Formulation and evaluation of sustained release floating drug delivery system of Metoprolol Tartrate

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Abstract:
The purpose of this research was to prepare a gastroretentive drug delivery system of Metoprolol tartrate. Sodium bicarbonate & citric acid were incorporated as a gas-generating agent. The effects of citric acid & sodium bicarbonate on drug release profile and floating properties were investigated. A 3^2 full factorial design was applied to systemically optimize the drug release profile. The amounts of hydroxypropylmethylcellulose K15M (X1) & hydroxypropyl methylcellulose K100M (X2) were selected as an independent variables & lag time (Y1), float time (Y2), percent drug release (Y3) were selected as dependent variables. According to the results of the full factorial design combination of HPMC K15M & HPMC K100M polymer favours the sustained release of Metoprolol tartrate from a gastroretentive formulation. A theoretical dissolution profile was generated using pharmacokinetic parameters of Metoprolol tartrate. No significant difference was observed between the release profile of batches F2,F3, F7, F8. But, batch F5 showed the highest release among all the batches, i.e. percent drug release (97.11%), and also same batch F5 have lag time (49 sec) and float time (12hrs) values.

Keywords: Metoprolol tartrate, gastroretentive, floating drug delivery, sustained release.

INTRODUCTION

Metoprolol Tartrate is a adrenergic β1-receptor antagonist. It is widely prescribed in hypertension, arrthymia, anginal conditions. The recommended adult oral dosage of Metoprolol Tartrate is 50,100 or 200 mg. The effective treatment of hypertension requires administration of 100 mg of Metoprolol Tartrate 2 times a day. The short biological half-life of drug (3-5 hours) also favors development of a sustained release formulation. A traditional oral sustained release formulation releases most of the drug at the stomach, thus the drug should have absorption window in stomach only. The gastroretentive drug delivery systems 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 gastrointestinal tract.[1,2] These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. This principle may be applied for improving systemic as well as oral delivery of Metoprolol Tartrate, which would efficiently reduce hypertension. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems modified-shape systems, high-density systems, and other delayed gastric emptying devices. The principle of buoyant preparation offers a simple and

practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. In context of the above principles, a strong need was recognized for the development of a dosage form to deliver Metoprolol Tartrate in the stomach and to increase the efficiency of the drug, providing sustained action. The present investigation applied an oral approach to the development of gastroretentive Metoprolol Tartrate dosage forms.[3]

PREFORMULATION STUDIES

Drug Identification

The average melting point of Metoprolol tartrate was determined by capillary method and was found to be 120°C ± 2°C, which is in good agreement with reported melting point.

The UV spectrum of Metoprolol tartrate solution (50 µg/ml) exhibited wavelength of absorbance maximum at 226 nm which complies with the reported.

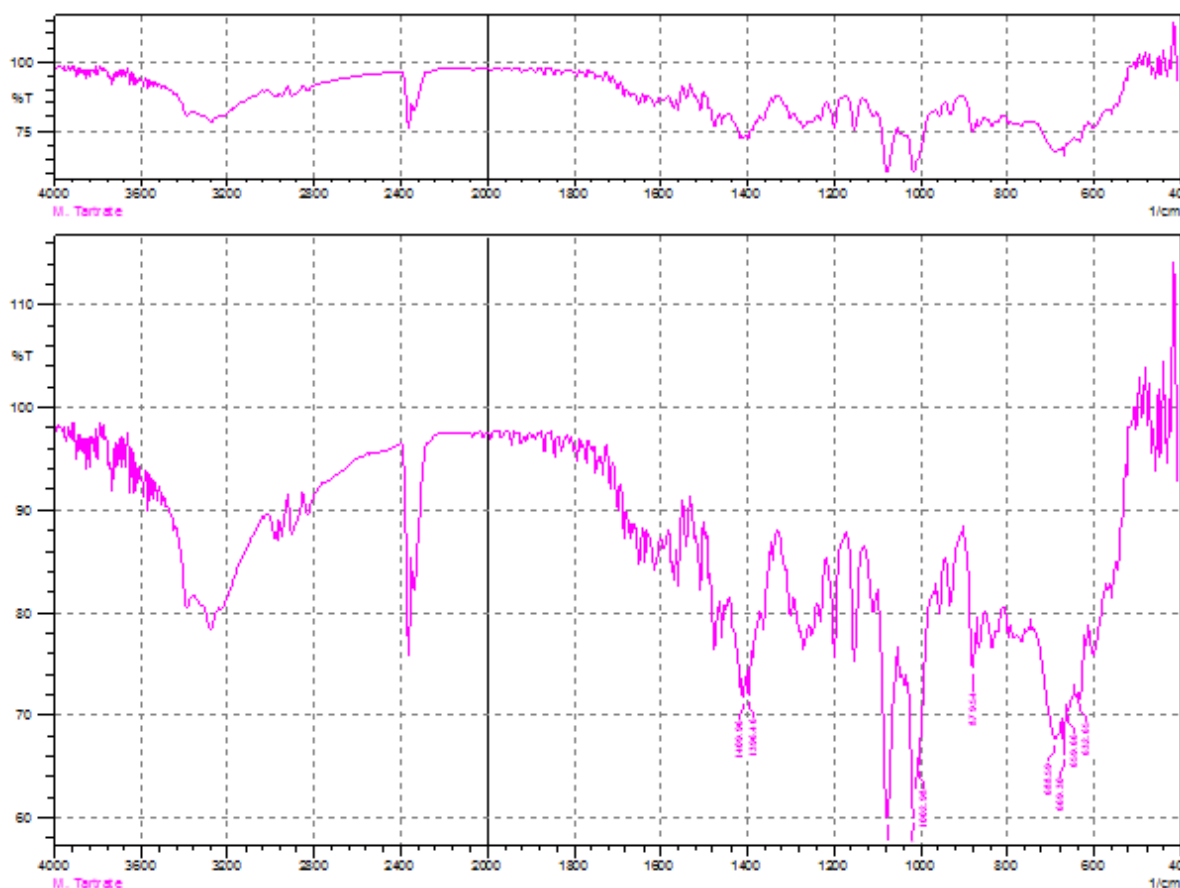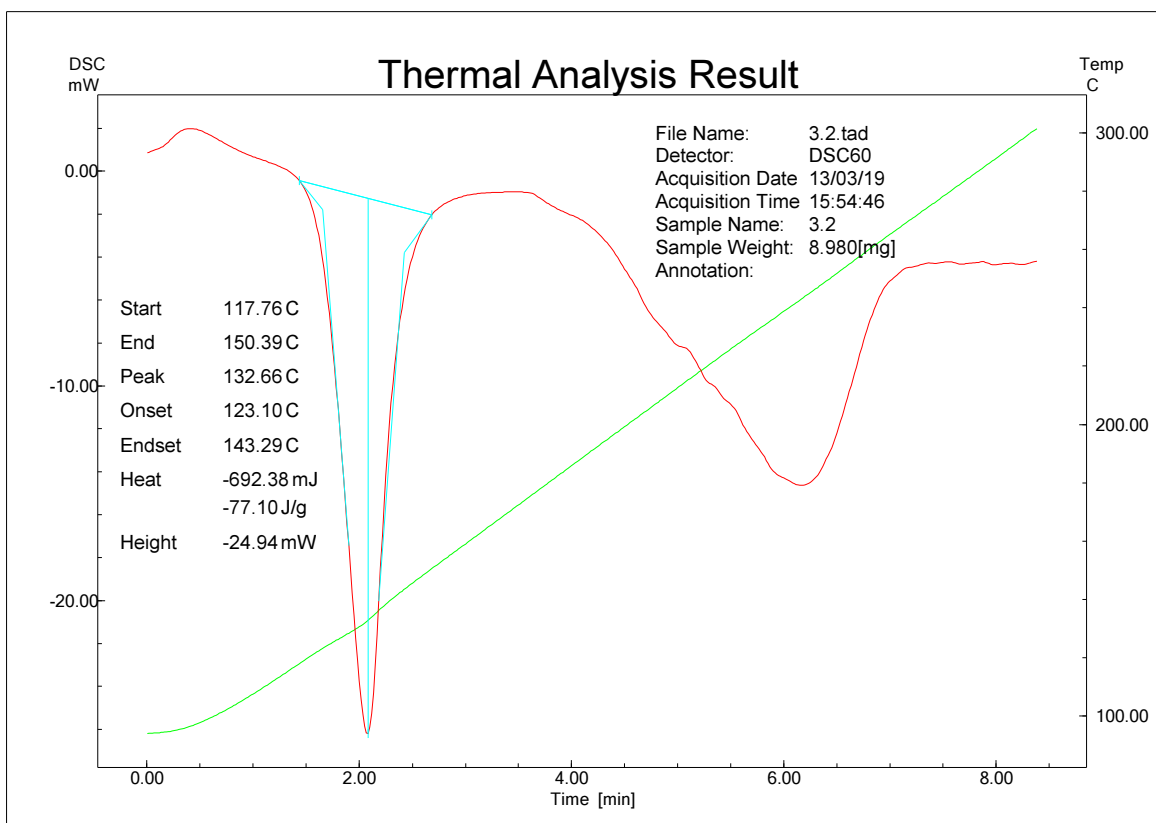The Infrared Spectrum of Metoprolol tartrate are shown in figure 1.

Figure 1: Infrared Spectrum of Metoprolol tartrate

DSC thermogram of Metoprolol tartrate showed one endothermic peak of fusion, having peak maximum of 132.66°C. This was in accordance with the reported. The DSC Thermogram of Metoprolol tartrate are shown in figure 2.

Figure 2: DSC Thermo gram of Metoprolol tartrate

On the basis of melting point, UV spectrum, Infrared spectrum and DSC thermogram the procured sample of Metoprolol tartrate was found to be of acceptable purity and quality. The sample was taken for further studies.

The standard calibration curve exhibited good coefficient of correlation as shown in table 1.

Table 1: Standard Calibration Curve Statistics

Sr. No	Parameters	Observations
1	Absorbance Maximum	226 nm
2	Slope	0.029
3	Intercept	0.012
4	Correlation Coefficient (r^2)	0.996

The pH solubility analysis revealed that Metoprolol tartrate at low pH values had higher solubility.

MATERIALS & METHODS:

Materials

Metoprolol tartrate was received as a gift sample from IPCA, Aurangabad. Hydroxypropylmethylcellulose (HPMC) K15M was received as a gift sample from ShinEtsu, & Hydroxypropylmethylcellulose (HPMC) K100M was received as a gift sample from DOW. All other ingredients were of analytical grade.

Table 2: Tablet Formulations for Lag time & Float time optimization:

Sr. No.	Ingredients (milligrams)	E1	E2	E3
1	Metoprolol tartrate	100	100	100
2	HPMC K15M	120	120	120
3	HPMC K100M	80	80	80
4	MCC PH 102	100	100	100
5	PVP K30	30	30	30
6	Sodium bicarbonate	75	100	120
7	Citric acid	50	70	80
8	Magnesium stearate	06	06	06

Table 3: Tablet Formulations for Preliminary Trials

Sr. No.	Ingredients (milligrams)	A1	A2	A3	A4	A5	A6	A7	A8	A9
1	Metoprolol tartrate	100	100	100	100	100	100	100	100	100
2	HPMC K15M	100	150	200	_	_	_	100	120	160
3	HPMC K100M	_	_	_	100	150	200	100	80	40
4	MCC PH 102	100	100	100	100	100	100	100	100	100
5	PVP K30	30	30	30	30	30	30	30	30	30
6	Sodium bicarbonate	100	100	100	100	100	100	100	100	100
7	Citric acid	70	70	70	70	70	70	70	70	70
8	Magnesium stearate	06	06	06	06	06	06	06	06	06

Methods

Preparation of Metoprolol Tartrate Floating Tablets

Metoprolol Tartrate was mixed with the required quantities of HPMC K15M, HPMC K100M, Sodium bicarbonate, Citric acid, Microcrystaline cellulose PH 102, Polyvinyl Pyrolidone K30 in polybag for 4-5 min. continuously, then the powder blend was lubricated with Magnesium Sterate (1% wt/wt) and compressed on 12 stations multipunch tablet machine. The tablets were round & flat with an average diameter of 10 $\pm$ 0.1mm and a thickness of 6.5 $\pm$ 0.2mm. The formulations of the preliminary trial batches (A1 to A9) are shown in Table 3. The formulations of the factorial design batches (F1 to F9) are shown in Table 4.

In Vitro Buoyancy Studies

The in vitro buoyancy was determined by floating lag time, per the method described by Rosa et al. [4] The tablets were placed in a **4**00-ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

In Vitro Dissolution Studies

The release rate of Metoprolol Tartrate from floating tablets was determined using *United States Pharmacopeia (USP)*. Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl, at 37 ± 0.5°C and 50 rpm. A sample (1mL) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-μ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 226 nm using a Shimadzu UV-1800 UV/Vis double-beam spectrophotometer (Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from a standard curve. The times for 50% and 80% drug release were calculated based on the Korsemeyer and Peppas model.[5]

Full Factorial Design

A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations. The amounts of HPMC K15M (X1) and HPMC K100M (X2) were selected as independent variables, and Lag time (Y1), Float time (Y2), Drug release (Y3) were selected as dependent variables.

Kinetic Modeling of Drug Release

The dissolution profile of all the batches was fitted to zero order, first-order,[6,7] Higuchi,[8-10] Hixon-Crowell,[11] Korsemeyer and Peppas,[5,12,13] and

Weibull models,[14-17] to ascertain the kinetic modeling of drug release. The method of Bamba et al was adopted for deciding the most appropriate model.[18]

RESULTS AND DISCUSSION

In Vitro Buoyancy Studies

Effervescent floating drug delivery was used to achieve in vitro buoyancy. Metoprolol Tartrate tablets prepared using polymers such as HPMC K15 M, HPMC K100 M & effervescent agents such as sodium bicarbonate & citric acid which induced CO_2 generation in the presence of dissolution medium (0.1N HCl). The gas generated is trapped and protected within the gel, formed by hydration of polymer thus decreasing the density of the tablet. As the density of the tablet falls below 1, the tablet becomes buoyant to provide in vitro buoyancy. Whitehead et al have demonstrated good correlation between in vitro and in vivo buoyancy of floating dosage forms.[19] To study the effect of sodium bicarbonate & citric acid concentration on floating lag time, batches E1,E2,E3 have difference of only concentration of effervescent agent which were monitor. Each batch containing 2:3,0.7:1,3:4 ratios of citric acid & sodium bicarbonate respectively. Results are shown in Table 2. Thus, batch E2 was achieve, optimum in vitro buoyancy.

In Vitro Dissolution Studies:

Under fed condition, the pH of stomach is elevated (~3.5), citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate. On Metoprolol Tartrate formulations citric acid has a stabilizing effect.[20] The pharmacokinetic parameters of Metoprolol Tartrate were used to calculate a theoretical drug release profile for a 12-hour dosage form.

Table 4: Formulation and Dissolution Characteristics of Batches in a 3^2 Full Factorial Design*

Batch code	Variable Level in Coded Form		Lag Time (Y1) (seconds)	Float Time (Y2) (minutes)	Percent Drug Release (Y3) (%)
	X1	X2			
F1	-1	-1	49	10	92.35
F2	1	1	55	22	81.71
F3	1	0	53	16	87.56
F4	0	-1	50	11	94.97
F5	1	-1	49	12	97.11
F6	0	0	55	14	93.88
F7	-1	0	50	11	92.09
F8	0	1	57	20	86.03
F9	-1	1	53	17	88.01

Coded values	Actual values†	
	X1	X2
-1	80	80
0	100	100
1	120	120

†X1 is amount of HPMC K15M in milligrams; X2 is amount of HPMC K100M in milligrams.

Factorial Design:

A 3^2 full factorial design was constructed to study the effect of the amount of HPMC K15M (X1) and the amount of HPMC K100M (X2) on the drug release from gastroretentive Metoprolol Tartrate tablets. The dependent variables chosen were Lag time (Y1), Float time (Y2), Percent Drug release (Y3).

*All batches contained 100 mg Metoprolol Tartrate, 100 mg sodium bicarbonate, 70 mg citric acid, 100 mg MCC PH 102, 30 mg PVP K30 and 1% wt/wt magnesium stearate.

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis using Microsoft excel. The Y_1, Y_2, and Y_3 values for the 9 batches (F1 to F9) showed a wide variation; the results are shown in Table 4. The data clearly indicate that the values of Y_1, Y_2, and Y_3 are strongly dependent on the independent variables.

Figures 3, 4 and 5 show the plot of the amount of HPMC K15M (X1) and amount of HPMC K100M (X2) versus lag time, float time & percent drug release respectively. The data demonstrate that both X1 and X2 affect the float time and drug release. It may also be concluded that the high level of X1 (amount of HPMC K15M) and the lower level of X2 (amount of HPMC K100M) favor the preparation of gastroretentive sustained release Metoprolol Tartrate tablets.
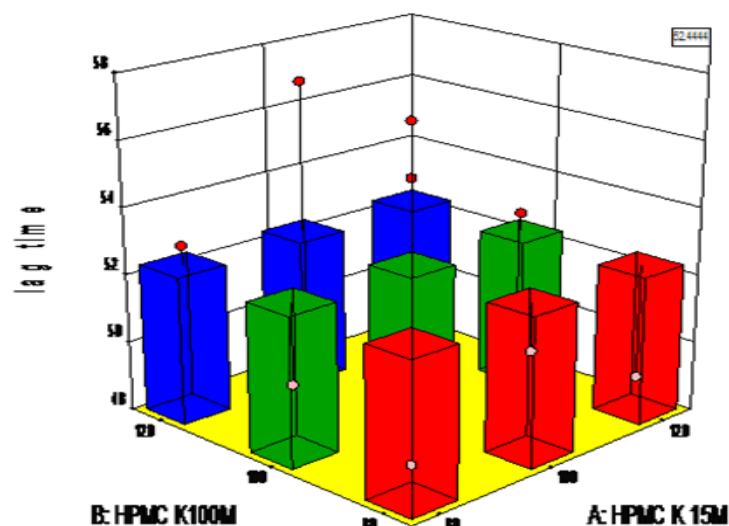
Figure 3: Response surface plot for lag time
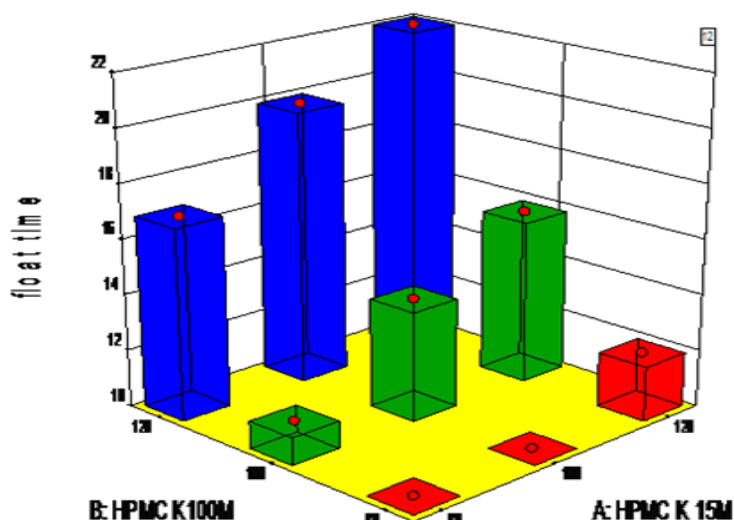
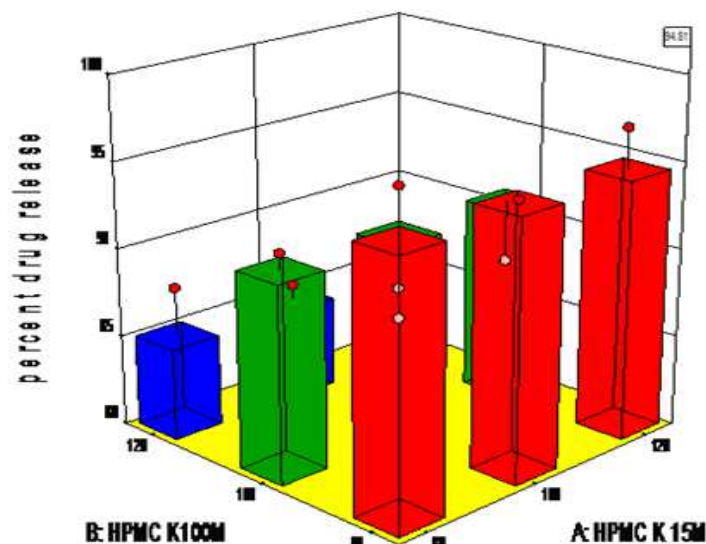**Figure 4:** Response surface plot for float time

Figure 5: Response surface plot for percent drug release

The similarity between the theoretical dissolution profile and the dissolution profile of F5 is clearly demonstrated in Figure 6.
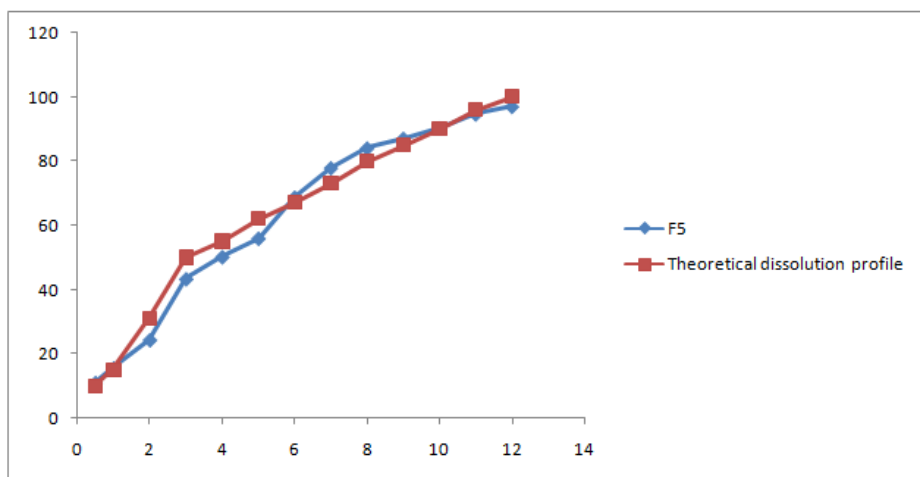

Figure 6: Comparison of in vitro dissolution profiles of batch F5 and theoretical dissolution profile: ♦ indicates Batch F5; ▯ indicates Theoretical dissolution profile:

In Vitro Buoyancy of Factorial Design Batches:

All the factorial design batches showed good in vitro buoyancy. The tablet swelled radially and axially. The average radial diameter after 8 hours was 15 ± 0.3 mm, while the thickness was 11 ± 0.4 mm. The figure also indicates that the tablet remained buoyant for 12 hours, but the tablet actually floated throughout the entire study. The in vitro buoyancy study was also conducted at an elevated pH condition (~4.5). The floating tendency remained unaltered at higher pH.

Kinetics of Drug Release

The dissolution data of batches F1 to F9 was fitted to zero-order, first-order, Higuchi, Hixson-Crowell, Korsemeyer and Peppas and Weibull models. The method of Bamba et al was adopted for deciding the most appropriate model.[18] The results of *F*-statistics were used to select the most

appropriate model. The release profile of the best batch F5 fitted best to the Korsemeyer and Peppas model (F = 1.66). This superiority is statistically insignificant with the Higuchi model (F = 1.85), but significant with the Weibull model (F = 17.5) as shown by the goodness-of-fit test (F ratio test). But priority should be given to the model with the lowest F value. Thus, it may be concluded that drug release from gastroretentive Metoprolol Tartrate tablets is best explained by

the Korsemeyer and Peppas model. The values of slope and intercept for the Korsemeyer and Peppas model are 32.90 and 0.428, respectively. The value of the slope indicates that the drug released by diffusion is of an anomalous type. However, batches F1 to F4 & F6 to F9 followed the Korsemeyer and Peppas model for drug release but showed nonanomalous diffusion. Kinetics of drug release is clearly demonstrated in Figure 7
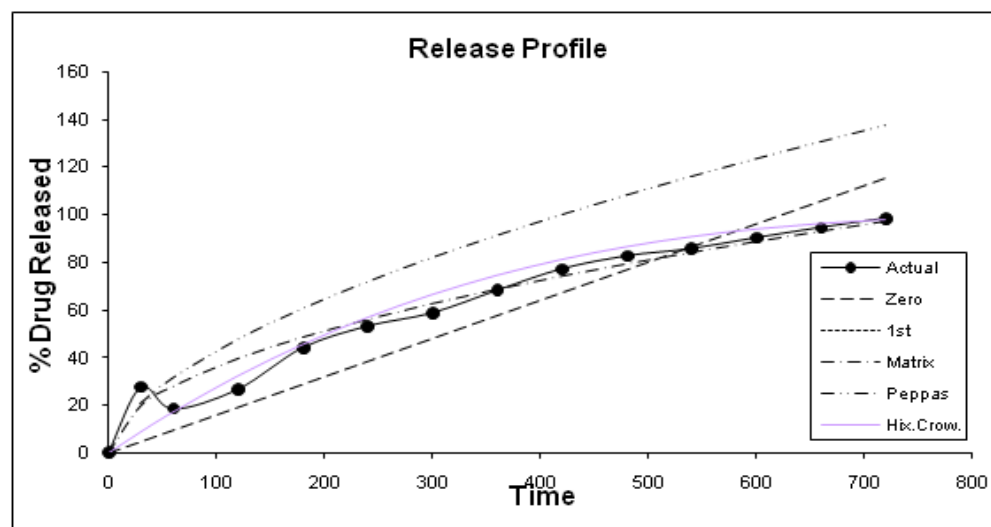

Figure 7: Kinetics of drug release

CONCLUSION

This study discusses the preparation of gastroretentive tablets of Metoprolol Tartrate. The effervescent-based floating drug delivery was a promising approach to achieve in vitro buoyancy. The addition of gel-forming polymer HPMC K15 M & HPMC K100 M and gas-generating agent sodium bicarbonate & citric acid were essential to achieve in vitro buoyancy. A systematic study using a 3^2 full factorial design revealed that the amount HPMC K15M & HPMC K100M had significant effect on percent drug release, lag time & float time. Thus, by selecting a suitable composition of release rate retardant

HPMC K15M, HPMC K100M the desired dissolution profile can be achieved.

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