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Research Article

Study of Release Kinetics and Statistical Optimization of Slow Release Effervescent Tablet Containing Ibuprofen

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Abstract

The work investigates the formulation development, evaluation and optimization of ibuprofen effervescent tablet using 3^2 factorial designs. The effect of variables viz. xanthan gum and sodium bicarbonate on drug release and hardness of ibuprofen effervescent tablets were analyzed and optimized. The optimized formulation showed the ibuprofen release in sustained manner over a period of 6h. The percentage drug release at 6h and hardness for optimized formulation was found to be 72.25 ± 1.85 and 4.50 ± 0.05 kg/cm^2. Ibuprofen effervescent tablets followed Korsmeyer-Pepas model with anomalous (non-Fickian) diffusion mechanism.

Keywords: Slow release effervescent tablet, statistical optimization, response surface plot

Introduction

Over past few decades, the astonishing progress in the drug delivery research has been carried out. Nonetheless, oral route is still considered as a preferable one for drug administration due to ease of administration, economical and patient compliance.[1] Various sustained and controlled drug delivery system have been investigated and developed in the arena of pharmaceutical research along with restriction of drawbacks of conventional dosage forms as well as its better clinical effect and adequate bioavailability.[2-4] Additionally, variables and too rapid gastrointestinal transit can result the incomplete drug release from the dosage form at the absorption site in the gastrointestinal tract leading weaken the efficacy of the administered dose.[5] Therefore, this has triggered to the development of gastroretentive drug delivery system. In gastroretentive drug delivery system, various approaches have been proposed for better improvement gastroretention in oral dosage form viz. floatation,[6] mucoadhesion,[7-8] sedimentation,[9] unfoldable, expandable, or swellable systems,[10] superporous hydrogel systems,[11] magnetic systems,[12] etc. Among them, Floating dosage forms are designed to be remained buoyant in stomach for several hours.[13] Floating or buoyancy technology is generally based on either effervescent or non-effervescent system. Being a topic of interest effervescent system includes matrices prepared with swellable polymers and effervescent components viz. sodium bicarbonate and citric acid or stearic acid. The matrices are fabricated such that the carbon dioxide (CO_2) gas is produced during interaction of effervescent materials and lead to get entrapped in in-situ porous gel network of hydrocolloids. As a result, it becomes low in density and ensures to remain buoyant in the stomach for long period of time to confer the delivery of medicaments in sustained manner.[14]

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with a short half-life (1.8-2h), and commonly used in the treatment of arthritis, post-operative and dental pain.[15] As its duration of action is short, repeated administration of the same single dose is necessary during 24h.[16] Therefore, development of buoyant system containing ibuprofen was attempted to improve gastroretention with sustained drug release for prolonged period to minimize the dosing frequency and chances of side effects.

The formulation optimization in pharmaceutical research requires proper selection of variables (factors) along with their restricted value as the factors that finally impose on the optimum product. This is not easy one to the formulator. Nonetheless, this can be easily analyzed and optimized the ultimate formulation using an established factorial design that secure least number of experimentation in a small period of time and cover factors in all possible combination.[17] Response surface methodology is extensively employed to optimize the formulations by securing a better understanding of the process or design in establishing the robustness of the formulation.[18] In this current research, we have aimed to formulate and optimize the best formulation of ibuprofen effervescent tablets using two independent variables viz. xanthan gum (X_1) and sodium bicarbonate (X_2) with their three levels and

their effects on R_{6h}(%) and hardness of the prepared tablets as responses have successfully performed after utilizing a full 3^2 factorial design.

Materials and Methods

Materials

Ibuprofen was a gift sample form Albert- David Ltd., India. Xanthan gum, sodium bicarbonate (B. S. Traders Pvt. Ltd .India) and lactose, microcrystalline cellulose, citric acid (Merck Ltd., India) and all other chemicals and reagents used were of analytical grade.

Experimental design

A 3^2 full factorial design was employed for experimental design where three factor underlying the different weight masses of xanthan gum (X_1), sodium bicarbonate (X_2), as two selected independent variables which were further varied at three level *i.e.* low level (-1), medium (0), high level (+1).The coded values were applied after performing the preliminary trials and are shown in Table 1. The drug releases (R_{6h}) and hardness (kg) were measured as dependant variable and their dependency on independent variables and statistical experimentation was extensively performed using Design-Expert® DX 8. Responses are shown in Table 2.

Formulation of floating tablet of ibuprofen

Floating effervescent tablets of Ibuprofen were prepared by the direct compression method after proper mixing of suitable ratios various polymer and others excipients. The drug, polymers and other excipients were first passed through sieve # 80. Then drug and all the materials were uniformly mixed and compressed on single punch tablet machine (Model no.189, Kilburn, Calcutta, India) using 9 mm round and concave punches (for batch size 10 tablets).

In vitro buoyancy study

The buoyancy of prepared tablets was determined using dissolution apparatus type-II (Campbell electronics, India).[19] Three tablets in each formulation batch were placed in the dissolution vessels containing 500 ml simulated gastric fluid (SGF) with required pH and set the system at 37±0.5ºC for 6h at 50 rpm rotating speed. The time required to float at the surface of dissolution medium (lag-time) and duration of buoyancy were calculated.

Hardness study

Six tablets from each formulation batches were placed in between spindle and anvil of Monsanto hardness tester. The desired pressure needed to hold the tablet in position is applied by moving the screw knob in clock wise direction thereafter the scale is moved so that the indicator is fixed at zero. The pressure is then applied till the tablet breaks. The reading is noted, which indicate the pressure at which tablets break up in to fragments.

In vitro drug release study

The *in vitro* release of prepared tablets containing ibuprofen was tested using dissolution apparatus type-II (Campbell Electronics, India). Ibuprofen tablets were placed into 900 ml of SGF (pH 1.2), maintained at 37±0.5°C and 50 rpm paddle speed. 5ml of aliquots was collected at regular time intervals, and same amount of fresh dissolution medium was replaced into dissolution vessel to maintain the sink condition throughout the experiment. The collected aliquots were filtered and further diluted suitably to analyze using a UV-VIS spectrophotometer (Thermo Spectronic UV-1, USA) by measuring absorbance at λ_{max} of 221 nm. It was done in triplicate ($n=3$).

Analysis of *in vitro* drug release kinetics and mechanism

To analyze the mechanism of drug release from these ibuprofen effervescent tablets ,the *in vitro* dissolution data were fitted to various mathematical models like zero order, first order, Higuchi, and Korsmeyer-Peppas models.[20-24]

Zero-order Model: $F = K_0 t$, where F represents the fraction of drug released in time t, and K_0 is the apparent release rate constant or zero-order release rate constant.

First-order Model: $\ln (1-F) = - K_1 t$, where F represents the fraction of drug released in time t, and K_1 is the first-order release rate constant.

Higuchi Model: $F = K_H t$, where F represents the fraction of drug released in time t, and K_H is the Higuchi dissolution rate constant.

Korsmeyer-Peppas Model: $F = K_P t^n$, where F represents the fraction of drug released in time *t*, K_P is the rate constant and *n* is the release exponent, this indicates the drug release mechanism.

Again, the Korsmeyer-Peppas model has been employed in the *in vitro* drug release behavior analysis of various pharmaceutical formulations to distinguish between various release mechanisms: Fickian release (diffusion-controlled release), non-Fickian release (anomalous transport), and case-II transport (relaxation-controlled release). When, $n \leq 0.5$, the drug release is Fickian. The n value between 0.5 and 1.0 is defined as non-Fickian release. When, $n \geq 1.0$, it is case-II transport and this involves polymer dissolution and polymeric chain enlargement or relaxation.[24]

Statistical analysis

Statistical optimization was performed using Design-Expert 8.0.6.1 software (Stat-Ease Inc., USA). All measured data are expressed as mean ± standard deviation (S.D). Each measurement was done in triplicate ($n = 3$).

Results and Discussion

Hardness study

The hardness of all formulation batches was in the range of 3.74 ± 0.05 to 4.69 ± 0.07 kg/cm^2 (Table 1). It was noted that the hardness of ibuprofen effervescent tablets was increased with increment the amount of xanthan gum and reduction of the amount of the sodium bicarbonate in the formulations. This could be ascribed to the porous infrastructure of tablets due to higher amount sodium bicarbonate that finally affects the hardness.

***In vitro* buoyancy study**

All formulation of ibuprofen effervescent tablets was found buoyant over a period of 6 h.

Buoyancy lag time of prepared tablets was in the range of 22 to 47 sec as shown in Table 1. This could be attributed that the high proportion of sodium bicarbonate present formulations helps to lower the buoyancy lag time and initiate the reaction in acidic release medium more rapidly in contrast to those tablets containing lower amount of sodium bicarbonate.[25] The buoyancy lag time of optimized product was found to be 22 sec.

***In vitro* drug release study**

The drug release vs. time curves for all formulations are shown in Fig. 1. All formulation showed sustained drug release profiles over a time period of 6h. The cumulative drug release from ibuprofen tablet formulations was found in a range of 74.35 ± 2.05 to 81.19 ± 2.15%. It has been observed that the drug release was controlled with the increasing amount of xanthan gum. Most reasonable enlightenment would be that greater degree of gum hydration occurs in presence xanthan gum in effervescent tablets which causes more intimate contact between particles of gums enhance possibility of entanglement of molecules of ibuprofen with swollen gum particles that finally lower the mobility of candidate drug in swollen matrices as well as drug release. Additionally, xanthan gum was found to produce a stiff gel and resulting to trim down the drug release from the tablet matrices.[26,27] But, increasing the amount of sodium bicarbonate comprehensively enhanced the release of the medicament because it instantly develops more porous in-situ gel network.

To analyze the mechanism of drug release from these ibuprofen effervescent tablets, the *in vitro* dissolution data were fitted to various mathematical models like zero order, first order, Higuchi, and Korsmeyer-Peppas models. The results of the curve fitting into these above-mentioned mathematical models are given in Table 4. The drug release pattern of effervescent tablets of formulation F-1 to F-3, F-5 and F-7 to F-O was correlated well with Korsmeyer-Peppas model (R^2 = 0.998, 0.997, 995, 0.991 and 0.994, 0.992, 0.997, 0.998) over a period of 6 h. On the other hand, other formulations, F-4 and F-6 were correlated with zero order model (R^2 = 0.987 and 0.988, respectively) over a period of 6 h, when their respective correlation coefficients in simulated gastric fluid were compared. The Korsmeyer-Peppas model has also been in use in the in vitro drug release behavior analysis of various pharmaceutical formulations to differentiate between various competing release mechanisms: Fickian release (diffusion-controlled release), non-Fickian release (anomalous transport), and case-II transport (swelling- controlled release). The value of release exponent (n) determined from in vitro ibuprofen release data of different effervescent tablets ranged from 0.653 to 0.808 in simulated gastric fluids shown in Table 4, which indicated anomalous (non-Fickian) diffusion. This could be attributed to the high water uptake by xanthan gum in effervescent tablets leading to higher swelling of the tablets matrices conferred the anomalous release mechanism of ibuprofen.

Optimization

A total 9 batches of formulation was prepared using a full 32 factorial design in which two variables were xanthan gum (X_1) and sodium bicarbonate (X_2) varied at three level as high, medium and low. Their influences on the responses like R_{6h} (%) and hardness (kg) in simulated gastric fluid (pH1.2) were comprehensively investigated in the current study using Design Expert 8.0.6.1 software which yield a first order polynomial equation consisting of a suitable correlation between the main factors (variables) and their interaction on obtained responses. The equation is given below,

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_1 X_2 + b_4 X_1^2 + b_5 X_2^2$$

Where Y = the dependent variable, while b_0 = the intercept, b_1, b_2, b_3, b_4 and b_5 = regression coefficient; X_1, and X_2 = main factors; X_1X_2 = interaction between main factors. In this study, a total 9 trial of ibuprofen tablets were designed and formulated and their relevant responses is depicted Table 2.

The model polynomial equation relevant to R_{6h} (%) as response was obtained:

$$R_{6h}(\%) = 92.84 - 26.43 \times 10^{-2} X_1 + 35.53 \times 10^{-2} X_2 - 4.00 \times 10^{-5} X_1 X_2 + 5.68 \times 10^{-4} X_1^2 - 2.03\, 10^{-3} X_2^2$$

The another polynomial equation relevant to hardness (kg) as response was obtained,

$$\text{Hardness (kg)} = 7.90 - 2.49 \times 10\text{-}2\, X1 - 3.64 \times 10^{-2} X_2 + 3.00 \times 10^{-5} X_1 X_2 - 7.33 \times 10^{-5} X_{12} + 1.20 \times 10^{-4} X_2^2$$

Data obtained from the experimentation were subjected into the "ANOVA" study, which assured that all models were found to be significant ($p < 0.05$) for all responses shown in Table 2. The final equation was confirmed by eliminating the non-significant term ($p > 0.05$) in polynomial equation,[6] and they are

$$R_{6h}(\%) = 92.84 - 26.43 \times 10^{-2} X_1 + 5.68 \times 10^{-4} X_1^2$$

$$\text{Hardness (kg)} = 7.90 - 2.49 \times 10^{-2} X_1 - 3.64 \times 10^{-2} X_2 - 7.33 \times 10^{-5}$$

The effect of two individual factors (X_1 and X_2) and their interaction (X_1X_2) on the R_{6h} (%) and Hardness (kg) have shown in the defined design space as response surface plots in Fig. 2 and Fig. 3, respectively. A numerical optimization technique based on the desirability approaches was employed to achieve new optimized formulation with desired responses. This adopted optimization technique also affirmed the desirable ranges of response parameters in which drug release at 6 h were limited to 72% $\leq R_{6h} \leq$ 70% whereas Hardness (kg) of tablets were restricted to 5 $\leq$ Hardness $\leq$4. In concern of variables, the ranges of factors were found as 275 $\leq X_1 \leq$250 and 135 $\leq X_2 \leq$125, respectively. The overlay plot indicating the region of optimal process variable settings was presented in Fig. 4. It validates and checks the optimization capabilities of these models with settings of optimal process variables by the design. The optimized desirable ranges for ibuprofen effervescent tablets were found to be; X_1 = 251.85 mg and X_2 = 134.65 mg. Table 3 lists the results of experiments with predicted responses by the mathematical models and those actually observed.

The optimized effervescent tablet containing ibuprofen (F-O) showed R_{6h} of 72.25± 1.85% and hardness of 4.58±0.05 kg/cm^2. The small error-values (3.75 and -1.74, respectively) indicate that mathematical models obtained from the 3^2 design were well fitted.

The numerical analysis was performed to acquire the optimal values of responses based on desirability criterion by the help of Design expert 8.0.6.1 software, which led to develop optimized (F-O) ibuprofen effervescent with respect to R_{6h} (%) and Hardness (kg), respectively. Table 2-3 depicts the results of predicted values obtained from the mathematical model and same practically observed.

Conclusion

Ibuprofen effervescent tablets were successfully formulated to remain buoyant in gastric fluid over a period of 6h with sustained release of medicament based on 3^2 factorial designs. The effects of xanthan gum and sodium bicarbonate on response parameters like % drug release and hardness were analyzed and optimized. The three dimensional surface response plot and corresponding contour plot revealed that increased amount of xanthan gum sustained the drug release as well as enhanced the hardness of the tablets. On other hand, increased amounts sodium bicarbonate lowered the both hardness and buoyancy lag time but insufficient to control the release of ibuprofen from the formulation. These ibuprofen effervescent tablets seem to be a promising gastroretentive drug delivery system.

Table 1. 3^2 factorial designs and their observed response value along with coded values in brackets

Formulation Code	Xanthan Gum (mg) X_1	Sodium biocarbonate (mg) X_2	Responses		
			R_{6h}(%)[a,c]	Hardness(kg)[c]	BLT(sec)
F-1	250.00(+1)	120.00(+1)	74.35±2.05	4.50±0.05	30
F-2	250.00(+1)	100.00(0)	76.45±2.12	4.60±0.07	36
F-3	250.00(+1)	80.00(-1)	77.15±1.88	4.65±0.04	47
F-4	200.00(0)	120.00(+1)	75.37±1.79	3.90±0.05	27
F-5	200.00(0)	100.00(0)	77.38±1.81	4.00±0.02	42
F-6	200.00(0)	80.00(-1)	77.05±2.05	4.20±0.05	45
F-7	150.00(-1)	120.00(+1)	78.55±1.90	3.70±0.04	22
F-8	150.00(-1)	100.00(0)	80.44±2.15	3.80±0.06	26
F-9	150.00(-1)	80.00(-1)	81.19 ±2.20	4.10±0.05	44
F-0	251.85	134.65	72.25±1.85	4.50±0.05	22

[a]R_{6h}(%) = cumulative drug release after 6h.cMean ± S.D, n=3; BLT(s) = buoyancy lag time in seconds.

Table 2. Summary of ANOVA for response parameters

Source	Sum of square	df[a]	Mean square	F-value	p-value prob>F
For R_{6h}(%)[b]					
Model	38.75	5	7.75	47.12	0.0047(S)
X_1	24.93	1	24.93	151.58	0.0012(S)
X_2	8.45	1	8.45	51.37	0.0056(NS)
$X_1 X_2$	6.4×10^{-3}	1	6.4×10^{-3}	0.039	0.8562(NS)
X_1^2	4.04	1	4.04	24.58	0.0158(S)
X_2^2	1.32	1	1.32	8.04	0.0058(NS)
For Hardness[c]					
Model	0.99	5	0.20	191.05	0.0006(S)
X_1	0.82	1	0.82	792.06	<0.0000(S)
X_2	0.094	1	0.094	90.40	0.0025(S)
$X_1 X_2$	3.60×10-3	1	3.60×10^{-3}	3.47	0.1593(NS)
X_1^2	0.067	1	0.067	64.82	0.0040(S)
X_2^2	4.67×10-3	1	4.67×10^{-3}	4.51	0.1239(NS)

X_1 and X_2 represent the amount of xanthan gum and sodium bicarbonate in mg, respectively; X_1X_2, is their interaction effect. S and NS indicate significant and non significant, respectively. [a]df indicates degree of freedom

Table 3. Result of experiments to assure optimization capability

Code	Xanthan gum (mg) X_1	Sodium bicarbonate (mg) X_2	Responses	
			R_{6h}(%)[a]	Hardness
			Actual values[b]	
F-O	251.85	134.65	72.25 ±1.85	4.50 ± 0.05
			Predicted values	
			71.98	4.58
		%Error[c]	3.75	-1.74

[a]R_{6h}(%)= cumulative drug release after 6h; [b]Actual values=Mean±SD, n=3; [c]Percentage of error (%)= (actual value - predicted value)/ predicted value × 100, F-O: optimized formulation

Table 4. Results of curve fitting of the in vitro ibuprofen release data from different various ibuprofen effervescent tablets in simulated gastric fluid (pH 1.2)

Formulation Code	Zero order R^2	First order R^2	Higuchi kinetics R^2	Korsmeyer-Peppas R^2	Diffusion exponent (*n*)
F-1	0.984	0.987	0.952	0.998	0.738
F-2	0.986	0.959	0.953	0.997	0.733
F-3	0.992	0.979	0.937	0.997	0.808

Formulation Code	Zero order R^2	First order R^2	Higuchi kinetics R^2	Korsmeyer-Peppas R^2	Diffusion exponent (*n*)
F-4	0.982	0.950	0.960	0.985	0.677
F-5	0.984	0.951	0.953	0.991	0.702
F-6	0.988	0.968	0.944	0.986	0.727
F-7	0.976	0.951	0.967	0.994	0.653
F-8	0.982	0.963	0.959	0.992	0.691
F-9	0.981	0.972	0.962	0.997	0.698
F-0	0.987	0.977	0.950	0.998	0.750

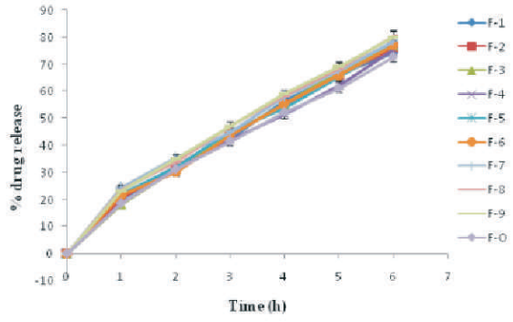
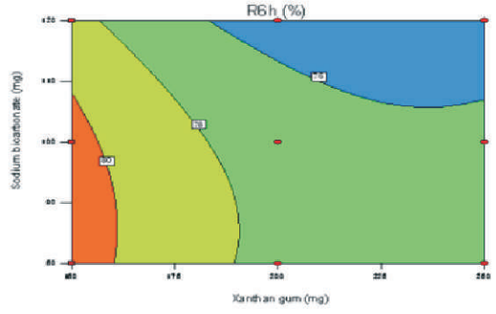
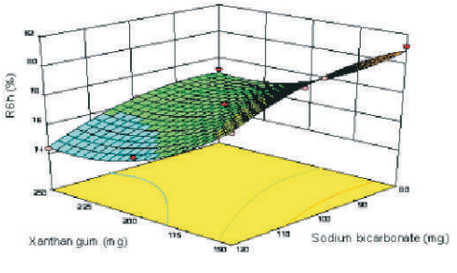


Fig. 1: Drug release curves for various ibuprofen effervescent tablets

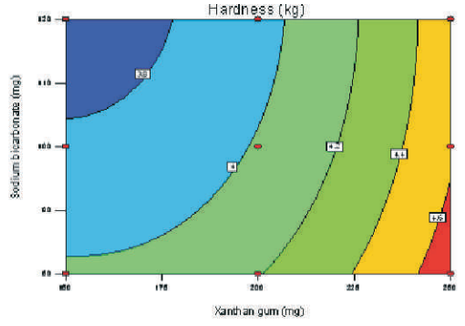


(a)

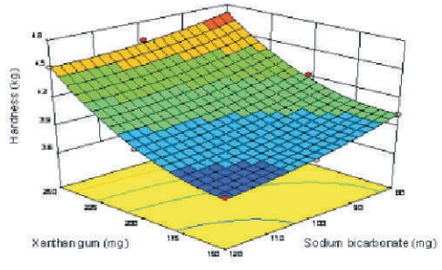


(b)

Fig. 2: Effects of xanthan gum and sodium bicarbonate on R_{6h} (%) as shown by (a) contour plot and (b) response surface plot



(a)



(b)

Fig. 3: Effects of xanthan gum and sodium bicarbonate on hardness as shown by (a) contour plot and (b) response surface plot

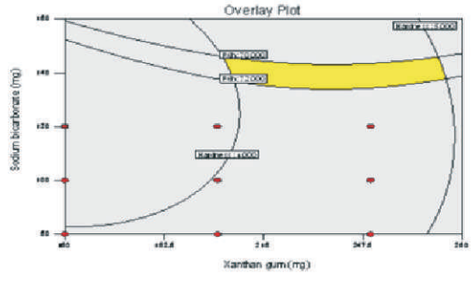


Fig. 4: The overlay plot indicating the region of optimal process variable settings

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