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OPTIMIZATION OF SOTALOL FLOATING AND BIOADHESIVE EXTENDED RELEASE TABLET FORMULATIONS

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ABSTRACT

A novel extended release sotalol HC1 tablet formulation which possesses a unique combination of floatation and bioadhesion for prolonged residence in the stomach has been developed. Tablets were produced by direct compression. A two-factor factorial, central, composite Box-Wilson experimental design was employed to develop and optimize the tablet formulation containing 240 mg sotalol HCl. The ratio of two major bioadhesive agents, sodium carboxymethylcellulose (NaCMC) to hydroxypropylmethylcellulose (HPMC), and the ratio of two direct compressible diluents, ethylcellulose (EC) to crosspovidone, were used as formulation variables (independent variables) for optimizing tablets response parameters, such as dissolution bioadhesive capability, tablet density and required compression force for producing 6 Kg hardness tablets. The data were also analyzed by means of quadratic response surface model. Response surfaces were generated as a function of formulation variables. An optimum direct compression, bioadhesive and floating tablet formulation of sotalol HC1 was achieved by considering the dissolution characteristic as primary objective and using required compression force, bioadhesive capability as constraints within the experimental region. The surface model was validated for accurate prediction of response characteristics.

INTRODUCTION

Oral sustained-release drug delivery have attracted considerable attention and recognition (1). However, in the cases of certain classes of active ingredients which are not suited to normal absorption conventional dosage forms can be disadvantageous (2). For example, some drugs will undergo a substantial change in solubility by passage from the acidic condition of the stomach to the neutral or alkaline condition of the intestine.

In recent years, many attempts have been made to provide dosage form which will provide longer transit time and more efficient absorption for specific drugs which have a window of absorption or stability problems. Floating dosage forms have been designed to possess sufficient buoyancy to float on the top of stomach contents and prolong gastric residence time of the dosage form (3-8). Also interest has been directed to the development or oral bioadhesive systems to locate the oral dosage form on the mucosal wall of stomach or intestine to increase the residence of the drug in the GI tract (9-12).

Floating and bioadhesive drug delivery systems are designed to provide the following advantages (1) increased and more effective absorption for drugs which have specific absorption sites (2) increased contact time for local activity in the stomach where such is required and (3) the ability to decrease dosing frequency.

Floating dosage forms are meant to remain buoyant on the gastric fluid when the stomach is full after a meal, however, as the stomach empties and the tablet is at the pylorus the buoyancy of the dosage form may be impeded (13). It will then become increasingly likely that the dosage form will pass through the pylorus into the small intestine. Thus, the buoyant ability of a floating drug delivery system in the stomach could be limited to only three or four hours. In bioadhesive drug delivery system, it is quite likely that the system becomes dislodged from the stomach mucosa wall when the stomach is full and the semi-liquid contents are churning around under the influence of peristaltic movement. Also, it should be noted that most of currently available oral floating and bioadhesive systems are made by wet granulation tabletting process and some other tedious and costly procedures.

The objective of this work was to develop a novel sustained-release tablet made by direct compression process. The tablet possesses an unique combination of bioadhesion and floatation to prolong the gastric residence time of sotalol HCl, a beta-blocker, which has high aqueous solubility and its absorption from the gastro-intestinal tract (GI) is limited to the upper part of the small intestine.

In this study, a computer optimization process using a Box-Wilson design experimental design (14, 15) was employed to develop bioadhesive and floating tablet formulations and determine the effects of formulation variables on the response properties of tablets. Finally, an optimum tablet formulation was selected using the technique of response surface methodology.

EXPERIMENTAL

Experimental Design

The two formulation variables and their ranges selected for optimization study are summarized in Table I, X1 represents the ratio of NaCMC (mg) to HPMC (mg) and the second variable, X2 represents the ratio of EC (mg) to polyplasdone XL (mg). All other formulation and processing variables were kept invariant throughout the study.

A total of thirteen experiments required in a two factor factorial, central, composite Box-Wilson experimental design is listed in Table II. This experimental design is based on factorial design with additional points added to estimate curvature of the response surface. As shown in Table II, the first sixteen experiments represent a half-factorial design for two factors at two levels represented by +1 and -1, analogous to the high and low values in any two level factorial design. For the remaining experiments, three additional levels, +1.414, 0, -1.414 were selected. The zero level represents a center point midway between the +1 and -1, the levels noted as +1.414 and -1.414 represent extreme values for each factor and the experimental levels were calculated by adding or subtracting one-half experimental unit to or from the experimental levels corresponding to +1 or -1 in the experimental design. The design also includes five replicate of center point allowing a lack-of-fit test for the mathematical model.

TABLE I - SUMMARY OF FORMULATION VARIABLES USED IN THE OPTIMIZATION PROCESS

FORMULATION VARIABLES	RANGE
X1: The ratio of NaCMC (mg) to HPMC (mg)	11/209 to 209/11
X2: The ratio of EC (mg) to Polyplasdone XL (mg)	17.6/102.4 to 102.4/17.6

Table III shows the translation of the experimental levels in the statistical design into experimental values. The response parameters measured on the resulting tablets are summarized in Table IV. The objective was to search the levels of the two independent variables that would produce tablets with the desired response parameters. These parameters are Y1, dissolution characteristic (diffusional exponent, n); Y2, the detachment force required to separate tablet from membrane; Y3, the required shear force; Y4, the required compression force for producing 6 kg hardness tablets; Y5, tablet density.

Preparation of Bioadhesive and Floating Tablets

Materials--- Sotalol hydrochloride (Bristol Myers-Squibb lot N0C07) was used as active ingredient in the formulation. The following materials were also used: sodium carboxymethylcellulose (NaCMC 7HF, Aqualon Co., Lot 67798), hydroxypropylmethylcellulose (HPMC, Methocel K15M Premium CR Grade, Dow Co., Lot MM89011881K), ethylcellulose, (EC, Ethocel Premium V-10, Dow Co., Lot 6161187), crosspovidone NF (Polyplasdone XL, GAF Chem. Co., Lot S01029), calcium carbonate (Amend Chem Co., Lot S37399805) and magnesium stearate (Fisher Scientific Co., Lot 742748). Tablets were prepared with the following formulations based on the experimental design described above.

Sotalol HCl	240 mg
NaCMC	11 to 209 mg

TABLE II -- BOX-WILSON EXPERIMENTAL DESIGN FOR TWO FACTORS

FACTORS:	X1	X2
BATCH#		
1	-1	-1
2	1	-1
3	-1	1
4	1	1
5	-1.414	0
6	1.414	0
7	0	-1.414
8	0	1.414
9	0	0
10	0	0
11	0	0
12	0	0
13	0	0

TABLE III -- TRANSLATION OF EXPERIMENTAL CONDITIONS

	-1.414	-1	0	1	1.414
Factors:					
X1=NaCMC (mg) / HPMC (mg) eu*: 70 mg	11/209	40/180	110/110	180/40	209/11
X2=EC(mg) / Polyplasdone (mg) eu*: 30 mg	17.6/102.4	30/90	60/60	90/30	102.4/17.6

* eu: experimental unit

TABLE IV -- RESPONSE PARAMETERS MEASURED IN THE OPTIMIZATION PROCEE

RESPONSE PARAMETERS

Y1: Dissolution (Diffusional Exponent, n)

Y2: Detachment Force (N)

Y3: Shear Force (N)

Y4: Required Compression Force (KN) for producing 6 Kg hardness tablets.

Y5: Tablet Density (g/cm^3)

HPMC	112 to 209 mg
EC	17.6 to 102.4 mg
Polyplasdone XL	17.6 to 102.4 mg
Calcium carbonate	80 mg
Magnesium stearate	2 mg

In the table formulation, NaCMC and HPMC were used as bioadhesive agents. When the tablet is in contact with gastric fluid, a combination of NaCMC and HPMC will also possess sufficient structure to form a gel layer and achieve an overall specific gravity lower than that of gastric fluid. Calcium carbonate was used to generate carbon dioxide, to enhance the buoyancy of the tablets.

Mixing--- All powders except magnesium stearate were sieved through sieve of mesh size 20. The components of the formulation were mixed for 15 minutes in a WAB type T2C turbula mixer.

Lubrication--- Magnesium stearate (40 mesh sieved) was added into powder blend as a lubricant and mixed for an additional 3 minutes before compaction process.

Compaction---Tablets were prepared by direct compression on an instrumented Stoke B-2 rotary press at 30 rpm using 3/8" flat face punches and die adjusted to obtain 6 kg hardness tablets, the required compression force was measured by the

piezoelectric force transducer located in the eyebolt. The tablet formulations were compressed in a random order.

Tablet Evaluation

In Vitro Dissolution--- Dissolution studies were conducted using the USP basket method. Six tablets were tested for each batch. The dissolution method was 900 ml or 0.1 N HC1 solution (pH 1.2) equilibrated at 37° C and stirred at 70 rpm. The dissolution samples were diluted and the concentration were determined on a Diode Array Spectrophotometer at 228 nm, the maximum absorbance of sotalol HC1.

Floating Capability--- The lag time required for the tablet to start floating on the top of basket in the dissolution study was measured. The duration of floatation under the rotating condition of the dissolution study was also determined for all formulations.

Measurement of Bioadhesiveness

Figure 1 shows the diagram of the custom-designed apparatus to be equipped with Instron Tensile Tester (Instron, model 1122) for bioadhesion measurement. The system consists of a small polyacrylic cylinder fastened to the side wall of a polyacrylic cubic vessel to hold the membrane by means of an O-ring. A rectangular aluminum mounting with a hole in the middle was used as a support to hold the tablet fixed over the surface of the biological tissue. The vessel was put on the lower plate of the Instron Tensile Tester, while the aluminum support was connected to the vertical rod and fixed to the upper clamp of the tensile tester.

After placing the tablet in the hole of the aluminum mounting, the stomach mucosa and tablet were brought together just to touch each other. The tablet and mucosal surfaces were held parallel. The vessel was filled with constant volume of distilled water (1000 ml) at 22° C. After 30 minutes (preswelling time), the force was measured and recorded as a function of time until the tablet had crossed the mucosa surface. Additionally, as can be seen from Figure 1, another polyacrylic cylinder is fixed to the bottom of the vessel to hold a mucosa horizontally by means of an O-ring for the determination of direct detachment force.

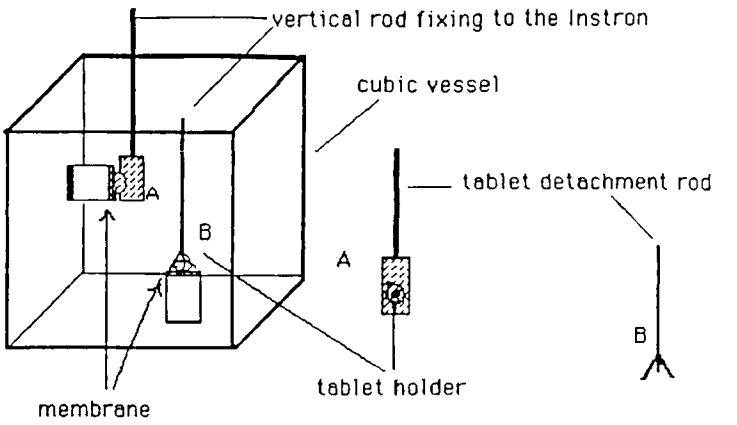

Figure 1. Apparatus for determination of bioadhesiveness of tablets; (A), Sliding Method, (B), Direct Detachment.

In the detachment force measurement, the tablet was stuck on to rectangular aluminum support with a cyanoacrylate glue, the tablet support was fixed to the upper clamp of the tensile tester and lowered to maintain in a similar fashion so that tablet and rabbit stomach mucosa surfaces were parallel. The cubic vessel was filled with constant volume (1000 ml) of pH 2 buffered solution at 22°C. After 30 minutes, the crosspiece was raised at constant speed (20 mm/min.) The detachment force was measured and recorded as a function of displacement, up to the total separation of the tablet surface and tissue. The adhesion work was determined by calculating the area under the curve necessary for detachment.

The biological tissue used in bioadhesion study was rabbit stomach mucosa, it was maintained in normal saline solution after the sacrifice of the animals.

Analysis of Data

All the statistical and regression analysis procedures on the response parameters were performed using the X-STAT software package. Statistical analysis was carried out which includes the calculation of mean values for each of the four response parameters in each of thirteen experiments

The sets of data obtained from the statistical analysis were then subjected to computerized regression analysis to determine the fit to a second-order model. These regression models include an intercept and main effect terms of each independent variable, two-way interaction terms and second order effect terms as shown in Table V.

RESULTS AND DISCUSSION

Dissolution results were analyzed using Equation 1, where $Mt/M\infty$ represents the fraction of drug released at time t, K is the kinetic constant characteristic of the drug/polymer system, t is the release time and n is an exponent characterizing the mechanism of release of the drugs (16).

$$M_t/M\infty = K_t^n \qquad \text{(Eqn. 1)}$$

Table VI summarizes the range of values of the diffusional exponent n, and the corresponding release mechanism.

The response properties of tablets obtained from all thirteen formlations in the experimental design are summarized in Table VII. The n values of sotalol dissolution are in the range of 0.36 to 0.60. The lag time of tablet floatation ranged from 5 seconds to 12 minutes. All tablet formulations exhibited floatation capability and remained buoyant for more than 24 hours in a dissolution medium subject to rotation. The measured detachment force of tablets in the bioadhesion study ranged from 1.0 to 2.1 Newton (N), the shear force ranged from 0.64 to 1.67 N. The required compression forces are in the range of 8.42 to 21.68 kilonewton (KN).

Each response parameter was fitted to the second-order polynomial model and the regression coefficient for each term in the regression model are shown in Tables VIII to XII. As can be seen, most of these standard error values are less than 50% of the absolute values of their regression coefficients indicating the adequacy of the model. Also, the high values of confidence level indicate these variable terms have standard significant effects on the response parameter. Although, there are some terms which do not contribute significantly at 90% confidence level to the model, however, these terms, as a group, do affect the shape of the contour plot.

TABLE V -- GENERAL QUADRATIC EQUATION:

$$Y=b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 + b_4X_1^2 + b_5X_2^2$$

TABLE VI -- DIFFUSIONAL EXPONENT AND MECHANISM OF DIFFUSIONAL RELEASE FROM CYCLINDRICAL SWELLABLE CONTROLLED RELEASE MATRIX SYSTEM

Diffusional exponent (n)	Drug release mechanism
< 0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) transport
0.89	Case II transport
n > 0.89	Super Case II transport

when the value of n = 0.89 means that the drug release is independent of time, the release is characterized as zero-order release.

TABLE VII -- SUMMARY OF RESPONSE PARAMETERS

	Diffusional Exponent, n	Detachment Force (N)	Shear Force (N)	Compression Force (KN)	Density (g/cm^3)	Lag Time (minutes)
BATCH #						
1	0.40	1.0	0.637	10.03	0.979	0.1
2	0.38	1.372	0.882	16.03	1.056	5
3	0.50	1.390	1.078	10.46	1.0036	7
4	0.51	1.67	1.225	19.37	1.077	8
5	0.42	1.26	0.833	8.42	0.997	0.5
6	0.36	1.519	1.078	21.68	1.099	7
7	0.54	1.25	1.029	11.88	0.979	0.1
8	0.60	2.107	1.666	15.08	1.077	12
9	0.58	1.127	1.372	13.46	1.056	8
10	0.59	1.201	1.354	13.21	1.055	8
11	0.58	1.131	1.298	12.95	1.056	8.5
12	0.59	1.135	1.342	13.06	1.056	8
13	0.59	1.126	1.364	13.16	1.056	9
Range	0.36-0.60	1.0-2.107	0.637-1.666	8.42-21.68	0.979-1.099	0.1-12

As shown in Table XIII, the high R^2 values of each response parameter equation indicate the good fit and adequacy of these models. It also implies that the regression equation explains a large portion of variation of response parameter about its mean. For each response parameter, the multiple correlation coefficient was greater than 0.91 indicating there are at least more than 91% of the total variations observed in the response parameter could be explained as being caused by the independent variables in the way described by the equation as shown in Table VIII to XII. An F test for the regression equation was performed and the calculated F value was significant at the 99% level for all response parameters revealing that these model terms are important for explaining variability. Also, the predicted minimum and maximum values for each response parameter show good agreement with the experimental results obtained from 13 batches shown in Tables XIV to XVI.

Table XIV lists the optimum values of formulation variables for obtaining the best values of each of the response parameters. This Table was generated from

TABLE VIII - Regression coefficients for DENSITY

Coefficient	Term	Standard Error	T-Value	Confidence Coef < > 0
0.8550	1 (constant)	0.0212	40.37	99.9%
0.000912	NACMC	0.0002	4.522	99.5%
0.003261	ETHYLCELLULOSE	0.0005	6.339	99.8%
-0.000004	NACMC*ETHYLCELLULOSE	0.0000	2.035	92.0%
-0.000001	NACMC^2	0.0000	1.237	73.3%
-0.000016	ETHYLCELLULOSE^2	0.0000	4.218	99.4%

Confidence figures are based on 7 degrees of freedom.

TABLE IX - Regression of Coefficients for DETACHMENTFORCE

Coefficient	Term	Standard Error	T-Value	Confidence Coef < > 0
1.484	1 (constant)	0.3009	4.932	99.6%
-0.001060	NACMC	0.0029	0.3701	31.2%
-0.02065	ETHYLCELLULOSE	0.0073	2.825	97.5%
-0.000011	NACMC*ETHYLCELLULOSE	0.0000	0.3660	31.0%
0.000016	NACMC^2	0.0000	1.652	85.6%
0.000248	ETHYLCELLULOSE^2	0.0001	4.685	99.6%

Confidence figures are based on 7 degrees of freedom.

TABLE X - Regression Coefficients for SHEARFORCE

Coefficient	Term	Standard Error	T-Value	Confidence Coef < > 0
-0.09344	1 (constant)	0.2594	0.3602	30.7%
0.01299	NACMC	0.0025	5.259	99.7%
0.01474	ETHYLCELLULOSE	0.0063	2.339	95.0%
-0.000012	NACMC*ETHYLCELLULOSE	0.0000	0.4522	35.2%
-0.000050	NACMC^2	0.0000	5.946	99.8%
-0.000054	ETHYLCELLULOSE^2	0.0000	1.175	70.9%

Confidence figures are based on 7 degrees of freedom.

TABLE XI - Regression Coefficients for COMPRESSIONFORCE

Coefficient	Term	Standard Error	T-Value	Confidence Coef < > 0
9.243	1 (constant)	1.353	6.833	99.8%
0.000360	NACMC	0.0129	0.0279	16.8%
-0.01459	ETHYLCELLULOSE	0.0328	0.4442	34.8%
0.000346	NACMC*ETHYLCELLULOSE	0.0001	2.575	96.4%
0.000177	NACMC^2	0.0000	4.051	99.3%
0.000092	ETHYLCELLULOSE^2	0.0002	0.3869	32.0%

Confidence figures are based on 7 degrees of freedom.

TABLE XII - Regression Coefficients for DENSITY

Coefficient	Term	Standard Error	T-Value	Confidence Coef < > 0
0.8550	1 (constant)	0.0212	40.37	99.9%
0.000912	NACMC	0.0002	4.522	99.5%
0.003261	ETHYLCELLULOSE	0.0005	6.339	99.8%
-0.000004	NACMC*ETHYLCELLULOSE	0.0000	2.035	92.0%
-0.000001	NACMC^2	0.0000	1.237	73.3%
-0.000016	ETHYLCELLULOSE^2	0.0000	4.218	99.4%

Confidence figures are based on 7 degrees of freedom.

TABLE XIII - REGRESSION SUMMARY AND PREDICTED RESPONSE PARAMETERS RANGES

	F-Ratio Regression	R^2	Predicted Values	
			Min.	Max
Diffusional Exponent, n	23.17*	0.95	0.61	0.37
Detachment Force	11.99*	0.90	1.02	1.79
Shear Force	14.35*	0.91	0.726	1.51
Compression Force	98.75*	0.99	9.6	20.1
Density	41.43*	0.97	0.969	1.09

* Implies at least 99% confidence regression equation is nonzero

the contour plots without placing any constraint on the response parameters. The optimum X1 and X2 levels for obtaining the highest diffusional exponent value, n, are 109 mg NaCMC/111 mg HPMC and 90 mg EC/30 mg polyplasdone XL while the optimum X1 and X2 levels for the minimum required compression force and tablet density are 40 mg NaCMC/180 mg HPMC and 30 mg EC/90 mg polyplasdone XL. In the case of detachment force, tablet formulation composed of 180 mg NaCMC, 40 mg HPMC, 90 mg EC and 30 mg polyplasdone XL would require the highest force, 1.79 N for direct detachment.

The dissolution release characteristic represented by the diffusional exponent value, n, was identified as the primary response parameter because a zero-

TABLE XIV - OPTIMUM VALUES OF FORMULATION VARIABLES TO OBTAIN BEST POSSIBLE RESPONSE PARAMETERS

	Diffusional Exponent, n	Detachment Force (N)	Shear Force (N)	Compression Force (KN)	Density
X1	105/115	180/40	120/100	40/180	40/180
X2	90/30	90/30	90/30	30/90	30/90
Diffusional Exponent, n	**0.61**	0.50	0.61	0.44	0.44
Compression	14	20.1	15	**9.6**	9.6
Detachment Force	1.6	**1.79**	1.62	1.06	1.06
Shear force	1.5	1.33	**1.51**	0.726	0.726
Density	1.07	1.09	1.07	0.969	**0.969**

TABLE XV - CHOICE OF OPTIMUM FORMULATION

Formulation Variable	Value
NaCMC/HPMC	105/115
Ethylcellulose/Polyplasdone XL	90/30

Contraints:
1. Compression Force < 14 KN
2. Shear Force > 1.1 Newton

order release was desired for this extended sotalol tablet formulation, also, in vitro dissolution may provide an indication of in vivo bioavailability. The diffusional exponent n value was maximized so as to obtain a near zero-order release characteristic. As shown in Table XV, two constraints were applied in obtaining the highest n value, the required compression force was constrained under 14 KN and the shear force was required to be more than 1.1 N. Additional constraints were the experimental range limits placed on values of two independent variables. The optimum formulation satisfied all constraints simlataneously and provided an optimum value for the primary concern, the highest n value.

The tablets were prepared on an instrumented B-2 rotary press according to the optimum formulation as shown in Table XIV, tablets properties were also determined. The comparison of predicted and experimental values for optimum formulation showed very good agreement and are shown in Table XVI. This reasonable prediction of the system's performance indicates the proposed model is valid.

TABLE XVI - COMPARISON OF PREDICTED AND EXPERIMENTAL VALUES OF RESPONSE VARIABLES FOR OPTIMUM FORMULATION

	Diffusional Exponent, n	Detachment Force (N)	Shear Force (N)	Compression Force (N)	Density
Constraint			>1.1 N	<14 KN	
Predicted	0.61	1.6	1.5	14	1.070
Experimental	0.62	1.72 (0.21)	1.4 (0.16)	14.3 (0.5)	1.064 (0.01)

* values in parenthesis represent standard deviation.

CONCLUSIONS

A computer optimization process utilizing Response Surface Methodology (RSM) has been applied to develop and optimize a novel extended release sotalol HC1 tablet formulation which possesses a unique combination of floatation and adhesion for prolonged residence in the stomach (15). The Box-Wilson experimental design was demonstrated to be an efficient tool for the design, evaluation, and optimization of a complex mixture for extended release with performance-related compositional constraints. Properties of the optimal formulation are very close approximation to the predicted profiles selected by surface response models. The optimized 240 mg sotalol HC1 extended-release tablets showed a satisfactory dissolution profile, strong bioadhesive capability in terms of detachment force and shear force and excellent floatation characteristics (lag time of floatation < 8 minutes, duration time of floatation > 24 hours), and these tablets can be manufactured by an efficient and economical direct compression process.

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