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Design and Development of a Self Correcting Monolithic Gastroretentive Tablet of Baclofen

Rishad R. JIVANI * [1], Chhagan N. PATEL [2], Nuruddin P. JIVANI [1]

[1] Smt. R.B.Patel Mahila Pharmacy College, Kailash nagar, Dist: Rajkot, Atkot-360040, Gujarat, India
[2] Shari Sarvajanik Pharmacy College, Mehsana-384001, Gujarat, India

* Corresponding author. E-mail: hellorishad@yahoo.com (R. R. Jivani)

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Abstract

The present investigation describes the design and development of self-correcting monolithic Gastroretentive system of baclofen. Tablets were prepared by direct compression method. Optimization was carried out using simplex lattice design. Drug released at 2h, 4h, 8h, and floating lag time were considered as response variables related to percentages of diluent (MCC), Polyethylene oxide (PEO) and sodium bicarbonate. Tablets were evaluated for in-vitro buoyancy, in-vitro drug release, swelling index and ex-vivo bioadhesion studies. The similarity factor (f_2) was used as a base to compare dissolution profiles. Drug release data was fitted into different kinetic models. The floating lag time and floating time were found to be 2min and 12h respectively. Increasing trend in bioadhesive strength was observed with an increase in the amount of PEO. The experimental values of Q2, Q4 and Q8 for check point batch were found to be 30.8%, 44.1% and 69.9% respectively. Similarity factor (f_2) for check point batch was 78.08. Kinetics of drug release from tablet followed Korsmeyer–Peppas model by anamolous non-fickian diffusion. It was concluded that gastroretentive tablet of baclofen can be prepared via floating and bioadhesion mechanism to increase residence time of drug in stomach and there by increases absorption.

Keywords

Baclofen • Gastro retentive drug delivery system • Simplex lattice design • Polyethylene oxide (PEO)

Introduction

The high cost involved in the development of a new drug molecule has diverted the pharmaceutical industry to investigate various strategies in the development of new drug delivery systems [1]. Drug release from the delivery devices can be sustained up to 24h for many drugs using current release technologies. However, the real issue in the development of oral controlled release dosage forms is to prolong the residence time of dosage forms in the stomach or upper gastrointestinal (GI) tract until the drug is completely released [2]. Rapid GI transit could result in incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose [3].

Several approaches are currently used to retain the dosage form in stomach. These include bioadhesive systems [4] swelling and expanding systems [5, 6], floating systems [7, 8], and other delayed gastric emptying devise [9, 10]. The principle of buoyant preparation offers a simple and practical approach to achieve increased residence time for the dosage form in stomach and sustained drug release.

The attainment of high gel viscosity, maintenance of constant gel layer or synchronous erosion/dissolution in a monolithic sense for linear drug release over a prolong period of time is not easily achievable. The various dynamic phases in the rate process of polymer relaxation, disentanglement and/or erosion during dissolution rate manifest themselves in a nonconstant manner hence realization of zero order drug release from such monolithic devices is difficult. It is reported that the limitation of hydrophilic polymer gel system by inducing *in situ* reaction between electrolytes and hydrophilic polymer, which produces a heterogeneous domain within the swollen gel boundary referred to as a “metamorphic scaffold” characterizes self correcting matrices [11].

Polyethylene oxide (PEO) is among various hydrophilic polymers that, in presence of water, control the release of the active moiety either by swelling or by swelling/erosion by forming a hydrogel. PEOs have been proposed as alternatives to cellulose or other ethylene glycol derivatives in the production of controlled release drug delivery system [12]. In present study high molecular weight PEO (mw = 7×10^6) was used since it is reported that it swells to greater extent and forms a stronger gel that is less prone to erosion. Further it also has mucoadhesive properties which may assist prolonging the gastric residence time [13]. The rate of drug release from hydrophilic matrix is dependant on various factors such as types of polymer, solubility of drug, polymer content, particle size of drug and polymer as well as types and amount of filler used in the formulation [14]. The adjustment of polymer concentration, viscosity grade and addition of different types and levels of excipients to the polymer matrix can modify the kinetics of drug release [15].

The present work describes the application of a novel “Self-correcting” hydrophilic matrix employing the principles of the colloidal chemistry “salting-out phenomenon to modulate the swelling and erosion kinetics of the matrix containing the drug, excipients, and electrolytes. The presence of these electrolytic compounds in the form of ionizable salts allows for non collapsible diffusion channels to form. The electrolytes also provide microenvironments within the tablet, whose pH is mediated by the nature of the electrolyte, thus, either enhancing or suppressing the solubility of the drug itself. As the matrix hydrates, the electrolytes and polymer compete for water of hydration with the drug,

resulting in controlled solubilization and diffusion of drug [16]. In the present study sodium bicarbonate was used as an electrolyte because it releases carbon dioxide in presence of acidic medium thus enabling the dosage form to float by entrapment of gas inside the matrices. PEO was used for its floating, mucoadhesive and drug release retardant properties [17]. While MCC plays very important role as filler as well as release modifier [18, 19].

Baclofen has absorption window in upper G.I. tract, and due to these, Often display low bioavailability [20]. Baclofen is difficult to formulate in to sustained release products because on arrival to colon (or even before) its absorption is low or non existent therefore in present investigation efforts have been made to increase the residence of baclofen at or above the absorption window by preparing Gastroretentive tablet for gastric retention considering fact that it is stable at gastric condition [21], applying a simplex lattice design for the optimization.

Results and Discussion

To achieve linear, bimodal or zero-order release, various strategies that seek to manipulate tablet geometry or structure have been developed, though many such strategies often increase the number of manufacturing steps and complexity of production, involving specialized equipment and non-conventional excipients. An alternative to physical modifications of tablet structure (layered and reservoir coated tablets) is modification of the simple monolithic matrix formulations.

Tab. 1. Formulation and dissolution characteristics of simplex lattice design batches

Code	Coded value			Actual values			Independent variables			
	X_1	X_2	X_3	X_1 (%)	X_2 (%)	X_3 (%)	Q_2	Q_4	Q_8	Floating lag time (Sec)
F1	1	0	0	72	15	5.0	35.23	49.85	98.78	125
F2	0	1	0	57	30	5.0	9.26	20.1	49.22	120
F3	0	0	1	57	15	20	18.12	39.77	73.81	90
F4	0.5	0.5	0	64.5	22.5	5.0	29.11	43.15	69.72	120
F5	0	0.5	0.5	57	22.5	12.5	28.11	40.38	67.76	64
F6	0.5	0	0.5	64.5	15	12.5	21.34	43.05	77.67	60
F7	0.33	0.33	0.33	62	20	10	37.13	49.51	75.94	78

Q_2, Q_4, Q_8, are percentage drug release at 2h, 4h, and 8h respectively. X_1= diluent (MCC), X_2= polymer (PEO), and X_3= sodium bicarbonate. Each batch contains 20mg of baclofen, 2% talc, and 1% of magnesium stearate, total weight of tablet was made to 250 mg.

Simplex lattice design was constructed (table 1). All the formulations, were prepared within the factor space. First-order liner interactive model (eq. 1) was derived. The coefficients were calculated using the procedure outlined by Bolton.

Eq. 1. $$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

Where Y is the response parameter and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1, X_2, and X_3) represent the average results of changing one factor at a time from its low to high value. The interaction (X_1X_2, X_1X_3, X_2X_3, and $X_1X_2X_3$) shows how the response changes when two or more factors are simultaneously changed. The fitted equation relating the percent drug released in 2h, 4h, 8h and floating lag time to the transformed factors is shown in (eq. 2–5).

Eq. 2. $$Q_2 = 35.23X_1 + 9.263X_2 + 18.21X_3 + 27.46X_1X_2 - 27.33X_1X_3 + 58.08X_2X_3 + 246.4X_1X_2X_3$$

Eq. 3. $$Q_4 = 49.58X_1 + 20.1X_2 + 39.77X_3 + 32.7X_1X_2 - 7.04X_1X_3 + 41.78X_2X_3 + 14\ 6.4X_1X_2X_3$$

Eq. 4. $$Q_8 = 98.78X_1 + 49.22X_2 + 73.81X_3 - 17.12X_1X_2 - 34.5X_1X_3 + 24.98X_2X_3 + 134.01X_1X_2X_3$$

Eq. 5. $$Floating\ \ lag\ \ time = 125X_1 + 120X_2 + 90X_3 - 10X_1X_2 - 17X_1X_3 - 180X_2X_3 + 180X_1X_2X_3$$

The Q_2, Q_4, and Q_8 values for all seven batches showed a wide variation i.e. the response ranged from a minimum of 9.3% to 37.1%, 20.1% to 49.9% and 44.9% to 98.8% respectively.The data clearly indicate that the Q_2, Q_4, and Q_8 is strongly dependent on the independent factors selected in the study.

Tab. 2. Summary of regression analysis for measured responses

Parameters	**Co- efficient of regression parameters**							
	b_1	**b_2**	**b_3**	**b_{12}**	**b_{13}**	**b_{23}**	**b_{123}**	**R^2**
Q_2	17.61	8.98	—	24.90	59.98	−20.02	299.214	0.977
Q_4	10.93	−18.83	—	30.87	41.82	−5.3	149.3	0.992
Q_8	24.65	−24.93	—	−13.51	25.86	−34.35	102.90	0.996
Floating lag time	125	120	90	−10	−80	−180	180	0.995

Tab. 3. Result of ANOVA for dependent variable

Source of variation	**DF**	**SS**	**MS**	**F**	**P**
		Q_2			
Regression	6	1259.10	209.85	49.61	<0.01
Residual	7	29.60	4.23		
Total	13	1288.715	99.132		
		Q_4			
Regression	6	1179.417	196.570	149.365	<0.01
Residual	7	9.212	1.316		
Total	13	1188.630	91.433		
		Q_8			
Regression	6	2578.265	429.711	278.795	<0.01
Residual	7	10.789	1.541		
Total	13	2589.054	199.158		

Replicated simplex lattices design was used for ANOVA study. The results of ANOVA suggest that *F* value calculated for Q_2, Q_4 and Q_8 is 49.61, 149.36, and 278.79

respectively (table 3). Tabulated *F* value found to be 3.87 at α= 0.05. Calculated *F* value is greater than tabulated for all dependent variables therefore factors selected have shown significant effects.

The electrolyte species (sodium bicarbonate) within the matrix would consequently compete for fluid species (0.1N HCl) at the outset and hence attract part of the fluid in order to dissociate. This initial competition for fluid (0.1N HCl) of hydration possibly 'dehydrates' the PEO molecules (salting-out phenomenon), leading to suppression of initial swelling. However, once sufficient fluid has been attracted by electrolyte species into the PEO matrix, the solubilized species undergo an efflux process, creating significant porosity within the hydrating network for more fluid penetration, after which an enhancement in peripheral swelling is take place.[16]

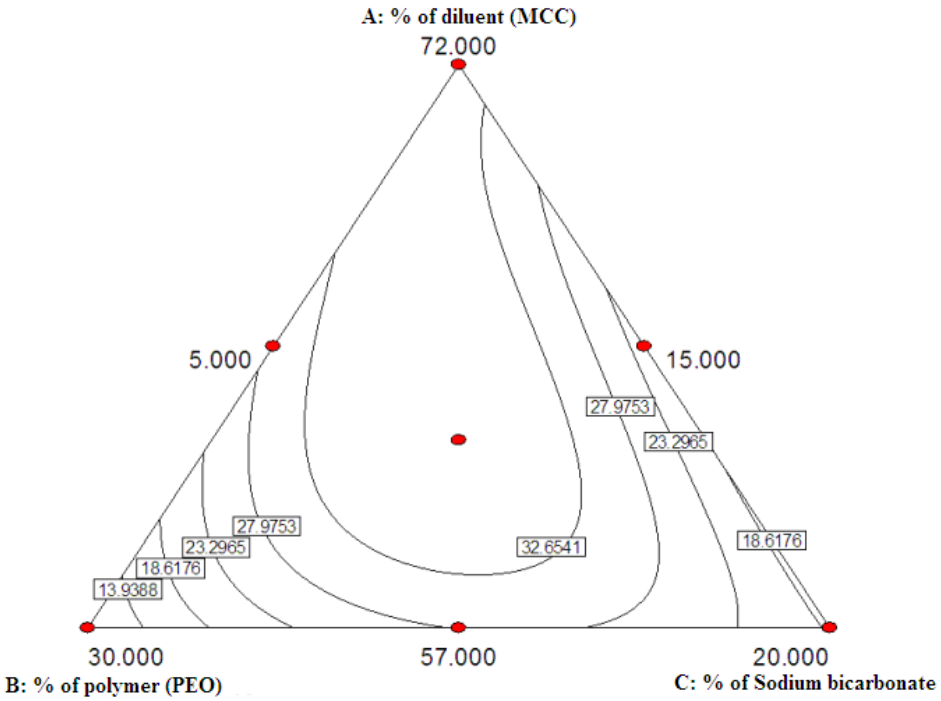

Fig. 1. Contour plot showing amount of drug release at second h (Q_2) using different combination of X_1, X_2 and X_3. The contour lines show percentage drug release at the end of second h.

To describe entire dissolution profile, 3 time points were selected. Percentage drug released at 2h (Q_2), 4h (Q_4) and 8h (Q_8) were selected as dependent variables. Figure 1 shows the effect of three different variables on drug release at 2h (Q_2). The magnitude of regression coefficient and the mathematical sign it carries (i.e. positive or negative) were used to draw conclusions. From result of regression analysis, it was observed that both % of diluent (MCC) and % of polymer (PEO) significantly contributed to Q_2 (P<0.05, tables 2 & 3). The drug release at 2h, increases with increasing % of diluent (MCC) and decreases with increasing % of polymer (PEO). Observed effect indicates that PEO forms rapid establishment of gel layer once fluid has been attracted by electrolyte species into the PEO matrix and controls the release at initial periods depending upon the content of

polymer. Increasing % of diluent (MCC) increases hydrophilicity of matrix which facilitate drug to come out from soft gel formed by polymer PEO.

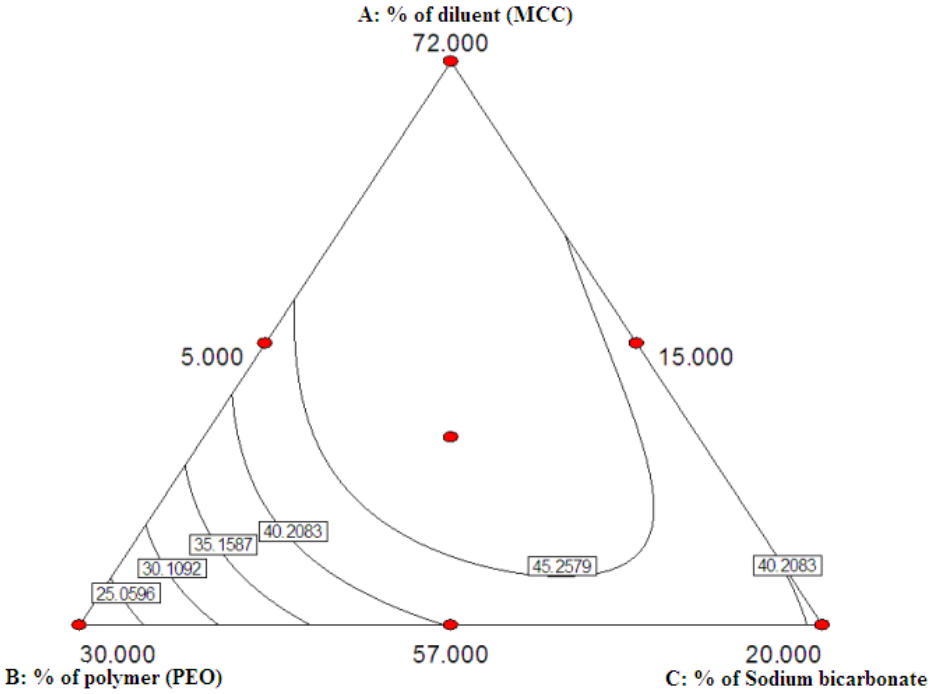

Fig. 2. Contour plot showing amount of drug release at four h (Q_4) using different combinations of X_1, X_2 and X_3. The contour lines show percentage drug release at the end of 4h.

Figure 2 shows the effect of independent variables on drug release at 4h (Q_4). From result of regression analysis and ANOVA, it was observed, both % of diluent and % of polymer significantly contributed to Q_4 (P<0.05, tables 2 & 3). The drug release at 4h, increases as % of diluent increases. This period is generally termed as a period of establishment of fully swollen gel layer depending upon the concentration of polymer present and other components of the systems mainly filler. Tablet containing microcrystalline cellulose as diluent, drug release is higher because it accelerates the diffusion of aqueous medium inside the matrix and opens up the channel for drug to get diffuse out.

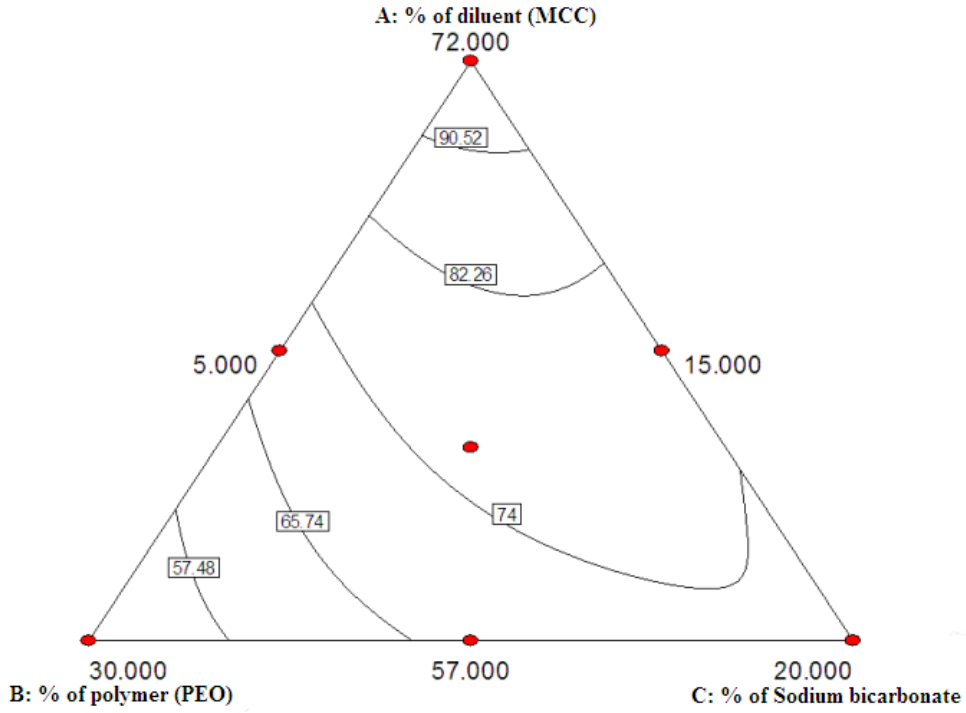

Fig. 3. Contour plot showing amount of drug release at eight h (Q_8) using different combinations of X_1, X_2 and X_3. The contour lines show percentage drug release at the end of 8h.

Figure 3 shows contour plot of Q_8 versus all three variables. Graph shows the effect of polymer PEO on release of baclofen. The drug release at 8h decreased as % of polymer PEO increased. From results of regression analysis and ANOVA, it was observed that % of PEO has significantly contributed to Q_8 (P<0.05, tables 2 & 3). This observed effect may be explained by assuming that as polymer percentage increased, it leads to stronger gel layer formation because the particles had more intimate contact with each other. This leads to increase in diffusion path length for the drug molecule. This period may be generally termed as period of dominance of erosion as it is expected that the water-front may reach the central core of the matrices for rapidly hydrating the highly hydrophilic polymer.

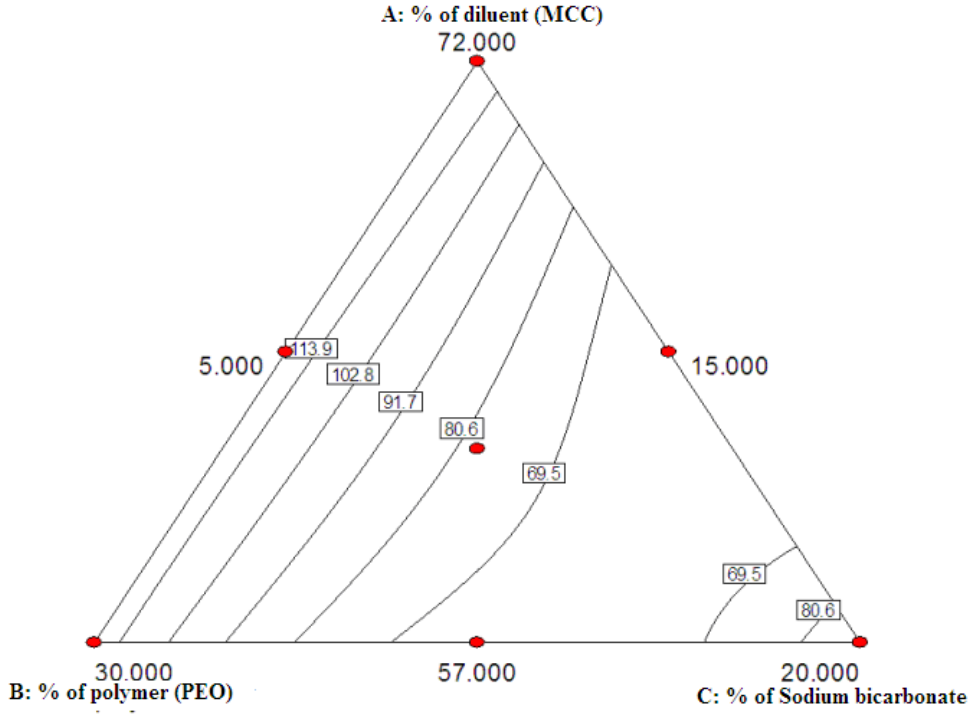

Fig. 4. Contour plot showing floating lag time using different combination of X_1, X_2 and X_3. The contour lines show floating lag time.

Figure 4 shows contour plot of floating lag time versus all three variables. Floating lag time was decreased as the concentration of sodium bicarbonate was increased which was observed between 1–2 minutes as the concentration of it was varied between 12.5% to 5%, irrespective of content of polymer and content of diluent. In present investigation sodium bicarbonate was used as elactctrolyte and it forms pore in matrix and releases carbon dioxide in presence of acidic medium. The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of tablet, and tablet remains buoyant.

The floating lag time for tablets of all batches was found to be less than 2min regardless of the content of polymer. The particles of polymer are close enough to permit faster establishment of gel layer leads to minimization of influence of filler blends used. The total floating time for tablets was found to be more than 12 h.

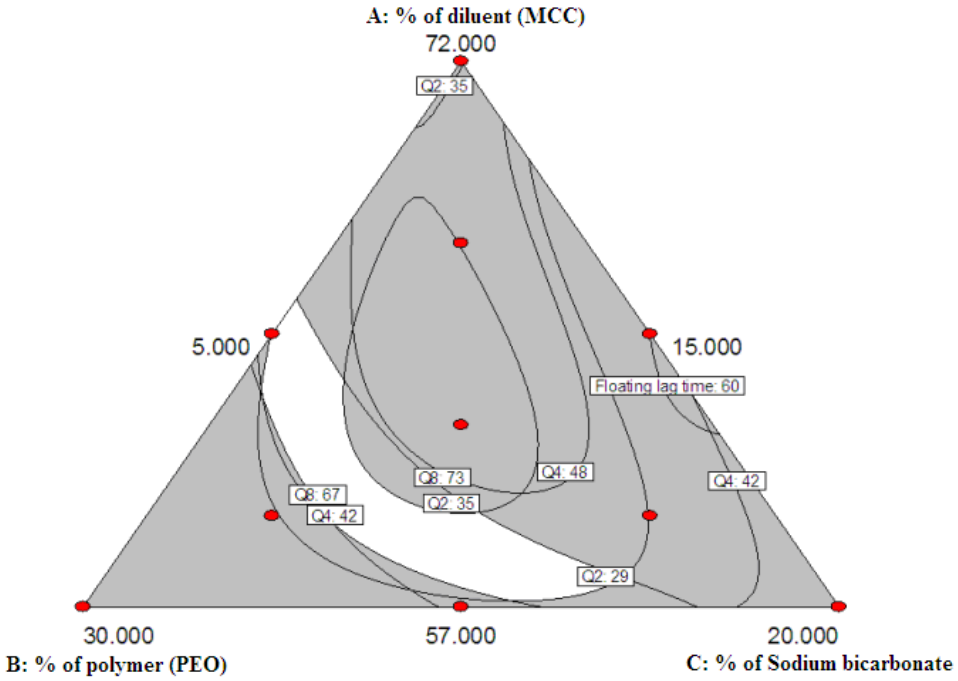

Fig. 5. Overlapping contour plots of all dependent variables

Figure 5 shows overlapping contour plot of all the dependent variables. Highlighted area suggests optimized area from these area check point batch were prepared The Check point batch (RJ1) containing X_1=63%, X_2=22.5% and X_3=6% was formulated, in order to get desirable release profile.

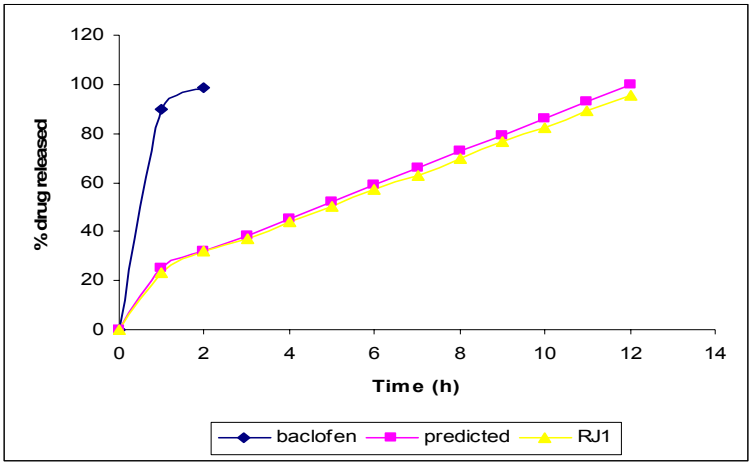

Fig. 6. Predicted and observed dissolution profile

The predicted and observed dissolution profile for check point batch (RJ1) along with standard baclofen is depicted in figure 6. The computed and experimental values for Q_2, Q_4 and Q_8 for check point batch (RJ1) were 32%, 45%, and 72%: 31.8%, 44.1% and 69.9% respectively. Due to fact that baclofen is having solubility more than 20 mg/ml in 0.1N HCl [21] it get dissolved very quickly [22], which is shown in figure 6. Similarity factor

(f_2) was calculated considering the ideal release profile as reference and batch RJ1 as test formulation. The computed value of f_2 was 78.08. Therefore, it was concluded that the two dissolution profiles were similar.

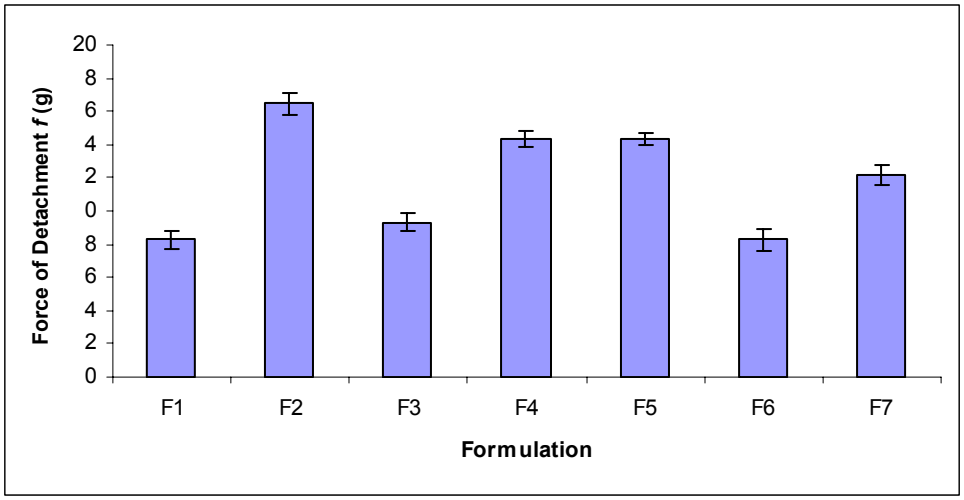

Fig. 7. *Ex vivo* Bioadhesion study of all Simplex lattice designed batches

The result of *ex vivo* bioadhesion study is shown in figure 7. Data depicts an increasing trend in bioadhesive strength, with an increase in the amount of PEO. Maximum bioadhesive strength therefore was seen at the highest level of the polymer. Glass-rubbery transition provides hydrogel plasticization resulting in a large adhesive surface for maximum contact with mucin and flexibility to the polymer chains for interpenetration with mucin. Increasing polymer amount may provide more adhesive sites and polymer chains for interpenetration with mucin, resulting consequently in the augmentation of bioadhsive strength.

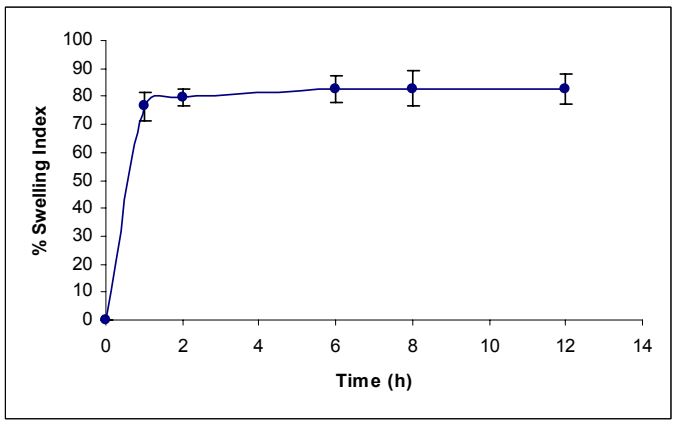

Fig. 8. Swelling study of check point batch

In designing a swelling controlled drug delivery system for constant drug delivery, apart from system configuration, the hydrophilic polymer employed is of crucial importance, as drug release is controlled by simultaneous aqueous medium diffusion into the matrix,

polymer chain relaxation and drug diffusion. Mechanistic drug release kinetics depends on the relative ratio of the rate of the polymer swelling at the glassy/rubbery front to the rate of polymer erosion/drug dissolution at the swollen polymer/dissolution front.

Swelling study of optimized batch (RJ1) is shown in figure 8. Swelling of tablet compacts of PEO occurs upon immediate hydration of the polymer. As the dry polymer becomes hydrated, the mobility of the polymer chains increase, thereby increasing the hydrodynamic volume of the polymer compact, which allows the compact to swell [23]. As polymer chains become more hydrated and the gel becomes more dilute, the disentanglement concentration may be reached, i.e., the critical polymer concentration below which the polymer chains disentangle and detach from a gelled matrix. These events result in simultaneous swelling, dissolution, and erosion [24]. PEO demonstrated a faster rate of water uptake and greater swelling particularly evident with high molecular weight PEO.

The in vitro drug release data of batch RJ1 were analyzed for establishing kinetics of drug release. Zero-order, first-order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas and Weibull models were tested. Korsmeyer-Peppas model showed least sum of square of residuals (SSR = 75.8) and Fischer's ratio (F=9.77). The mechanism of release of baclofen from the formulated batch was by anamolous non-fickian diffusion i.e. diffusion coupled with erosion.

Conclusion

The present work was carried out to develop a self correcting monolithic tablet containing baclofen. The methodology adopted for preparation of Gastroretentive tablet was very simple and cost effective. It was observed that for the development of controlled-release dosage form of baclofen, polymer like PEO which imparts hydrophilic environment leads to more uniform drug release. Self correcting monolithic Gastroretentive tablet of baclofen can be prepared using PEO via floating and bioadhesion approach to increases residence time of drug in stomach and there by increases absorption

Experimental

Materials

Baclofen was received as gift sample from Sun pharmaceutical Ltd., Vadodara (India). Poly (ethylene oxide) WSR 303, (Polyox® mw = 7×106) was received as a gift sample from Dow Chemical Company, New Jersey (USA). Sodium bicarbonate purchased from S.D.Fine chemicals, Mumbai, India. All other ingredients were procured from Lesar chemicals, Vadodara (India) and of analytical grade. All materials used for study conformed to USP 24 standards.

Methods

Simplex Lattice Design

A simplex lattice design was adopted to optimize the formulation variables [25]. In this design, 3 factors were evaluated by changing their concentrations simultaneously and keeping their total concentration constant. The simplex lattice design for a 3-component

system can be represented by an equilateral triangle in 2-dimensional space (figure 9). Seven batches (F1-F7) were prepared, one at each vertex (A, B, C), one at the halfway point between vertices (AB, BC, AC), and one at the center point (ABC). Each vertex represents a formulation containing the maximum amount of 1 component, with the other 2 components at a minimum level. The halfway point between the 2 vertices represents a formulation containing the average of the minimum and maximum amounts of the 2 ingredients represented by 2 vertices. The center point represents a formulation containing one third of each ingredient. Three independent variables, X_1 = percentage of diluent (MCC), X_2 = percentage of polymer (PEO), and X_3= percentage of sodium bicarbonate were selected. The amount of drug release at 2h (Q_2), amount of drug release at 4h (Q_4), amount of drug release at 8h (Q_8) and floating lag time were taken as responses.

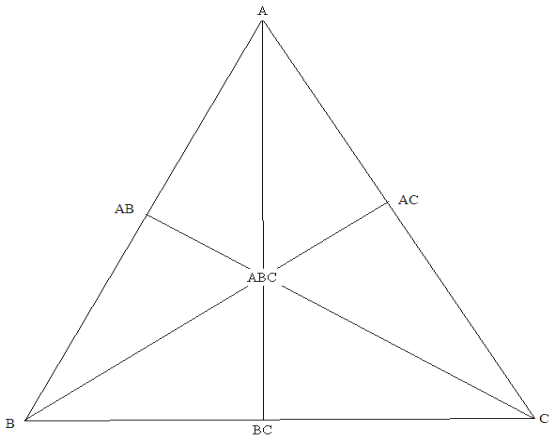

Fig. 9. Equilateral triangle representing simplex lattice design for 3 components (A, B, and C)

Preparation of Baclofen gastroretentive Tablets

Baclofen 20mg was mixed with require quantity of polymer (PEO), sodium bicarbonate, and diluent (MCC) by mixing in laboratory cube blender for 15min., the powder blend was then lubricated with magnesium stearate (1%) for additional 3min and compressed on 10 station rotary tablet machine (Rimek, Ahemdabad,India) using 6mm standard flat face punch. Compression force was adjusted to obtain tablets with hardness in range of 5-6 kg/cm^2.

In Vitro Buoyancy Study

The in vitro buoyancy was observed by floating time and floating lag time studies. The test was performed using USP 24 type II paddle apparatus using 900 ml of 0.1N HCL (pH= 1.2) at a paddle rotation of 50 rpm at 37± 0.5°C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium were noted as floating lag time and total floating time respectively.

In Vitro Drug Release Study

The in vitro drug release study was performed using USP 24 type II paddle apparatus using 900 ml 0.1 N HCL (pH= 1.2) at a speed of 50 rpm at 37± 0.5°C. The samples were withdrawn at predetermined time intervals for period of 12 h and replaced with the fresh

medium. The samples were filtered through 0.45 μm membrane filter, suitably diluted and analyzed at 267 nm using double beam UV/Vis spectrophotometer (Shimadzu Corporation, UV-1601, Japan). The content of drug was calculated using equation generated from standard calibration curve. The test was performed in triplicate. High reproducibility of data was obtained (SD<3%), hence only average values were considered.

Swelling Index Study

The swelling index is the volume in milliliters occupied by 1 gram of a drug, including any adhering mucilage, after it has swollen in an aqueous liquid for 4 h. Swelling study of check point batch (RJ1) was carried out in Distek Dissolution System (USP I Apparatus) using 40-mesh baskets at 50 rpm in degassed water. Hydrated compacts were removed at predetermined times over a 12h period to measure swelling by water uptake using following formula. (n=3)

$$\text{Weight gain (\%)} = (\text{Wet weight} - \text{Original weight}) / \text{Original weight} * 100$$

Ex Vivo Bioadhesion Study

All seven batches were studied for Bioadhesion strength using a modification of the assembly described by Sigh et al [26]. Tablet bioadhesion studies were done using rat stomach tissue. The stomach tissue was used immediately after sacrificed the animal for this study. The detachment force, i.e. the force required to separate the tablet from the tissue surface was determined. The tablet was lowered onto the mucosa under a constant weight of 5 g for a total contact period of 1 min. (n=3)

Kinetics of Drug Release

The dissolution profile of all the batches was fitted to various models such as zero-order, first-order, Higuchi [27], Hixon-Crowell [28], Korsmeyer and Peppas, [29–31] and Weibull models [32, 33] to ascertain the kinetic modeling of drug release. The least value of sum of square of residuals (SSR) and Fishers ratio (F) were used to select the most appropriate kinetic model [34].

Criteria for Optimized Batch

Four limits were selected based on theoretical release profile calculated using pharmacokinetics data of baclofen. (1) Percentage of drug release at 2h (Q_2) = 32% (2) Percentage of drug release at 4h (Q_4) = 45% (3) Percentage of drug release at 8h (Q_8) = 72%. (4) Floating lag time= 80 Second.

Comparison of dissolution profiles

The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles are considered to be similar when f_2 is between 50 and 100. The dissolution profiles of products were compared using f_2. This similarity factor is calculated by following formula,

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} \left(R_t - T_t \right)^2 \right]^{-0.5} \times 100 \right\}$$

Where, n is the number of dissolution time and R_j and T_j are the reference and test dissolution values at time t.

Statistical Analysis

The statistical analysis of the Simplex lattice design batches were performed using Microsoft Excel®. To graphically demonstrate the influence of each factor on responses, the contour plots were generated using Stat Ease, Inc. (Minneapolis, MN) Design Expert 7.1.6 software.

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Authors' Statement

Competing Interests

The authors declare no conflict of interest.

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