


Table.3. Disintegration time for the 9 batches

Batch	Disintegration time (min)	Batch	Disintegration time (min)
A 1	12.5	B 3	11.0
A 2	11.5	C 1	12.5
A 3	11.0	C 2	12.0
B 1	12.0	C 3	12.0
B 2	11.0		

Table.4. Full Factorial Design Layout*

Batch Code	Variable Levels in Coded Form		Disintegration Time	Drug release
	X_1 (mg)	X_2 (mg)	Disintegration Time(min)	Drug release (%)
A_1	-1	-1	12.5	58.131
A_2	0	-1	11.5	66.211
A_3	1	-1	11.0	63.231
B_1	-1	0	12.0	68.172
B_2	0	0	11.0	75.312
B_3	1	0	11.0	70.234
C_1	-1	1	12.5	69.127
C_2	0	1	12.0	73.141
C_3	1	1	12.0	69.311

***Coded value for -1 X_1 =20mg and X_2=2.0 mg; for 0 X_1 =40mg and X_2=2.5 mg; 1 X_1 =60mg and X_2=3.0mg;**

Table 5: Calculations For Testing The Model In Portions*

For disintegration time					
	DF	SS	MS	F	R^2
Regression					
FM	5	3.03	0.61	65.40	0.9909
Error					
FM	3	0.028	9.259		
For drug release					
	DF	SS	MS	F	R^2
Regression					
FM	5	209.34	41.87	68.86	0.9914
Error					
FM	3	1.82	0.61		

***(DF): Degree Of Freedom, (SS): Sum of Squares, (MS) Mean of Squares, (F): Fischer's Ratio, (R^2) Regression Coefficient, (FM): Full Model**

Table.6.Summary of Regression Analysis Results

For Disintegration Time						
RESPONSE	B 0	B 1	B2	B3	B4	B5
FM	11.11	-0.50	0.25	0.25	0.33	0.58
For drug release						
RESPONSE	B 0	B 1	B2	B3	B4	B5
FM	74.70	1.22	4.00	-1.23	-5.19	-4.71

Table.7.Optimized formula obtained and their desirability

Name	Goal	Lower limit	Upper limit
Factor A	In range	20	60
Factor B	In range	2.0	3.0
Disintegrate time	Minimize	11	12.5
Drug release	Maximize	58.131	75.312

Table.8.Predicted Solution

Factor A	Factor B	Disintegration time	Drug release	Desirability	Remarks
46.53	2.52	11	74.7007	0.982	Selected

Table.9.Optimized batch B_2

Starch (mg)	Binder (%)	Disintegration time(min)	Drug release (%)
40	2.5	11	75.312

Figure.3.Desirability contour graph of optimized batch B_2

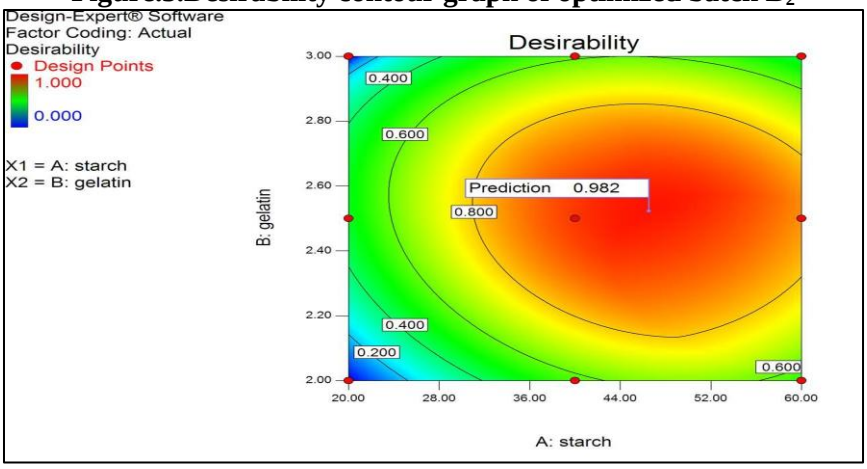


Figure.4.Desirability 3D graph of optimized batch B_2

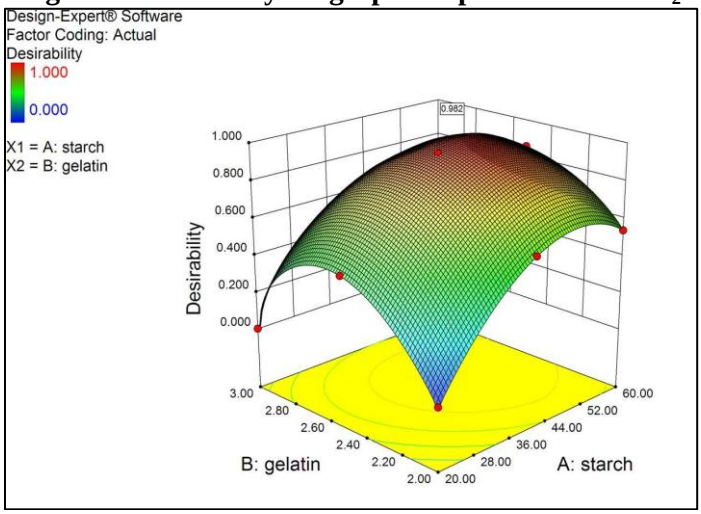


Figure.5.Disintegration time contour graph of optimized batch B_2.

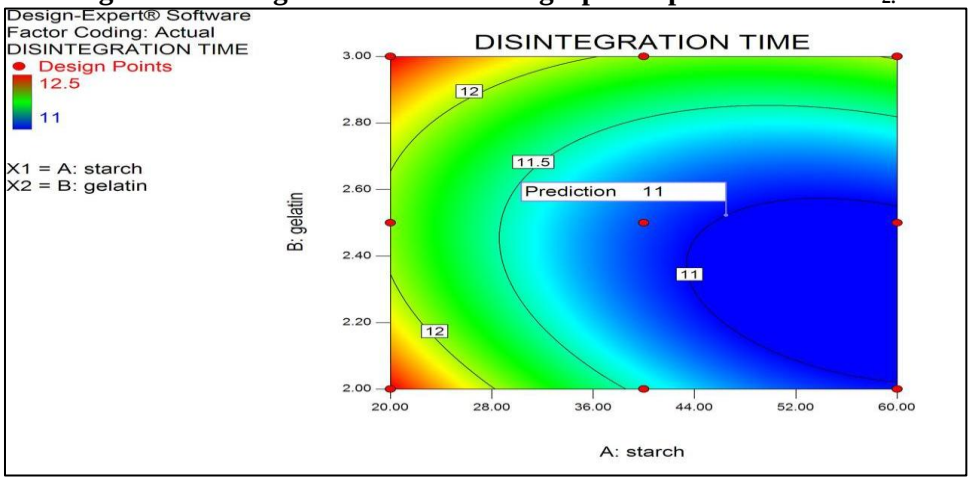


Figure.6.Disintegration time of 3D graph of optimized batch B_2

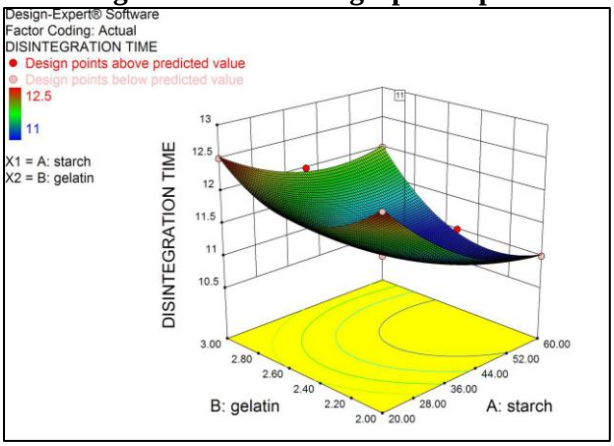


Figure 7: Drug release contour graph of optimized batch B_2

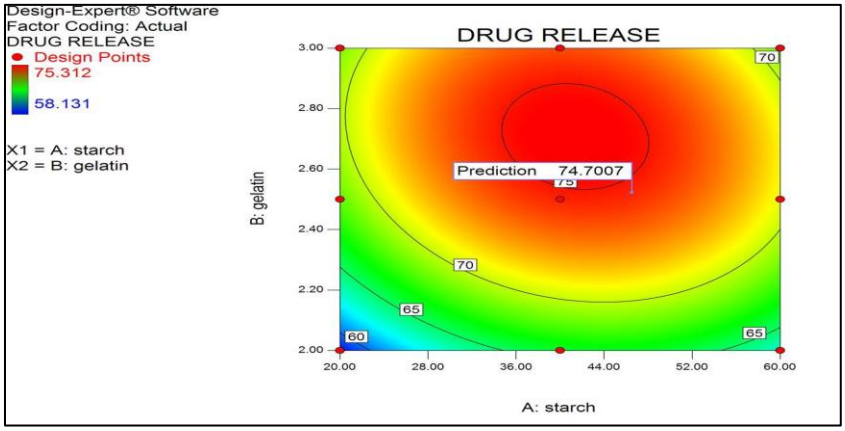


Figure 8: Drug release 3D graph of optimized batch B_2

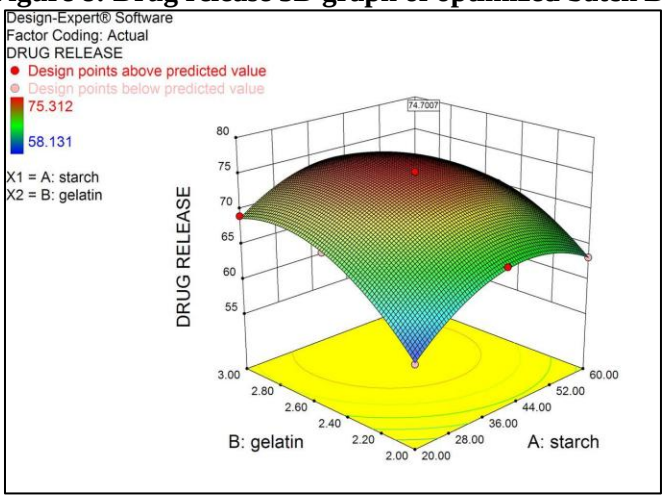
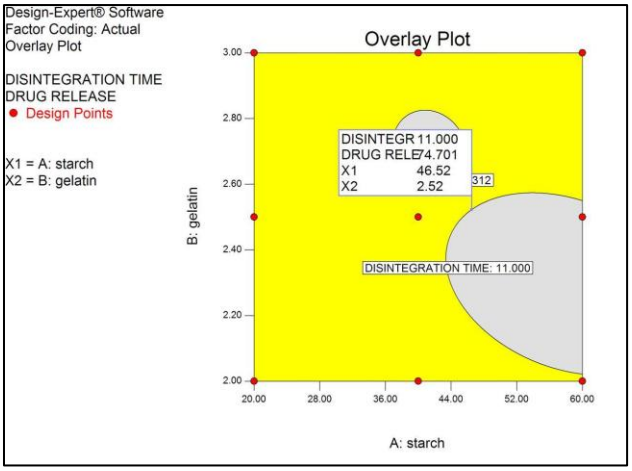


Figure 9: Desirability graphical optimization of Batch B_2



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