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Research Article

Hydrophilic polymers based sustained release matrix tablets of Ibuprofen: Optimization of formulation using Box-Behnken statistical design

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Abstract

The current study was aimed to formulate sustained release matrix tablets of Ibuprofen; a Propionic acid derivative, and is non-steroidal anti-inflammatory agent (NSAID) with analgesic and antipyretic properties and optimize by using a 3-factor 3-level Box-Behnken statistical design as an optimization tool. Matrix tablets were prepared by direct compression technique using HPMC(X1), NaCMC(X2) and Xanthan Gum(X3) as independent variables and % release at 2hr (Y1), % release at 12hr (Y2) and hardness (Y3) of tablet were selected as dependent variables. Regression analysis was performed on dissolution data and construct polynomial regression models for these response variables. Polynomial models were further validated using ANOVA and results indicate that all the polymers used have significant effect on selected response ($p<0.05$). Contour plots were drawn to evaluate the effect of polymer combination on selected responses. The results obtained from kinetic modeling indicate that drug release follows the non-fickian diffusion process. Hence Box-Behnken statistical design facilitates the formulation and optimization of Ibuprofen sustained release matrix tablets to achieve better bioavailability.

Keywords: Matrix tablets, Sustained release, Ibuprofen, Ant-inflammatory, Box-Behnken statistical design

1. Introduction

Controlled release (CR) formulations are gaining more popularity in the field of medical sciences because of better patient compliance, capable of achieving constant plasma concentration within therapeutic range for prolonged period of time and decrease in the incidence and severity of unwanted effects which occur due to high levels of plasma concentration (Raghuram et al., 2003). Hydrophilic matrix systems are widely used in oral controlled release drug delivery systems particularly cellulose derivatives such as HPMC

because of its good compressibility characteristics, compatibility and availability in various viscosity grades which can be used to obtain desired release rate (Chopra et al., 2006). Ibuprofen, a non-steroidal anti-inflammatory (NSAID) drug that belongs to propionic acid derivative group has analgesic, antipyretic and anti-inflammatory activity. Sustained release tablets of Ibuprofen are required to prevent fluctuation of drug in blood due to its shorter Half-life (2-4hrs) and rapid excretion of drug from urine (Dabbagh and Beitmashal, 2005).

Statistical experimental design provides an economical means to obtain desirable information about an experimental method by just performing a few number of experimental runs; it also helps to determine any type of interactions among study variables and also used to predict the chances of experimental errors (Atkinson et al., 2007). Various types of designs are being used now days for research and development in industrial practice including Response surface methodology, Fractional factorial designs, D and A-optimal designs and full factorial designs (Stetsko, 1986). RSM is helpful in mathematical modelling and analysing the responses when independent variables are changed and can also be used for optimization of the process when maximum and minimum limits are defined (Myers et al., 2009).RSM can be expressed graphically in form of contour plots (three dimensional plots) which are helpful to observe the effect of two variables on response at one time. Response surface methodology (RSM) using 3-factor 3-level Box-Behnken statistical design was used for our present study which is an independent, rotatable or nearly rotatable, quadratic design having the treatment combinations at midpoints of the edges of the process space and at the center (Shah et al., 2009).

Hence, the aim of the present work was to formulate sustained release matrix tablets of Ibuprofen containing HPMC, NaCMC and Xanthan Gum in combination for the 1st time using direct compression method and evaluate the effect of various polymers on the release profile of matrix tablets and optimize the release profile using Box-Behnken statistical design.

2. Materials and Methods

Ibuprofen was gifted from Abbott Laboratories (pvt) Ltd. (Karachi, Pakistan). Hydroxypropyl methyl cellulose (HPMC) K15M was purchased from Fluka chemie AG (Switzerland). Xanthan Gum and NaCMC was gifted from Himont Pharmaceutical (pvt) Ltd (Lahore, Pakistan). Magnesium stearate and Lactose was purchased from Merck co. (Germany). Distilled water and phosphate buffer were prepared in Pharmaceutics research Lab., The Islamia University of Bahawalpur.

2.1 Preparation of compressed matrix tablets of Ibuprofen

Tablets were formulated by direct compression method using Single punch machine (Emmy, Pakistan). All the ingredients were measured separately using analytical weighing balance (Shimadzo, AUX 220) and then all the materials were blended in a cubic mixer for 15 minutes except magnesium stearate. Now measured amount of lubricant (magnesium stearate) was added to the above powdered mixture and further blended for 5 minutes. This powdered mixture was then compressed directly at constant compression pressure using normal concave tooling.

Table 1: Composition of matrix tablets of Ibuprofen

Ingredients	**Amount (mg)**
Ibuprofen	50
HPMC	20-40
NaCMC	10-30
Xanthan Gum	10-30
Mg Stearate	2
Avicel Q.S	200

2.2 Experimental statistical design

A 3-factor, 3-level Box-Behnken statistical design was used as standard protocol for optimization and evaluation of main, quadratic, and interaction effects of various formulation ingredients of in-vitro release profile of sustained release matrix tablets of Ibuprofen (Shah et al. 2009).Various dependent and independent variables along with their actual and coded levels used in this study are given in table 1.

Table 2: Actual and coded levels used in Box-Behnken design

Coded levels	**-1**	**0**	**1**
X1: HPMC	20	30	40
X2: NaCMC	10	20	30
X3: Xanthan Gum	10	20	30

2.3 Physical evaluation of tablets

Tablets were evaluated for Weight variation (n=20), Thickness (n=10), Hardness (n=10) and Friability (n=10).

2.4 In-vitro drug release studies

Dissolution studies were performed using automatic dissolution apparatus (USP apparatus II, paddle rotating method) rotated at 50rpm which was attached to the auto sampler (Watson Marlo, Stockholm, Sweden) and 900ml of phosphate buffer solution of pH 6.8 was used as dissolution medium with temperature maintained at 37C0 ± 0.5C0. Dissolution studies for each batch were performed in triplicate while maintaining the same experimental condition for each formulation. Aliquots of 5ml were filtered and withdrawn at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, and 24 hrs by auto sampler. UV-Spectrophotometer (U2020, Irmeco, Germany) was used to analyse various samples at 254nm and the results of release profiles were evaluated using MS-Excel software and values were obtained by interpolation of Excel graph.

2.5 Kinetic modelling of drug release studies

The kinetic models such as zero order (eq3.1), 1st order (eq 3.2), Higuchi, s (eq 3.3), and Korsmeyer-Peppas model (eq 3.4) were used to evaluate in-vitro release data of all 17 formulations. These models can be represented by following equations (Chopra et al.2006).

Models	**Equations**	
Zero order	$Qt=K0t$	(1)
First order	$\log Qt = \log Q0 - K1t$	(2)
Higuchi' model	$Qt= KH\ t^{1/2}$	(3)
Korsmeyer-Peppas	$Mt/M0= Kkpt^{n}$	(4)

Where

Qt is the initial drug amount of drug that released at time t,

K0, K1, KH, and KKP are release rate constant for zero order, 1st order, Higuchi model, and Korsmeyer-Peppas model respectively, where ''t'' is the time.

3. Results and Discussion

3.1 Physical evaluation of matrix tablets

Results obtained from in process evaluation for Ibuprofen matrix tablets showed that all the batches of tablets were within the limits of USP. The average tablet weight ranged between 200.1 to 204.1 mg, hardness of tablets ranged between 3.1 and 12 kg/cm2, thickness ranged between 3.9 to 4.3 mm and friability of tablets ranged from 0.20% to 0.60%.

3.2 In-vitro Drug release studies

17 different formulations were prepared according to 3-factors, 3-level Box-Behnken design using HPMC K15(X1), NaCMC(X2) and Xanthan Gum (X3) as release retarding polymers and Cumulative percent drug release are given in figure 1.The results indicate that tablet batches having higher concentration of all polymers such as A-4,A-12 and A-8 shown better release retarding properties and within 24hrs they release the drug up to 70-80% resulting in better sustained effects. All polymers are hydrophilic in nature so they retard the release of drug by swelling mechanism due to hydration of their chains. When a tablet matrix containing a swellable polymer comes into contact with a dissolution medium, a progressive change occur in state of polymer usually towards the glassy state due to which swelling process take place which is evidenced by the formation of a thick gel layer on the surface of the tablet, which is responsible for controlling drug release rate from the matrix tablets (Siepmann and Peppas 2001).

Due to this reason formulations having high concentration of hydrophilic polymers, swelling is the main controlling factor for drug release. While the tablet batches such as A-9,A-1 and A-2 having less total polymer concentration release the drug releases up to 80-90% within 10-15hrs.So it can be concluded that all HPMC, NaCMC and Xanthan Gum has better release retarding properties at higher concentrations.

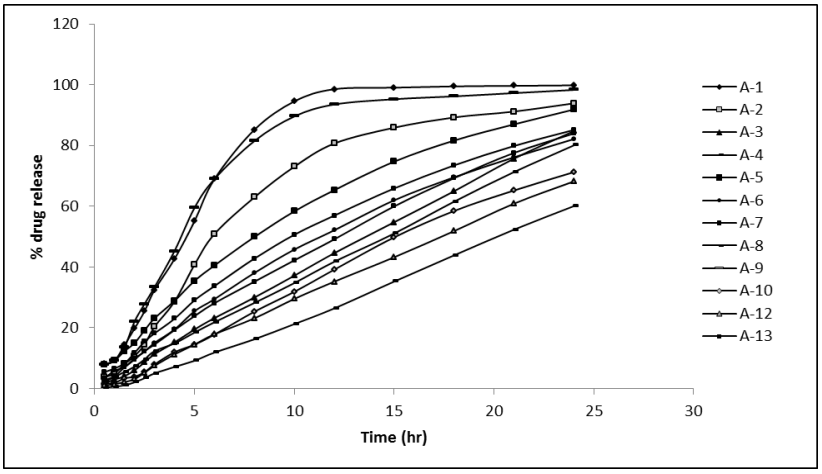

Figure 1: Graphical representation of cumulative percent drug release of Ibuprofen at various time intervals using HPMC, Xanthan Gum and NaCMC as release retarding polymers

Optimum formulation of sustained release tablets of Ibuprofen can be obtained by using 3-factors, 3-level Box-Behnken statistical design , by comparing the release profiles of three formulations (A-4, A-8 and A-12) containing maximum amount of three types of polymers as given in figure 2. It is clear from the graph that drug is released in a slower rate from all the three tablet formulations. Almost 80% of drug release was obtained in a more desirable and sustainable manner from tablet formulation A-8 in 24 hours while less than 70% drug was released at slower rate in formulations A-4 and A-12. As formulation A-8 contains equal amounts of HPMC, EC and NaCMC, it is therefore regarded as optimum sustained release formulation of Ibuprofen.

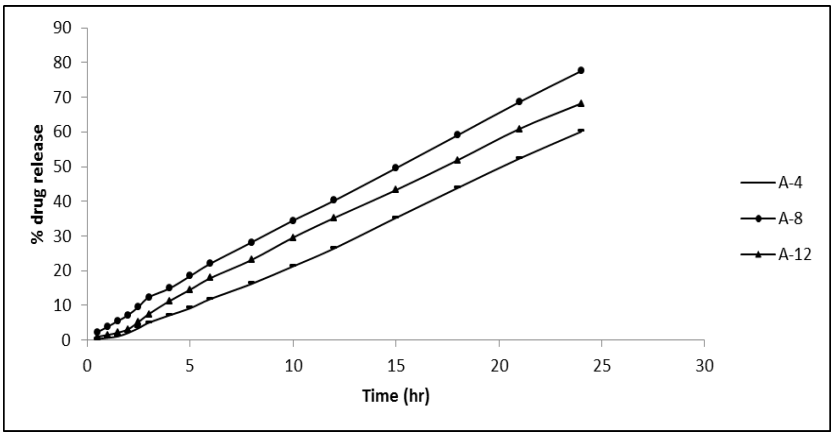

Figure 2: In vitro release of optimum formulation of Ibuprofen sustained release matrix tablets

From the release kinetic data obtained as given in table 3 it was clear that the best fitted model representing the drug release is zero order especially when the total polymeric contents increased it will reach up to 0.997 as in batch A-8 having highest total polymeric contents. While the batches having high concentration of cellulosic polymers i.e. HPMC and NaCMC follow the 1st order release rate as in case of A-5 and A-7 because the polymer swelling is the main mechanism for drug release in these formulations. The mechanism of drug release from all the matrix formulations was further confirmed by the use of Korsmeyer-Peppas model. The critical value n (diffusion coefficient) found for these formulations was ranging from 0.554-0.998 indicating non-fickian diffusion (anomalous) mechanism of drug release thus it can be concluded that drug release from the matrix involve the combination of different mechanisms such as polymer swelling, drug dissolution as well as matrix erosion.

Table 3: Modelling of dissolution data showing release kinetics of Ibuprofen sustained release matrix tablet

Batch	**Zero Order**	**1st Order**	**Higuchi**	**Korsmeyer-Peppas**
	R2	**R2**	**R2**	**n**
A-1	0.904	0.859	0.888	0.554
A-2	0.923	0.873	0.897	0.656
A-3	0.997	0.848	0.8015	0.856
A-4	0.996	0.869	0.793	0.998
A-5	0.863	0.942	0.951	0.647
A-6	0.993	0.868	0.85	0.918
A-7	0.919	0.931	0.932	0.707
A-8	0.997	0.866	0.833	0.972
A-9	0.91	0.87	0.902	0.532
A-10	0.994	0.869	0.811	0.896
A-11	0.992	0.876	0.852	0.911
A-12	0.993	0.859	0.781	0.954
A-13	0.991	0.863	0.835	0.968

3.3 Optimization results by using RSM (Box-Behnken statistical design)

A 3-factor, 3-level Box-Behnken statistical design was used for optimization with its selected response variables is given in table 4. Independent variables with all possible combinations and the resultant dependent variables (Y1, Y2 and Y3) are also given in table 4.

3.4 Mathematical modelling for multiple linear regression analysis (MLRA)

Multiple linear regression analysis (MLRA) was performed of all selected response variables by using design expert software (version 7.0.0) and mathematical relationship was developed among them in form of polynomial regression equations which are given below for each selected response variable.

$$Y1=9.26 – 5.47X1 – 2.27X2 – 1.96X3 - 2.19X1X2 - 3.28X1X3 - 0.043X2X3 \quad (4.1)$$

$$Y2=40.40 – 28.83X1 – 3.50X2 – 5.53X3 - 0.79X1X2 - 3.84X1X3 – 1.68X2X3 + 15.48X12 + 8.85X22 +0.090X32 \quad (4.2)$$

$$Y3=12.70 – 3.67X1 – 5.76X2 + 1.10X3 - 0.98X1X2 – 0.13X1X3 - 0.050X2X3 – 0.27X12 + 2.33X22 + 1.35X32 \quad (4.3)$$

Polynomial equations represent coefficient of intercept, 1st order terms, interaction terms and quadratic terms. It is clear from these polynomial equations that HPMC has greater release retarding property as compare to Xanthan Gum and NaCMC. The result of combination effect of different polymers is also obtained from these equations which indicate that by combining the polymers the retarding property further enhanced. One way analysis of variance (ANOVA) was used for the statistical validation of these polynomial models provided by design expert software given in tables 5. The results of ANOVA for each response variable are considered significant if the value of P is less than 0.05using level of significance at 5% (Shah et al. 2009).It is clear from the table that linear contribution of all the polymers have significant effect on release of drug which is indicated by S in the table, means that all have release retarding properties and can be used to formulate the matrix tablets. Similarly the interaction effects of all polymers also have significant effect on release represent in table with S and indicate that when we combine these polymers the release retarding property further increased which is also cleared from the various contour plots.

Table 4: Responses observed by using Box-Behnken statistical design for sustained release matrix tablets of Ibuprofen

Batch	X1	X2	X3	Y1 (%)	Y2 (%)	Y3 Kg/cm^2
A-1	20	10	20	12.78	98.55	4.1
A-2	30	20	20	9.74	79.68	12.7
A-3	40	10	20	2.95	40.63	14.7
A-4	40	30	20	2.06	29.55	24.5
A-5	30	10	10	14.02	64.32	9
A-6	30	30	10	6.67	42.29	13.6
A-7	30	10	30	10.77	51.75	11.5
A-8	30	30	30	6.25	37.7	16.6
A-9	20	20	10	20.08	94.52	2.6
A-10	40	20	10	2.92	38.15	15.9
A-11	20	20	30	8.01	45.37	6.2
A-12	40	20	30	2.32	29.12	15.6
A-13	30	20	20	7.18	39.32	11.8
A-14	30	20	20	7.52	39.13	12.1
A-15	30	20	20	7.1	39.35	12.2
A-16	30	20	20	7.93	40.09	12
A-17	30	20	20	7.23	39.46	12.0

3.5 Contour plots and response surface analysis

Contour plots as obtained from the statistical design are helpful in studying the effect of two factors i.e. HPMC and NaCMC on response at one time as given in figures 3 and it is clear that HPMC and NaCMC varies in a linear way, and indicating that with increasing concentration of both polymers the release of a drug become reduced. Similarly when we observe the effect of Xanthan Gum and HPMC as given in figure 4 it is clear that HPMC and Xanthan Gum has a nonlinear relationship and at low polymer concentration the release of drug was high while with increasing concentration of polymers the drug release becomes reduced. Similarly the hardness of tablet also increased with increasing concentration of all the polymers and which have negative effect on the release of drug results in more sustaining effect of drug release.

Table 5: ANOVA for response surface quadratic model analysis of variance

Source	Sum of Squares	df	Mean Square	F Value	P-value	Significant
Model	373.42	6	62.24	17.57	0.0001	S
X1	239.08	1	239.08	67.5	0.0001	S
X2	41.21	1	41.21	11.64	0.0066	S
X3	30.76	1	30.76	8.68	0.0146	S
X1X2	19.27	1	19.27	5.44	0.0419	S
X1X3	43.09	1	43.09	12.17	0.0058	S
X2X3	7.39	1	7.396	2.088	0.0045	S
Residual	35.42	10	3.54	------	------	------
Lack of Fit	35.29	6	5.88	182.54	0.0001	S
Pure Error	0.13	4	0.032	-------	-------	------

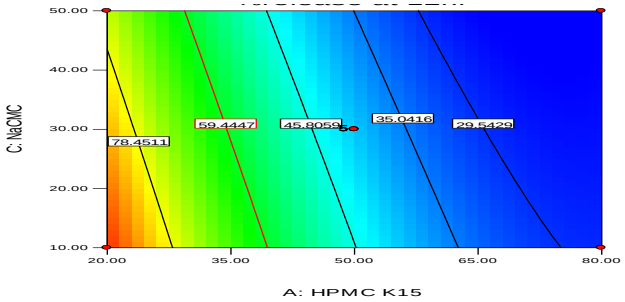

Figure 3: Contour plot showing effect of HPMC and NaCMC on response

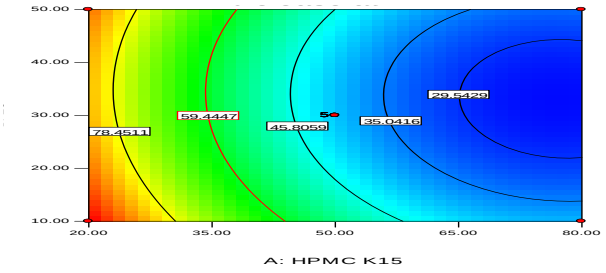

Figure 4: Contour plot showing effect of HPMC(X1) and Xanthan Gum on response

5. Conclusion

Sustained release matrix tablets of Ibuprofen was prepared by direct compression method using HPMC K15, Xanthan Gum and NaCMC as matrix forming polymers and optimized using 3-factor 3-level Box Behnken design with 17 experimental runs. The quantitative effects of various polymers on release rate could be evaluated using various polynomial equations in form of linear, quadratic and interaction terms. Box-Behnken statistical design could be used as an optimization tool and to study the interaction effect between the combinations of different polymers on release rate of drug. Thus Box-Behnken statistical design is very efficient in optimizing various drug delivery systems. All the polymers used in study have significant effect on release rate of drug as was indicated by results of ANOVA. Drug release following zero-order kinetic indicate that matrix tablets of Ibuprofen can successfully be used for oral drug delivery which release the drug at constant rate up to 24hrs.

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