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Research Article

Formulation Development and Optimization of Floating Matrix Tablet of Pregabalin

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ABSTRACT

Pregabalin has a short elimination half-life and is absorbed in the small intestine and the ascending colon in humans but is poorly absorbed beyond the hepatic flexure. The purpose of this study was to develop a gastro retentive effervescent controlled release drug delivery system with swelling and floating properties. Tablet formulations were designed using hydroxyl propylmethylcellulose (HPMC K15M) and sodium alginate (Na alginate) as release-retarding polymer(s) and sodium bicarbonate ($NaHCO_3$) as a gas former. Floating behavior, swelling study and drug release studies were performed in 0.1 N HCl (pH1.2) at 37 ± 0.5°C. The tablets showed acceptable physicochemical properties. Drug release profiles of all the 12 batches formulated followed zero order. Statistical analysis of data done by design expert software revealed that the desired physicochemical properties of effervescent matrix tablets could be achieved by optimization through 3^2 full factorial designs. The optimized batch was promising and exhibited excellent floating properties, swelling properties and sustained drug release characteristics. This optimized batch was stored at 40˚C /75% RH for 3 months according to ICH guidelines. It was concluded that combination of HPMC K15M, sodium alginate, and sodium bicarbonate showed good swelling, floating and drug release characteristics.

INTRODUCTION

Pregabalin is an analogue of the neurotransmitterγ-amino butyric acid (GABA), which has analgesic, anticonvulsant, and anxiolytic effects. The worldwide brand name of Pregabalin is Lyrica®, which is available in more than 60 countries. Pregabalin has been studied in the treatment of patients with diabetic peripheral neuropathy(DPN), post herpetic neuralgia (PHN), generalized anxiety disorder (GAD), and social anxiety disorder (SAD) and as an adjunctive therapy in adults with partial-onset seizures [1].

Pregabalin is available as an immediate release (IR) formulation in capsules and is administered to patient's two or three times daily (BID or TID). Many patients receiving Pregabalin or other drugs, which are administered two or more times daily would likely benefit from once daily dose.

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The convenience of once daily dosing generally improves patient compliance, especially for elderly patients and for patients taking multiple medications. Once per day dosing may also lessen or prevent potentially undesirable dose-related effects by reducing peak blood levels (C MAX) and may also increase drug efficacy by increasing minimum plasma concentrations [2].

Once daily dosing of Pregabalin, however, presents numerous challenges. Conventional extended release (ER) compositions are problematic for dosing because Pregabalin is not absorbed uniformly in the gastrointestinal (GI) tract. Clinical studies indicate that Pregabalin is absorbed in the small intestine and the ascending colon in humans, but is poorly absorbed beyond the hepatic flexure. This suggests that the mean absorption window for Pregabalin is, on average, about six hours or less and release from a conventional extended release dosage form beyond six hours would thus be wasted because the dosage form has traveled beyond the hepatic flexure [2]. So

retention of drug in the stomach will be beneficial to improve the absorption of the drug.

The gastro intestinal tract (GIT) is the major route of drug delivery to the systemic circulation. The normal gastric emptying time is 46.5 ± 5.5 minutes. Oral controlled release dosage forms are not suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the GIT. This is due to the relatively less transit time of the dosage form in these anatomical segments. Thus after only a short period of less than 6 h, the controlled release formulation travels through the upper GIT and the drug is released in little, non absorbing distal segment of the GIT. This results in a short absorption phase, which is then accompanied by lesser bioavailability. Such problems can be overcome by Floating Drug Delivery System (FDDS) [3].

The present study was carried out to design, develop and optimize the effervescent based floating matrix tablets of Pregabalin. The gastroretentive drug delivery system can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT. Several approaches are currently used to prolong gastric retention time like floating drug delivery systems [4], swelling and expanding systems [5], bioadhesive systems [6], modified shape systems [7], high-density systems [8], and other delayed gastric emptying devices. Among them the principle of buoyant preparations offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.

MATERIALS AND METHODS

Materials

Pregabalinwas provided by Cadila Healthcare Ltd., (Ankleshwar) and hydroxypropylmethylcelluloseK15M (HPMC K15M) was provided by Genuine Chemical co.(Mumbai, India). Low viscosity sodium alginate was purchased from SD Fine Chemicals Ltd. (Mumbai, India). Polyvinyl pyrrolidone K30 and Avicel pH 102 were purchased from Balaji Drugs. Magnesium Stearate was purchased from Genuine Chemical co. (Mumbai, India). Sodium bicarbonate was obtained from Suvidhinath Laboratory (Vadodara, India).

Preparation of floating matrix tablets

Tablets containing 150 mg Pregabalin were prepared, according to the design depicted in Table 1, by wet granulation method. Pregabalin and release-retarding polymers (HPMC K15M, sodium alginate), a gas-forming agent ($NaHCO_3$), Avicel pH 102 were accurately weighed and transferred to a mortar. Polyvinyl pyrrolidone K30 (PVP K30) was weighed and dissolved in isopropyl alcohol (IPA). Wet granulation was carried out by adding PVP K30 solution in powder mixture and dried. Granules were passed through sieve #22 to get uniform size granules. Then magnesium stearate was weighed and added into above granule mixture. This granule mixture was compressed using Rimek tablet compression machine equipped with 10.3 mm concave punch.

3^2 Full factorial Design

A 3^2 randomized full factorial design was used in development of the dosage form. In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed using all possible 9 combinations. In the present investigation, the ratio of hydroxyl propyl methyl cellulose (HPMC) K4M: sodium alginate (X_1) and percentage of polyvinyl pyrollidoneK30 (PVP K30) (X_2) were selected as independent variables. The percentage drug release at 2 hours(Q_2),percentage drug release at 6 hours (Q_6), percentage drug release at 12 hours (Q_{12}), % swelling index (%SI) and % compressibility index (%CI) were selected as dependent variables. The experimental design with corresponding formulations is outlined in Table 1. Blends of HPMCK4M and sodium alginate were evaluated at 75:25, 50:50and 25:75, while percentage of PVP K30 was evaluated at 2%, 3%, and 4% of total tablet weight.

Physical properties of granules

The method for measurement of angle of repose, bulk density, tapped density; compressibility index and Hausner's ratio were determined by procedure stated in the US pharmacopoeia [9].

Physical properties of floating tablets

The thickness, hardness, weight variations, and content uniformity of fabricated tablets were determined by procedure stated in the Indian Pharmacopeia 2010 [10].

In-vitro buoyancy studies

The floating behaviour of the tablets was visually determined, in triplicate, according to the floating lag time method described by Rosa et al. [11]. Briefly, a tablet was placed in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a

Table 1: Formulation ingredients of floating matrix tablets

Batches	Pregabalin (mg)	HPMC K15M(mg)	Sodium Alginate (mg)	Sodium Bicarbonate (mg)	PVP K30(%)	Magnesium Stearate (mg)	Avicel pH 102 (mg)
B1	150	75	25	40	2	2	Quantity Sufficient to 400 mg
B2	150	50	50	40	2	2	
B3	150	25	75	40	2	2	
B4	150	75	25	40	3	2	
B5	150	50	50	40	3	2	
B6	150	25	75	40	3	2	
B7	150	75	25	40	4	2	
B8	150	50	50	40	4	2	
B9	150	25	75	40	4	2	
B10	150	50	50	40	3	2	
B11	150	50	50	40	3	2	
B12	150	45	55	40	3.84	2	

Table 2: Evaluation of powder granules ready for compression

Batch No.	Angle of Repose (θ)	Bulk density (Gm./cm^3)	Tapped Density (gm./cm^3)	% Compressibility	Hausner's Ratio
B1	33.72°±1.81	0.33±0.01	**0.462±0.01**	32.81±1.12	1.48±0.021
B2	31.64°±1.20	0.34±0.006	0.484±0.14	30.38±0.54	1.44±0.012
B3	30.84°±1.31	0.417±0.017	0.589±0.035	29.19±1.32	1.41±0.025
B4	31.46°±0.67	0.31±0.006	0.435±0.018	29.55±3.35	1.39±0.007
B5	30.28°±1.37	0.467±0.013	0.656±0.024	28.14±0.46	1.39±0.08
B6	29.43°±1.36	0.432±0.01	0.566±0.019	25.25±0.67	1.336±0.01
B7	27.80°±1.08	0.395±0.009	0.517±0.015	23.63±0.55	1.31±0.009
B8	27.06°±0.36	0.492±0.014	0.613±0.021	19.68±0.55	1.25±0.006
B9	25.87°±0.78	0.454±0.019	0.526±0.017	14.78±0.56	1.16±0.008
B10	31.18°±0.86	0.469±0.016	0.617±0.014	28.78±0.76	1.40±0.005
B11	30.67°±0.65	0.417±0.024	0.588±0.017	28.19±0.67	1.41±0.05
B12	30.84°±0.28	0.3125±0.016	0.4±0.013	19.35±0.46	1.23±0.004

Table 3: Evaluation of floating matrix tablets

Batch No.	Average weight (mg) (n=10)	Thickness (mm) (n=5)	Hardness (kg/cm^2) (n=5)	Friability (%) (n=20)	Floating Lag Time (sec.) (n=5)	Total Floating Duration (Hrs.)	Assay (%) (n=5)
B1	393.5±9.20	4.88±0.019	6.1±0.16	0.88	40.83±4.62	>24	92.60
B2	400.7±7.29	4.89±0.038	5.8±0.34	0.86	21.17±2.99	>24	98.15
B3	400.1±2.23	4.90±0.011	6.4±0.17	0.55	25.83±1.83	Up to 24	99.94
B4	397.3±7.04	4.87±0.032	6.7±0.26	0.35	56.5±5.68	>24	90.61
B5	399.9±5.03	4.89±0.017	5.6±0.46	0.75	38±4.24	>24	94.98
B6	401.2±4.44	4.90±0.026	7.0±0.11	0.25	38.5±5.50	>24	96.77
B7	396.4±9.14	4.87±0.019	6.6±0.14	0.74	28.67±3.50	<24	92.4
B8	402.2±7.15	4.91±0.012	6.3±0.21	0.43	14.17±1.47	>24	100.53
B9	403.8±8.17	4.91±0.031	5.9±0.27	0.61	28.35±3.29	>24	100.13
B10	398.8±3.13	4.89±0.005	6.2±0.16	0.66	31.25±2.78	>24	100.92
B11	400.3±3.43	4.90±0.024	6.7±0.19	0.58	52.67±2.16	>24	100.53
B12	400.4±3.57	4.90±0.037	6.2±0.12	0.80	12.35±1.49	>24	97.72

Table 4: Release kinetics for batches B1 – B12

Batch no.	Higuchi kinetics	Zero order kinetics	First order kinetic	HixonCrowel kinetic	KorsmeyerPeppas		Mechanism of drug release
	R^2	R^2	R^2	R^2	R^2	N	
B1	0.9685	0.9641	0.7283	0.9128	0.9502	0.691	Non-Fickian
B2	0.9776	0.9527	0.5986	0.9793	0.8629	0.923	Non-Fickian
B3	0.9483	0.9786	0.8150	0.9753	0.9761	0.655	Non-Fickian
B4	0.9766	0.9415	0.6763	0.9633	0.9122	0.782	Non-Fickian
B5	0.9877	0.9855	0.7792	0.9911	0.9923	0.695	Non-Fickian
B6	0.9743	0.9184	0.5324	0.9662	0.8763	0.912	Non-Fickian
B7	0.9929	0.9601	0.5322	0.9777	0.9398	0.635	Non-Fickian
B8	0.9906	0.9547	0.6517	0.9887	0.9841	0.521	Non-Fickian
B9	0.9502	0.9882	0.7182	0.9984	0.9934	0.737	Non-Fickian
B10	0.9934	0.9854	0.7650	0.9948	0.9942	0.748	Non-Fickian
B11	0.9972	0.9718	0.6599	0.9928	0.9503	0.933	Non-Fickian
B12	0.9811	0.9900	0.7650	0.9889	0.9862	0.773	Non-Fickian

Table 5: Summary of results of multiple regression analysis for response Y1 to Y5

Dependent Variables	Y1= Q_2		Y2= Q_6		Y3= Q_{12}		Y4= %SI		Y5= %CI	
	P value	Coefficients	P value	Coefficients	P value	Coefficients	P value	Coefficients	P value	Coefficients
Intercept	<0.0001	30.63	<0.0001	65.63	<0.0001	91.13	<0.0001	195.93	<0.0001	25.20
X1	0.00024	–5.37	0.005	-3.08	0.0005	-4.848	0.0004	-30.48	0.0002	-4.473
X2	0.011	–2.28	0.002	-3.83	0.021	-2.056	0.003	20.445	0.019	-1.453
X11	0.49	0.52	0.073	-1.77	0.520	0.525	0.262	-5.657	0.428	0.455
X12	0.90	0.12	0.189	-1.50	0.127	1.743	0.244	-7.427	0.592	-0.378
X22	0.63	0.46	0.499	-0.72	0.564	0.588	0.077	12.492	0.314	0.741

Table 6: Summary of results of regression analysis for responses Y1 to Y5 for fitting to quadratic model

Quadratic model	R^2	Adjusted R^2	Predicted R^2	SD	% CV
Y_1	0.9531	0.9062	0.7375	1.42	4.60
Y_2	0.9314	0.8628	0.3043	1.57	2.43
Y_3	0.9391	0.8782	0.4212	1.52	1.65
Y_4	0.9557	0.9114	0.6704	8.96	4.51
Y_5	0.9604	0.9208	0.6172	1.06	4.16

Table 9: Results of stability study of optimized batch B12

Tested after time	Hardness (kg/cm^2)	Floating test		Drug Content (%)	Swelling index (%)	% Drug release after 12 hrs.
		FLT (sec)	TFT (hrs.)			
0	6.2±0.26	11.4±1.52	>24	97.72%	214.65±0.64	90.64±0.65
1 month	6.1±0.45	11.7±1.34	>24	98.52%	218.65±0.82	90.25±1.34
2 months	6.1±1.23	13.3±1.65	>24	97.25%	216.49±1.34	91.56±0.94
3 months	5.9±0.85	15.64±1.75	>24	96.83%	213.78±0.56	91.35±0.76

water bath at 37 ± 0.5°C. The floating lag time "the time between tablet introduction and its buoyancy" and total floating duration "the time during which tablet remains buoyant" were recorded[12].

Assay

Ten tablets were finely powdered; quantities of the powder equivalent to 60 mg of Pregabalin were accurately weighed and transferred to a 100 ml of volumetric flask, dissolved in water and sonicated for 5 min., the volume was then completed with water, shaken well for 5 min. and filtered into a dry flask. To 5.0 mL aliquots of the filtrate taken in stoppered tubes, 1.0 mL of ninhydrin solution (2.0% w/v) was added and solution heated on a water bath at a temperature of 70-75°C for 20 minutes. Solutions were cooled to room temperature and the absorbance values noted in triplicate at 402.6 nm against reagent blank using a UV spectrophotometer [13].

Swelling studies

The swelling behavior of tablets were measured in glass containing 200 ml of HCl (0.1 N) which was maintained at 37 ± 0.5 °C. At regular time intervals, the tablets were removed from glass and the percentage of swelling was calculated using the following equation [12, 14]

$$\% \text{ Swelling index} = \frac{W_2 - W_1}{W_1} \times 100 \quad \ldots\ldots\ldots (1)$$

Where W_2 is the weight of the swollen tablets, and W_1 is the initial weight of the tablets. The measurement was carried out in triplicate (n = 3).

***In vitro* drug release study**

Drug release studies of the prepared floating tablets were performed, in a USP Dissolution Tester Apparatus, type-II (Paddle method) (Dissolution Test Apparatus-TDT_06T (Electrolab, Mumbai, India)) at 37 ± 0.5°C. The paddles rotated at a speed of 100 rpm. The tablets were placed into 900 mL of 0.1N HCl solution (pH 1.2). Aliquots of 10 ml were withdrawn from the dissolution apparatus at different time intervals and filtered through a whatmann filter paper no 1(0.45 µm). The drug content was determined spectrophotometrically at a wavelength of 402.5 nm. To the aliquots of the filtrate taken in test tubes, 2.0 mL of ninhydrin solution (2.0% w/v) was added and solution heated on a water bath at a temperature of 70-75°C for 20 minutes. Solutions were cooled to room temperature and the absorbance values noted in triplicate at 402.6 nm against reagent blank using a UV spectrophotometer. At each time of withdrawal, 10 ml of fresh medium was replaced into the dissolution flask [13].

Kinetic modeling of drug release profiles

The dissolution profiles of all formulae in 0.1 N HCl were fitted to zero-order, first-order, Higuchi [15] and Korsmeyer–Peppas kinetic models [16]. The model with the highest correlation coefficient was considered to be the best fitting one.

Statistical analysis of drug release profiles

Data obtained from all gastric floating tablet formulations were analyzed using Design Expert software and used to generate the study design and the response surface plots. Polynomial models, including linear, interaction and quadratic terms were generated for all the response variables using the software. The best fitting model was selected based on comparisons of several statistical parameters, including the coefficient of variation (CV), coefficient of determination (R^2) and adjusted coefficient of determination (adjusted R^2) provided by Design Expert software [12, 17].

The relationship between the dependent and independent variables was further elucidated using response surface plots. These plots are useful to study the effects of various factors on the response at a given time and to predict the responses of dependent variables at intermediate levels of independent variables. Subsequently, a numerical optimization technique using the desirability approach and a graphical optimization technique using overlay plots were used to generate new formulations with the desired responses [12, 17].

RESULT AND DISCUSSION

Physical properties of granules

All formulations were evaluated for angle of repose, bulk density, tapped density, % compressibility and Hausner's ratio. Results are shown in Table 2.

Angle of repose of all batches varies from 25.87° to 33.72°. Angle of repose less than 30 indicates good flow property. Compressibility index vary from 14.78% to 32.81%. Compressibility index 12 to 16% indicates good compressibility. Hausner's ratio varies from 1.16 to 1.48. Hausner's ratio less than 1.25 indicates good compressibility. Here Batches B6-B9, B12 showed excellent flow property and compressibility, which is favorable for compression of tablets.

Physical properties of floating tablets

Prepared tablets of all batches were evaluated for weight variation, thickness, hardness,

friability, floating lag time, total floating duration and assay. Results of all batches are shown in Tables 3.

All the batches passed physicochemical test for weight variation, friability, floating lag time and drug content study.The thickness of all tablet batches ranged from 4.87-4.91 mm. The friability of all the batches less than 1% which is complied as per pharmacopeia specification 2010 [10].All formulations floated in the 0.1 mol/L HCl for more than 7 h showing good matrix integrity during this extended period of time [17]. The percentage drugs content of the all batches were found between 90.61% and 100.92%, which is within acceptable limits indicating dose uniformity in each batch.

Floating lag time and duration

The investigated gastric floating systems employed $NaHCO_3$ as a gas-forming agent dispersed in a hydrogel matrix (HPMC K15M and sodium alginate). The in vitro testing revealed the ability of most formulae to maintain buoyant more than 24 h(Table 3). This suggests that the gel layers, formed by the investigated polymers, enabled efficient entrapment of the generated gas bubbles. The possible increase in tablet porosity made it float on the test medium (0.1 N HCl) for this extended period of time.

These matrices are fabricated so that upon arrival in the stomach, carbon dioxide gas is liberated by the acidity of the gastric contents and is entrapped in the jellified hydrocolloid. A decrease in specific gravity causes the dosage form to float on the chime [18].

FLT was less than 60 s for all formulations studied. TFT was longer than 24 h formost formulations. In the optimized formulation, CO_2 was generated after 12 s and floated for more than 24 h.

Swelling studies

Swelling ratio describes the amount of water is contained within the hydrogel at an equilibrium and is a function of the network structure, hydrophilicity and ionization of the functional groups.

Swelling study was performed on all the batches for 24 hrs. The results of swelling index are given in the plot of %swelling index against time (hrs.) is depicted in Figure 1.

From the results it was concluded that swelling increases as the time passes because the polymer gradually absorbs water due to hydrophilicity of polymer. The outer most hydrophilic polymer hydrates and swells and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is repeated towards new exposed surfaces, thus maintaining the integrity of the dosage form.

In the present study, the higher swelling index was found for tablets of batch B7 containing higher concentration of HPMC K15M (75mg) and sodium alginate (25mg). As concentration of HPMC K15M increases, swelling of tablet increases.

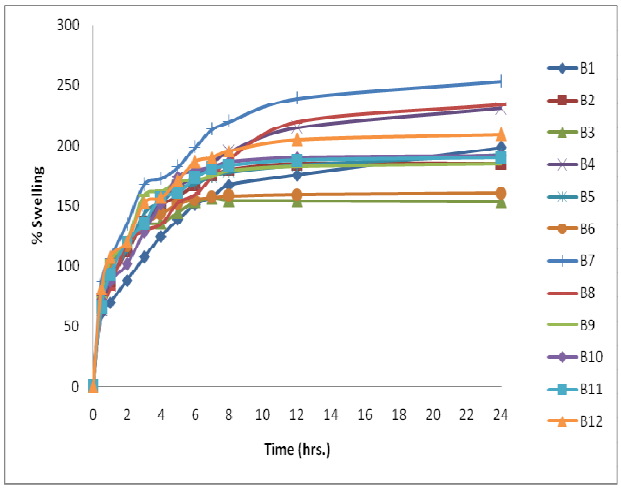
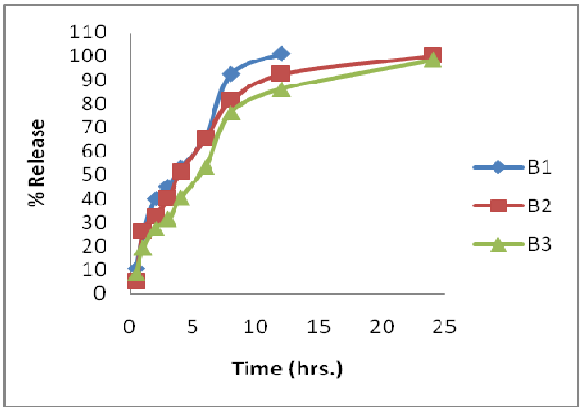


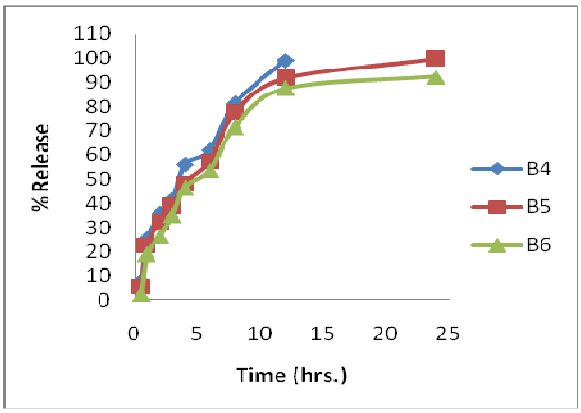
Figure 1: Swelling Index of Batches B1-B12

***In vitro* dissolution studies**

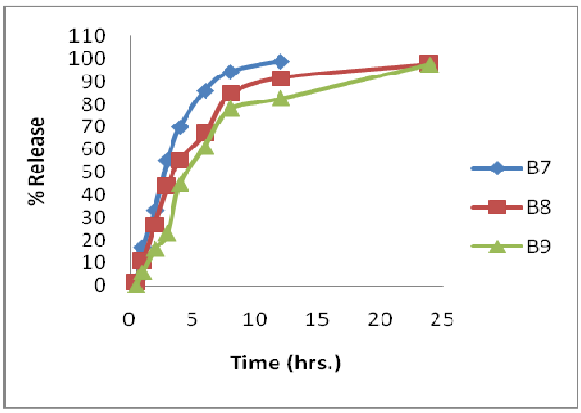
The percentage of Pregabalin released from the prepared GFT formulations is shown in Fig. 2.The *in vitro* release ofPregabalinfromtheformulations B1, B4 and B7 reached90%inless than12h; release from B2, B5, B8, B10 and B11 exhibited 90% at the end of 12 h; release from B3, B6, B9 and B12 required more than 12 h.The results show that drug release is retarded as the amount of sodium alginate and concentration of PVP K30 increase [17].



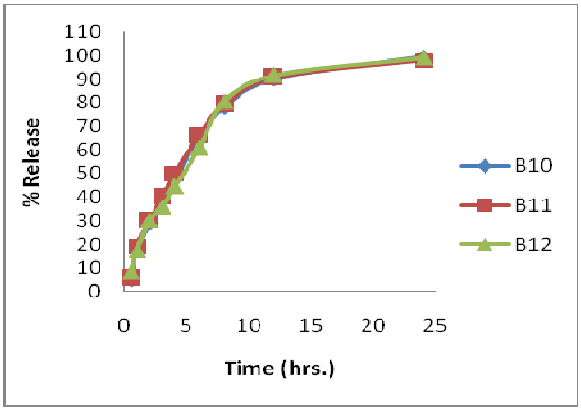
(A)



(B)



(C)



(D)

Figure 2: Dissolution profile of floating tablet formulations (A) B1 to B3, (B) B4 to B6, (C) B7 to B9 and (D) B10 to B12

Drug release kinetics

The drug release from the polymeric systems is generally by diffusion and is best described by Fickian diffusion. But in the case of the formulae containing swelling polymers like HPMC K15M and/or Na alginate, other processes take place, like relaxation of polymer chains, imbibition of water causing polymers swelling and considerable volume expansion [6, 19]. Korsmeyer and Peppas equation [16] superposes two apparently independent mechanisms of drug transport, Fickian diffusion and a case-II transport, for the description of drug release from a swelling polymer. For a matrix tablet, when n takes the value of 0.5, it indicates diffusion-controlled drug release and for the value 1, it indicates swelling-controlled drug release. Values of n between 0.5 and 1 can be regarded as an indicator for both the phenomena (anomalous transport). The values of n with the corresponding correlation coefficients for all the formulae are shown in Table 4. It is clear that all formulae haven values between 0.45 and 0.89, indicating anomalous transport. The relative complexity of the prepared formulae may indicate that the drug release is controlled by more than one process; a coupling of diffusion and erosion.

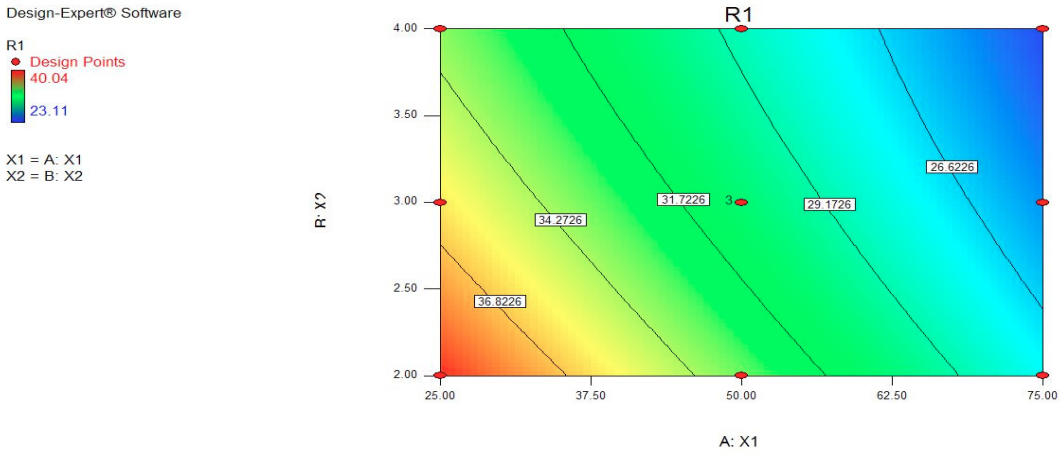
From the Korsmeyer Peppas equation, the diffusion exponent ranges from 0.521 to 0.933. From the results, all the batches exhibited non-Fickian release. Coefficients of correlation (R^2) were used to evaluate the accuracy of the fit. The R^2 values are given in Table 4. Drug release mechanisms follow Zero order, Higuchi order, Krosmeyer Pappas and Hixoncrowel kinetic rather than first order.

Data analysis

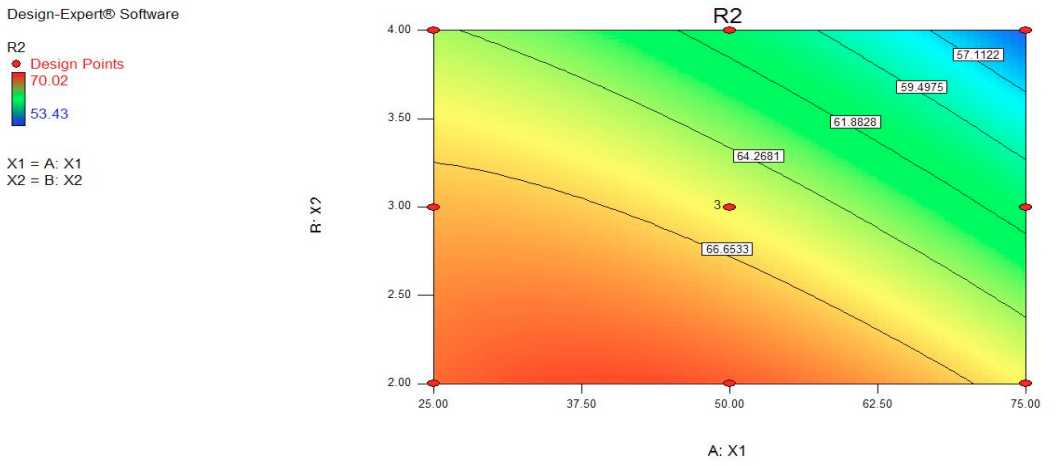
All responses were fitted to quadratic models using Design Expert software. All dependent variable responses are shown in Table 5.Using the polymers HPMC K15M and sodium alginate with PVP K25 as a binding agent, 12 batches of formulation were prepared within the experimental design to obtain GFTs, which were evaluated for swelling properties and drug release profile.

The values of probability>F were found to be <0.05 for all responses indicating that the models are significant. The calculated R^2 value in the present model is close to zero indicating a good model as shown in Table 6. The comparative values of R^2, SD, and %CV are given in Table 6 along with the regression equation generated for each response (Table 7). A positive value represents an effect that favors the optimization, while a negative value indicates an inverse relationship between the factor and the response. It is evident that both independent variables, viz., the ratio of HPMC K15M: sodium alginate (X_1) and concentration of PVP K30 (X_2) have negative effects on the four responses, viz., Q_2 (%), Q_6 (%), Q_{12} (%) and %CI (%) but X_2 have positive effect on %SI.

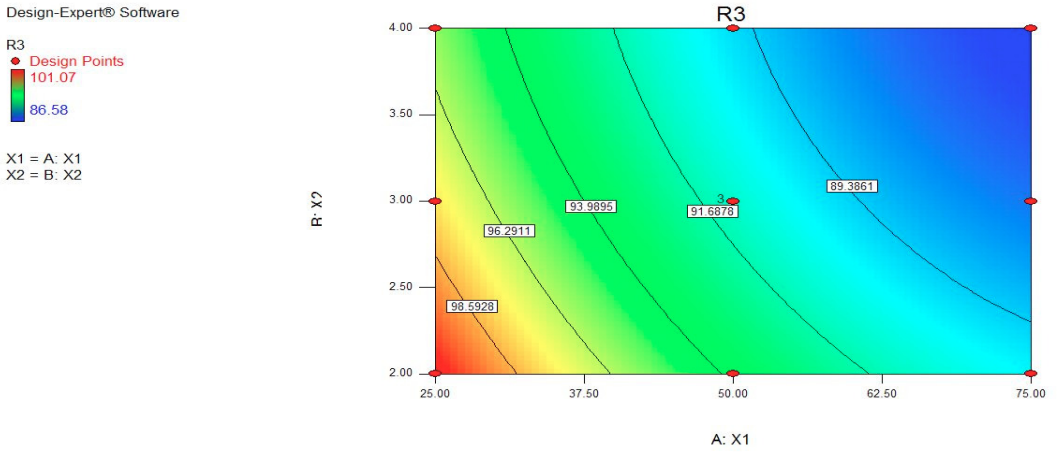
The contour and response surface plots for all responses of all formulation factors are shown in



Q_2

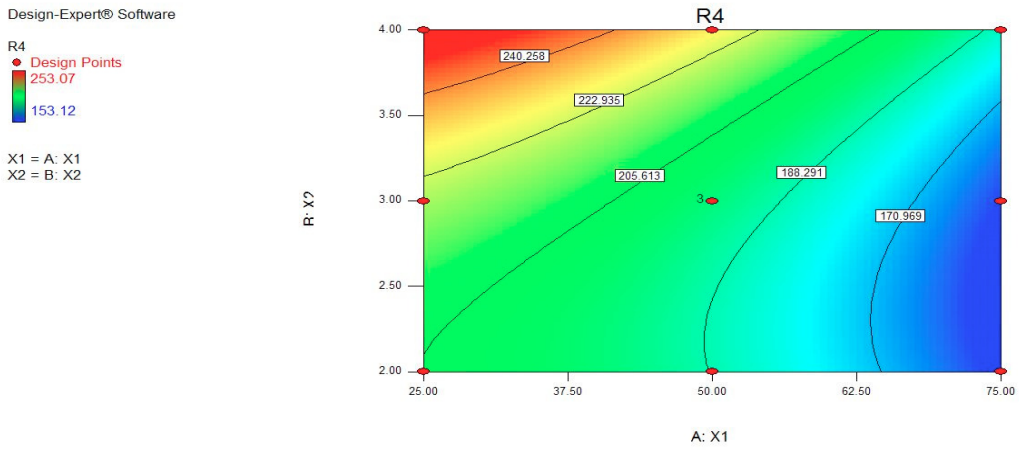


Q_6

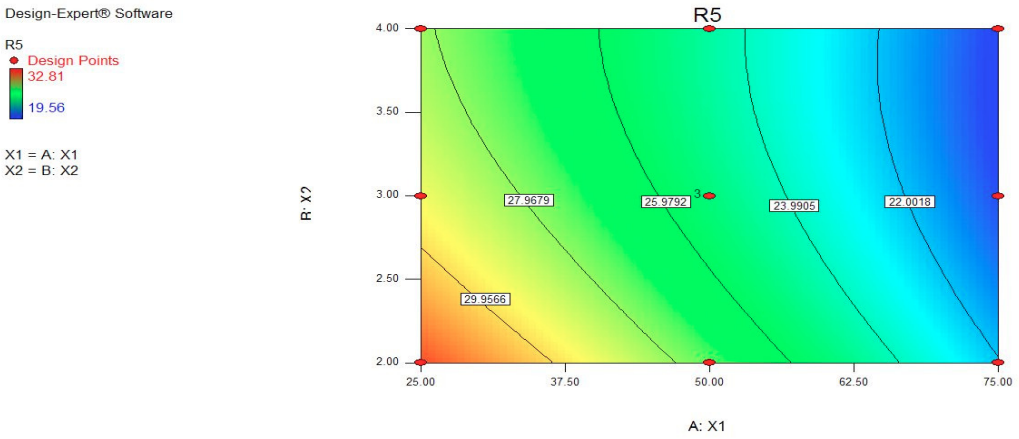


Q_{12}

Figure 3 and 4. The contour and response plots of the response surface as a function of two factors at a time, with all other factors fixed, are more helpful in understanding both the main and interaction effects of the two factors [17].

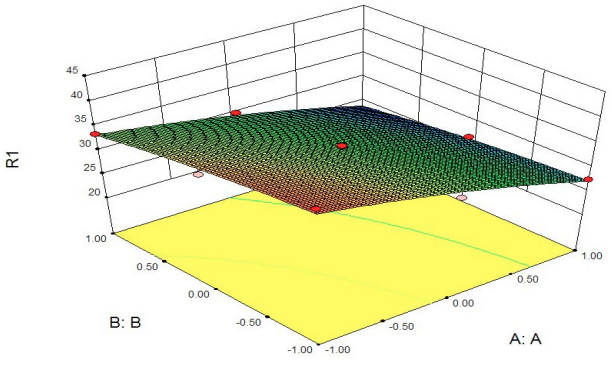


%Swelling Index

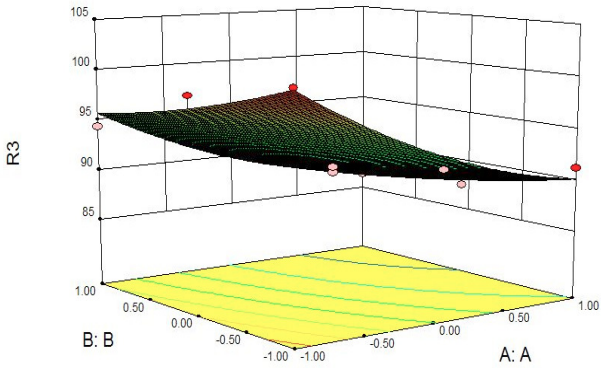


% Compressibility Index

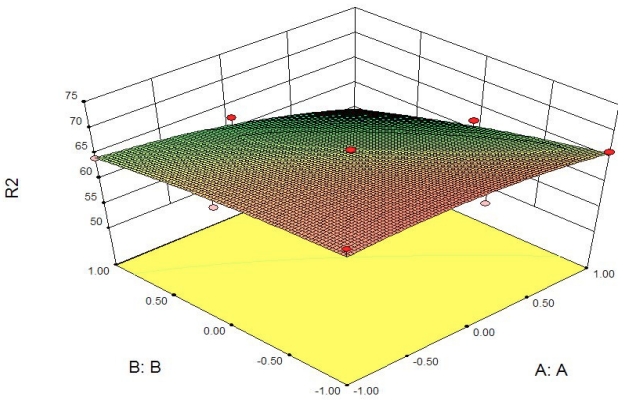
Figure 3: The Contour plots for all the dependent variables



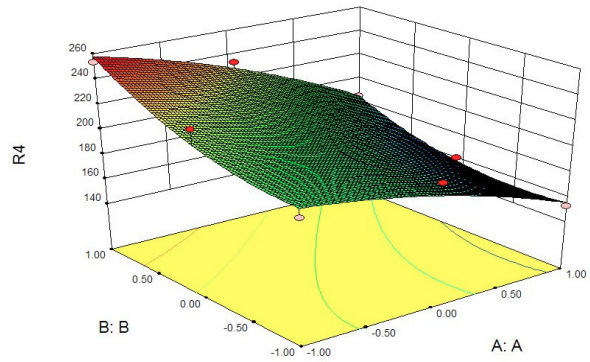
Q_2



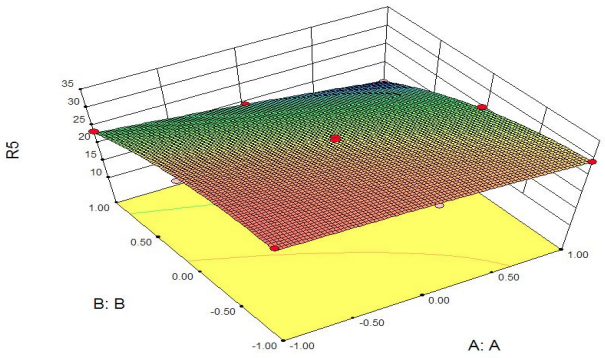
Q_{12}



Q_6



% Swelling Index (%SI)



% Compressibility Index (%CI)

Figure 4: The 3-D plots for all the dependent variables

Table 7: Summary of quadratic polynomial equation for responses Y1 to Y5 for fitting to quadratic model

Quadratic model	Quadratic polynomial equation
Y_1	$Y_1 = 30.63 - 5.37\ X_1 - 2.28\ X_2 + 0.52\ X_1X_2 + 0.12\ X_1^2 + 0.46\ X_2^2$
Y_2	$Y_2 = 65.63 - 3.08\ X_1 - 3.83\ X_2 - 1.77\ X_1X_2 - 1.50\ X_1^2 - 0.72\ X_2^2$
Y_3	$Y_3 = 91.13 - 4.85\ X_1 - 2.06\ X_2 + 0.52\ X_1X_2 + 1.74\ X_1^2 + 0.59\ X_2^2$
Y_4	$Y_4 = 195.93 - 30.48\ X_1 + 20.45\ X_2 - 5.66\ X_1X_2 - 7.43\ X_1^2 + 12.49\ X_2^2$
Y_5	$Y_5 = 25.20 - 4.47\ X_1 - 1.45\ X_2 + 0.45\ X_1X_2 - 0.38\ X_1^2 + 0.74\ X_2^2$

The optimum formulation was selected based on the criteria of attaining the constraints of variables response. Upon 'trading of' various response variables and comprehensive evaluation of feasibility search and exhaustive grid search, the formulation composition with concentration of HPMC K15M (45mg), sodium alginate (55mg) and PVP k25 (3.84%) were found to fulfill the maximum requisite of an optimum formulation because of optimum Q_2, Q_6, Q_{12}, %swelling index and % compressibility index considering the applied constraints on other. The constraints were shown in Table 8.

Stability study

Stability study was done to see the effect of temperature and humidity on tablets during the storage time. The optimized batch tablets were kept under condition of 40ºC/75% RH for 3 months. Tablets were evaluated periodically (0, 1, 2 and 3 months) for appearance, hardness, friability, swelling index, floating test, drug content and *in vitro* drug release. Results of stability study are given in Table 9.

No significant changes were observed in any of study parameter during study period. So, batch B12 is stable

Table 8: Results of optimized batch for response variables

Response variables	Constrains	Predicted value	Experimental value
$Y_1 = Q_2$ (amount of drug release after 2 hrs.)	25≤ Y1 ≥30	28.06%	29.26%
$Y_2 = Q_6$ (amount of drug release after 6 hrs.)	58≤ Y2 ≥63	60.907%	60.74%
$Y_3 = Q_{12}$ (amount of drug release after 12 hrs.)	86≤ Y3 ≥91	89.013%	90.64
Y_4= % Swelling index	201≤ Y4 ≥228	215%	214.65
Y_5= % Compressibility index	18≤ Y5 ≥25	23.68%	19.99%

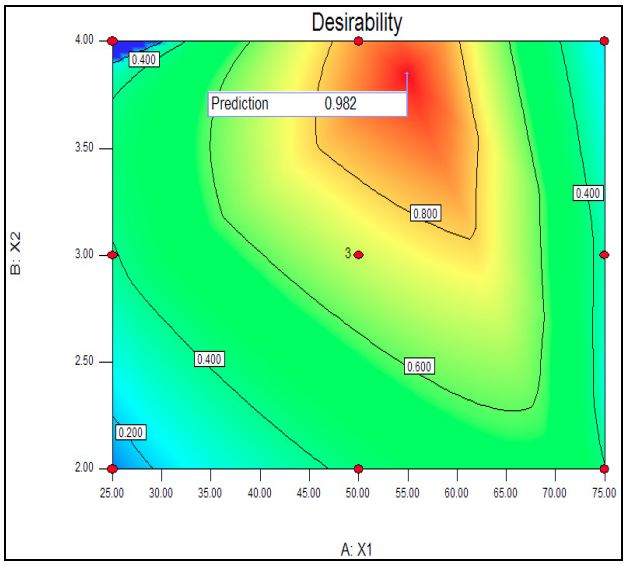


Figure 5: Desirability plot of optimized batch B12.

CONCLUSION

The present investigation deals with the formulation, development and optimization of effervescent based floating matrix tablet of Pregabalin using HPMC K15M and sodium alginate with PVP K25 as a binding agent. Combination of HPMC K15M and sodium alginate were used as release rate controlling polymers. Optimization was done using 3^2 full factorial designs at 3 levels and 2 factors. From the polynomial equation and contour plots generated, the 2 independent factors showed significant effect on dependent variables. The

controlled release of Pregabalin was observed and good fit to the zero order and Higuchi model was demonstrated. The optimized batch B12 (3.84% of PVP K25, 45 mg of HPMC K4M and 55 mg of sodium alginate) exhibited the selected dissolution criteria. Thus the effervescent floating matrix tablets using HPMC K15M and sodium alginate is suitable to get site-specific delivery and controlled release.

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