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Research Article

OPTIMIZATION AND ACESSING THE INFLUENCE OF XANTHAN GUM, EFFERVESCENT COMPONENTS AND HARDNESS ON FLOATATION BEHAVIOR AND DRUG RELEASE OF GASTRO-FLOATING CAPTOPRIL TABLET

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ABSTRACT

This research purposed to optimize, investigate and evaluate the influence of xanthan gum, sodium bicarbonate-citric acid as effervescent components and hardness on floatation behavior and drug release of gastro-floating captopril tablet with floating system. A 2^3 full factorial design (8 runs) was applied to optimize the floating captopril tablet using xanthan gum (X_1), ratio of effervescent components (X_2) and hardness (X_3) as independent variables. Optimum area was determined by superimposed contour plot of floating lag time (Y_1), cumulative drug release at 60min (Q_{60}) (Y_2) and drug release constant rate (Y_3) using Design Expert® software. Xanthan gum, effervescent components and hardness were affected the floatation behavior and drug release. Hardness was the most dominant factor affected the floatation behavior and drug release. Based on superimposed contour plot, the optimum area was in range of xanthan gum 58–100mg, sodium bicarbonate 45–63mg, citric acid 7–25mg and hardness at 70–98N.

Key words: Xanthan gum, Effervescent components, Hardness

INTRODUCTION

Captopril (CAP) is an angiotensin converting enzyme inhibitor as hypertension treatment with half-life about 2h. CAP as highly water soluble drug is most stable at acidic condition and unstable in intestine or pH increases with degradation reaction. These indicate a promising potential as gastroretentive drug delivery system to improve the bioavailability and prolong the drug release (Nur and Zhang, 2000).

Floating drug delivery system with effervescent system is using effervescent components to accelerate floatation and matrix to control the drug release. Sodium bicarbonate and acid system act as effervescent components, increasing of bicarbonate proportion reduced floating lag time and floating time. Excess the effervescent components causing the drug release uncontrolled and tablet cannot maintain their integrity (Jaimini *et al*., 2007). Baumgartner *et al*. (2001) showed that hardness affected on floatation behavior. Low compression force causing tablet float in medium and tablet sink when high compression force was applied (Chen *et al*., 2013).

Initial burst release indicates the drug release at initial time before reach the constant release. Burst release promotes high doses release uncontrolled (dose dumping) and reduce life time of controlled release formulation (Huang and Brazel, 2001). Xanthan gum (XG) provide several advantages than hydroxyl propyl methyl cellulose (HPMC) with no initial burst release effect in water soluble drug with rapidly hydration, more reproducible and release the drug followed by zero-order release (Bhardwaj *et al*., 2000). HPMC act as retarding release agent for sustained release formulation, form firm gel resistant of diffusion and erosion (Siepmann and Peppas, 2012). Combination of both polymers eliminate the limitations on single polymer system and may be suitable for formulation of sustained release matrix of highly water soluble drug to reduce the initial burst release effect (Tiwari *et al*., 2011).

Table I. A 2^3 factorial design models and the results of floating lag time and drug release

Formula	Coded factor level			Results		
	X_1	X_2	X_3	Y_1 (sec)	Y_2(%)	Y_3 (mg/min)
F1	-1	-1	-1	19.5±1.4	30.86±1.54	0.1041±0.0006
Fa	+1	-1	-1	24.8±3.9	25.69±1.89	0.0866±0.0008
Fb	-1	+1	-1	10.3±1.2	34.43±2.18	0.1100±0.0021
Fab	+1	+1	-1	28.2±3.4	26.02±0.72	0.0975±0.0050
Fc	-1	-1	+1	4881.0±118.4	31.22±3.27	0.0885±0.0036
Fac	+1	-1	+1	3620.8±92.8	25.45±2.74	0.0760±0.0028
Fbc	-1	+1	+1	1913.8±64.9	25.52±0.60	0.0803±0.0017
Fabc	+1	+1	+1	1102.2±84.1	17.35±2.29	0.0731±0.0008

Coded level	-1	+1
X_1 : XG (mg)	20	100
X_2 ; Sodium bicarbonate-citric acid ratio	6:4	9:1
X_3 ; hardness (N)	60	120

This study aimed to optimize, investigate and evaluate the influence of XG, sodium bicarbonate-citric acid as effervescent components and hardness on floatation behavior and drug release of gastro-floating CAP tablet with floating system using 2^3 full factorial design.

MATERIAL AND METHOD

CAP was purchased form Afine Chemicals Limited (Hangzou, China), Methocel® K15M (HPMC K15 M) as gift from Colorcon (USA), Avicel® PH101 (MMC) (Shin-Etsu, Japan), Plasdone® K29/32 (PVP K30) (Ashland, USA), XG (Qingdao ICD Biochemistry, China), citric acid (Waifang Ensign, China), sodium bicarbonate (Honghe Chemicals, China), magnesium stearate (Peter Greven, Germany), and talk (Bratachem, Indonesia) were purchased from Bratachem Chemicals (Surakarta, Indonesia) and all the chemicals in pharma-ceuticals grade. Calsium sulfate (Merck, Germany), ethanol (Merck, Germany), methanol (Merck, Germany), hydrochloric acid (Mallinckrodt, Ireland) all the chemicals in analytical grade and demineralized water.

Drug-excipients compatibility study

Drug-excipients compatibility study was conducted using FT-IR Shimadzu 8400S (Kyoto, Japan) to determine the interaction between CAP and excipients. The pure drug and mixtures (in equal ratio) with excipients were scanned using potassium bromide pellets in the range of wavenumber 4000-400cm^{-1}.

Tablet preparation

Tablets were formulated using CAP as drug model 50mg, Methocel® K15M 120mg, Plashdone® 15mg, calcium sulfate 30mg, talk 7.2mg, magnesium stearate 0.8mg, effervescent components (using ratio of sodium bicarbonate-citric acid with total amount 70mg) and XG based on factorial design model according in tablet I. Wet granulation method was employed for formulation. All of the components in formula except magnesium stearate and talk were passed through sieve no.30 separately and mixed in the cube mixer for 15min 30rpm followed by addition 10% PVP in ethanol solution to the blend until elastic mass of wet granules were achieved. Mass of wet granules were passed through sieve no.16 and were dried in oven at temperature 40°C for 3h. The dried granules were passed through sieve no.18 and mixed with magnesium stearate and talk in cube mixer for 5min 30rpm.

Tablet compression

The tablet compression process using single punch machine tablet model TDP-1 Shanghai (China), granules were weighted

manually 400mg and compressed using flat-face punch (diameter 10mm). The hardness was maintained at 60N for low level and 120N for high level of hardness factor.

Physical properties of CAP floating tablet

Physical properties of tablets were conducted by thickness of tablet using calipers (accuracy 0.02mm), friability using Erweka GMB-H friability tester, hardness using Stokes Mosanto hardness tester and drug content.

Floatation behavior characterization

Floating lag time (FLT) and floating time (FT) of tablets were determined using 200mL of HCl 0.1mol/L in a beaker glass. The time required tablet to rise to the surface and float constantly as FLT and the total duration of floating in medium as FT were determined.

In-Vitro drug release

The drug release was determined using dissolution tester (Electrolab TDT 08L) type apparatus II (paddle method) standard USP XXXII using sinker to avoid the tablet float, where 900mL of HCl 0.1mol/L were used as dissolution medium was maintained at 37±0.5°C at 50 rpm of speed rotation for 6h. Aliquots of 5mL were withdrawn at 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360min with replacement of 5mL of the fresh media. All the samples were diluted with dissolution medium (when necessary) and were analyzed at 202.9nm using an UV-Vis Hitachi U-2900 spectrophotometer.

Drug release kinetics

Several mathematic models were applied to analyze the drug release data to find the best fitting equation models i.e. zero-order release, first-order release, Hixson-Crowell, Weibull, Higuchi release, non linier regression using quadratic model and Korsmeyer-Peppas equation. The release mechanism based on the exponential diffusion value (*n*) of Korsmeyer Peppas equation. The best fitting equation based on goodness of fit using coefficient of determination (R^2) and least square fit i.e. AIC (Akaike's Information Criterion) and RMSE (root mean square error). Drug release kinetics and mechanism were computed using open source software KinetDS® version 3.0 (Mendyk *et al*., 2012) and DDSolver® version 1.0 (Zhang *et al*., 2010).

Statistical analysis and optimization

Data obtained (FLT, Q_{60} and drug release constant rate) were analyzed using Design Expert® software version 7.1.5 (Stat-Ease Inc., Minneapolis, MN, USA). Factorial models, including the intercept, main effect and interactions were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The models were evaluated based on several statistical parameters, including the determination coefficient (R^2), adjusted determination coefficient (Adj. R^2), predicted determination coefficient (Pred. R^2) and adequate precision (adeq. precision).

The significant effect of factor on response were determined by F test or p value of analysis of variance (ANOVA) with confidence interval of 95% (p=0.05) were also calculated using Design Expert® software. Contour plots were constructed based on equation of responses, these plots are useful to elucidate interaction effects of factor on responses. The optimum formula determined using superimposed contour plot was obtained from combination of contour plot for each parameter (Bolton and Bon, 2004).

RESULT AND DISCUSSION

Drug-excipients compatibility studies

FT-IR spectra of CAP with mixtures of HPMC and XG (polymers), CAP-effervescent components, and CAP-all excipients were presented in figure 1. The principal peaks of CAP were at wavenumbers 1589.34 and 1747.51cm^{-1} were assigned carbonyl stretching vibration of amide and carboxylic acid respectively. Peaks at 1332.81 was assigned O-H binding vibration, 1228.66cm^{-1} was assigned C-O stretching vibration, 1203.58cm^{-1} was assigned C-N stretching vibration, 2565.33cm^{-1} was assigned a thiol group (SH) stretching vibration. Degradation and incompatibilities were showed by new strong or sharp peak at 650-600cm^{-1} as disulfide form (S-S) and disappeared vibration of thiols group, those were not found in CAP mixtures with effervescent components, polymers and all excipients. There was no significant shift of principal peaks of CAP in the mixture of CAP

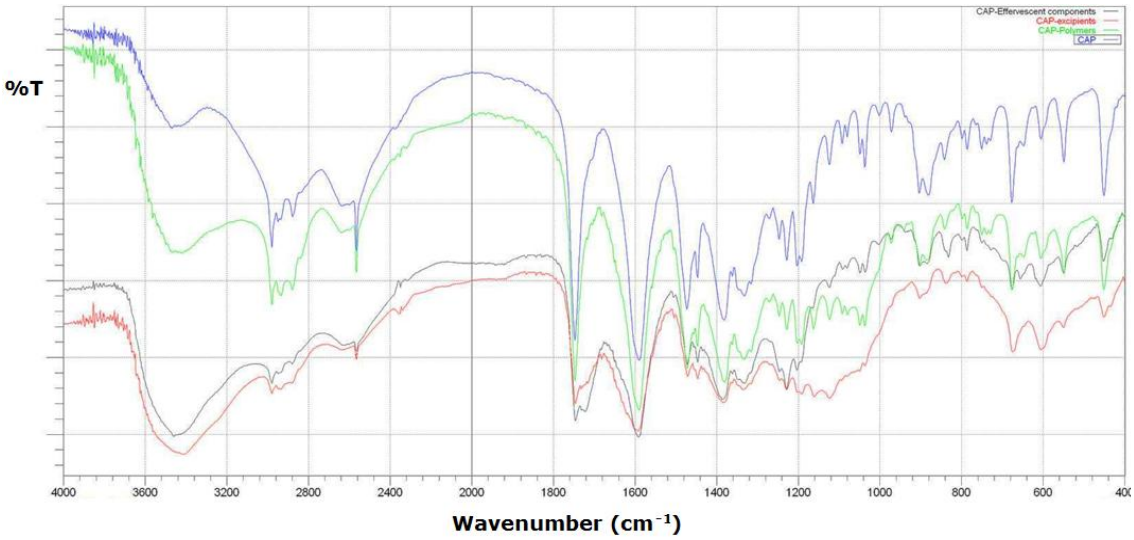

Figure 1. FT-IR spectrum of mixture between CAP and excipients (blue band : CAP, green band : CAP-polymers, black band : CAP-effervescent components, red band : CAP-all excipients)

with polymers, effervescent components and all excipients, thus indicating that no chemical interaction between drug and excipients.

Physical properties of tablets

Physical properties of tablet showed that at low level and high level of hardness factor was successfully controlled respectively at 60N (59-63N) and 120N (116-121N), results showed not significant different statistically ($p>0.01$) for each level. The hardness of tablets affected friability of tablet, at high level (0.00-0.02%) provided lower friability than low level (0.06-0.12%) of hardness factor. Difference of tablet thickness was affected of the compression force, while adjusted the deepness of upper punch to achieve the hardness according to the hardness level and difference of compressed mass properties. The drug content required the standard reference with not less than 90% and not more than 110% (46.41-53.90 mg) (USP, 2009).

Floating properties

FLT for all formulation within 10-4481s (Table I) and all of the formulas provided duration of FT more than 24h. Based on the FLT, MLRA approach using factorial design method for studied the response of factor in FLT was expressed in equation 1.

$$\mathbf{Ln(Y_1) = 5.39 + 0.049X_1 - 0.33X_2 + 2.43X_3 + 0.064X_1X_2 - 0.26X1X3 - 0.20X_2X_3 - 0.13X_1X_2X_3} \quad \textbf{…….. (1)}$$

Ratio maximum data and minimum data in FLT more than 10 (496.2) thus the FLT must be transformed in natural log (ln) for required plot of the residual distributed normally. Eq. 1 showed that hardness was the most dominant in increasing FLT. Increasing the hardness reduced the porosity and increased the density thus causing longer of FLT. Previous work showed the hardness and compression force affected the buoyancy properties (Baumgartner *et al.*, 2000; Chen *et al.*, 2013). Enhancement of XG level increased the bulk and tapped density (data not shown) thus affected in increasing FLT and increasing the filler (MMC) (when XG level decreased) provided shorter FLT.

Enhancement of the effervescent components ratio (increasing sodium bicarbonate proportion) reduced the FLT. Sodium bicarbonate as gas generating agent produce gas after reaction with acidic medium and gas entrapped in swollen matrix then tablet becomes buoyant. Increasing the proportion of sodium bicarbonate provided shorter FLT (Rao *et al.*, 2009; Srikant *et al.*, 2011; Hu *et al.*, 2011). FLT was not only affected by the factors

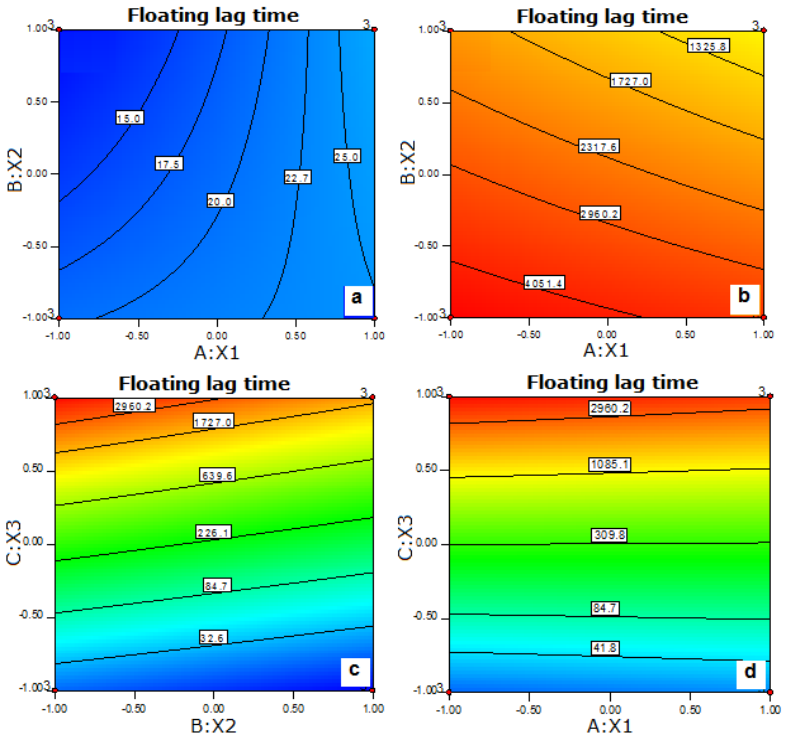

Figure 2. Contour plot of FLT a) X_3 at low level, b) X_3 at high level, c) X_1 at low level and d) X_2 at low level.

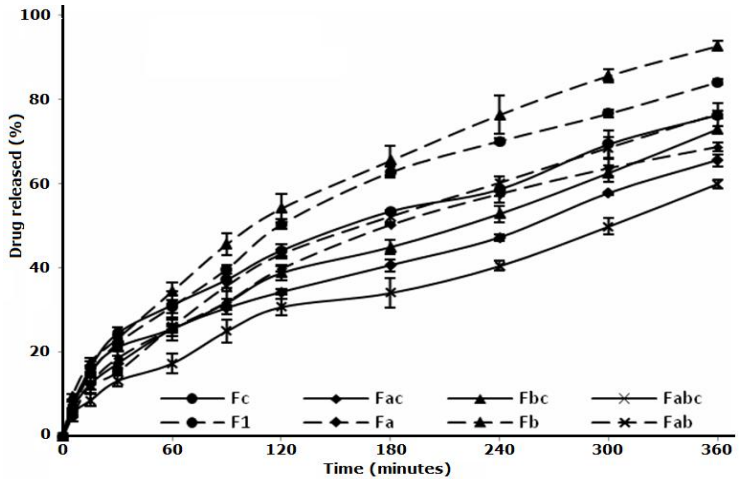

Figure 3. Drug release profiles of CAP gastro-floating tablet.

optimized, however FLT was affected by interaction of each factor. Interaction between X_1-X_2 increased the FLT, interaction between X_2-X_3 and X_1-X_3 reduced FLT and interaction of all factors reduced FLT. The model in significant term ($p<0.05$) and all of the factors and their interactions provided significant effect in FLT ($p<0.05$). Interaction of factor on FLT was showed by contour plot (Figure 2).

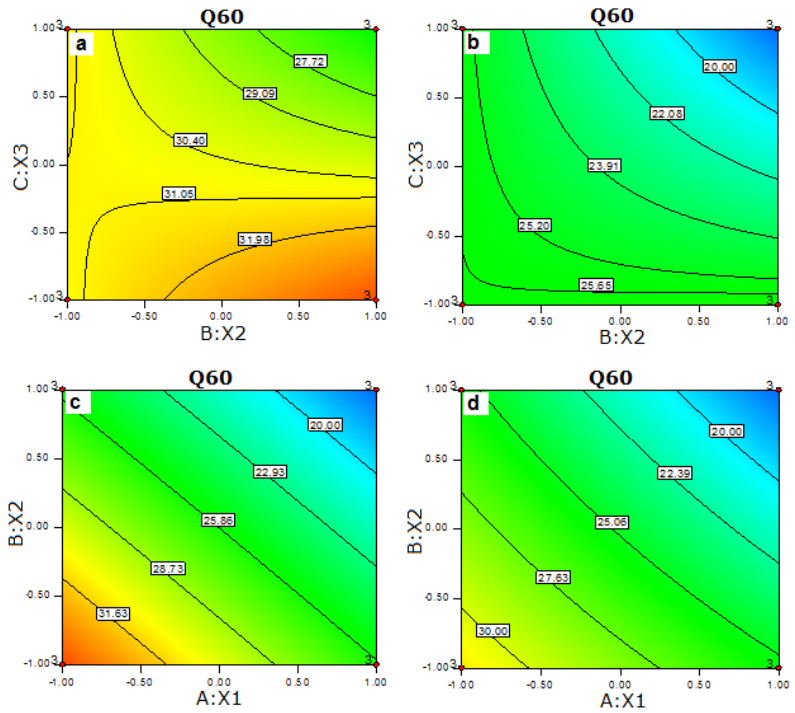

Figure 4. Contour plot of Q_{60} a) X_1 at low level, b) X_1 at high level, c) X_2 at high level and d) X_3 at high level.

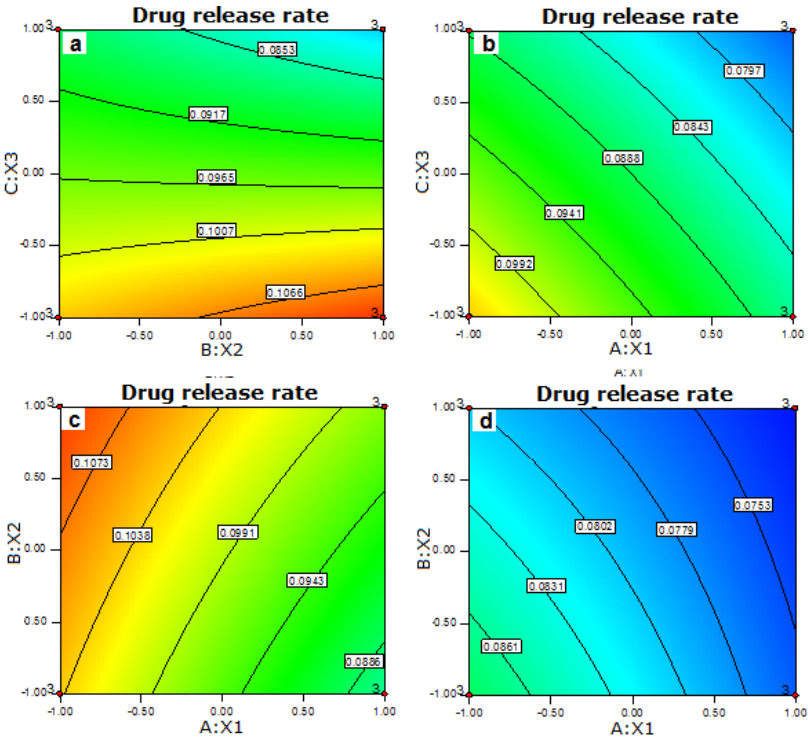

Figure 5. Contour plot of drug release rate a) X_1 at low level, b) X_2 at low level, c) X_3 at low level and d) X_3 at high level.

Drug release

Drug release of from gastro-floating CAP tablet was showed in figure 3. All formulas had similarity on drug release pattern. Formulas with low level of hardness factor showed the higher drug release than formulas with high level of hardness. Increasing of hardness reduced the porosity and water-uptake thus decreased drug release (Ferrero and Jimenez-Castellanos, 2014).

Increasing the sodium bicarbonate promoted the drug release, sodium bicarbonate produce gas after reaction with acidic medium that causing the matrix became porous and the drug diffusion pass through the porous/ channel, hence increased the drug release. Citric acid accelerated the effervescent reaction thus increased the drug release at initial time. Drug release of all formulas were retarded for 6h.

Based on the Q_{60}, MLRA approach using factorial design method for studied the response of factor in Q_{60} was expressed in equation 2.

$$\mathbf{Y_2 = 27.07 - 3.44X_1 - 1.24X2 - 2.18X_3 - 0.70X_1X_2 - 0.045X_1X_3 - 2.21X_2X_3 + 0.10X_1X_2X_3 \ldots\ldots(2)}$$

Eq. 2 showed that XG was the most dominant factor to reduce the drug release at 60min. CAP as drug model have highly soluble drug in matrix HPMC showed the initial burst release effect (Patel *et al*., 2008). Combination of HPMC and XG reduced initial burst release rather than single polymer (Mughal *et al*., 2011; Tavakoli *et al*., 2006). Increasing hardness and reducing the citric acid proportion reduced the Q_{60}. Q_{60} was not only affected by the factors optimized, however interaction of each factor affected Q_{60}. Interaction between X_1-X_2, X_2-X_3 and X_1-X_3 reduced Q_{60} and interaction of all factors increased Q_{60}. The equation of Q_{60} had significant term ($p<0.05$). XG, effervescent components and interaction between effervescent components and hardness provided significant effect on drug release at initial time ($p<0.05$). Interaction of factor was elucidated using contour plot (Figure 4).

Drug release rate constant (Y_3) based on the slope of zero-order release kinetics. MLRA approach using factorial design method for studied the response of factor in Y_3 was expressed in equation 3.

$$\mathbf{Y_3 = 0.089 - 6.213x10^{-3}X_1 + 7.125x10^{-4}X_2 - 0.010X_3 + 1.296x10^{-3}X_1X_2 + 1.288x10^{-3}X_1X_3 - 3.487x10^{-3}X_2X_3 + 4.583x10^{-5}X_1X_2X_3 \ldots\ldots\ldots(3)}$$

Eq. 3 showed that hardness was the most dominant on reducing the drug release rate, increasing of effervescent components level increased the drug release rate, with increasing the sodium bicarbonate-citric acid ratio. XG reduced the drug release rate, increasing the polymer concentration reduced the drug release and drug release rate (Mostavafi *et al*., 2011). Interaction between X_1-X_2 and X_1-X_3 increased the drug release rate, interaction between X_2-X_3 reduced the drug release rate. Main effects (X_1, X_2 and X_3), interactions of each factor and all factors affected the drug release rate. Eq. 3 had significant term ($p<0.05$) and the XG, hardness and interaction of each factor provided significant effect on drug release rate ($p<0.05$).

Based on statistical parameters of factorial design method, R^2 measure the influence of factor to the response in equation, thus the higher of R^2 more preferable ($\ln(Y_1)$ = 0.999, Y_2 = 0.890 and Y_3 = 0.971). Adj. R^2 ($\ln(Y_1)$ = 0.999, Y_2 = 0.851 and Y_3 = 0.959) and Pred. R^2 ($\ln(Y_1)$ = 0.998, Y_2 = 0.752 and Y_3 = 0.936) should be within 0.200 of each other. Adeq. precision showed the signal to noise ratio, adeq. precision more than 4 was desirable model ($\ln(Y_1)$ = 140.7, Y_2 = 14.1 and Y_3 = 24.4) thus all response had adequate equation to describe the response.

Optimum formula was achieved from combination of contour plot for each parameter based on the goal ($\ln(Y_1)$: min, Y_2 : min and Y_3 : min) and importance ($\ln(Y_1)$: 4, Y_2 : 2 and Y_3 : 4). Based on superimposed contour plot optimum area was in range XG 58-10mg, sodium bicarbonate 45-63mg, citric acid 7-25mg and tablet compressed in range 70-98 N of hardness

Drug release kinetics and mechanism

Drug release kinetic was to describe the drug release from the dosage form. Controlled release formulation, swelling, diffusion and erosion are the most important rate-controlling mechanism and kinetics. Mechanism and kinetics of drug releases were affected by

Table II. Kinetics model of drug release from gastro-floating CAP tablet

Model	Statistics	F1	Fa	Fb	Fab	Fc	Fac	Fbc	Fabc
Zero-order	R^2	0.939	0.947	0.954	0.959	0.946	0.969	0.976	0.978
	RMSE	6.37	4.88	5.93	4.69	5.06	3.22	3.10	2.55
	AIC	64.06	58.74	62.63	57.93	59.45	50.41	49.63	45.78
First-order	R^2	0.941	0.977	0.950	0.974	0.909	0.904	0.907	0.941
	RMSE	4.11	4.97	4.3	3.93	6.90	5.98	6.42	4.37
	AIC	52.25	56.04	53.30	51.33	62.61	59.73	61.15	53.48
Higuchi	R^2	0.991	0.993	0.996	0.986	0.995	0.989	0.986	0.966
	RMSE	2.55	1.93	1.80	2.88	1.67	2.07	2.50	3.34
	AIC	42.68	37.07	35.69	45.15	38.29	42.06	44.38	54.94
Hixson-Crowell	R^2	0.947	0.914	0.957	0.948	0.861	0.873	0.876	0.925
	RMSE	6.29	6.52	6.07	5.58	8.51	6.89	7.41	4.94
	AIC	60.76	61.46	60.05	58.34	66.80	62.59	64.03	55.93
Quadratic	R^2	0.968	0.967	0.957	0.971	0.908	0.912	0.902	0.943
	RMSE	5.17	4.31	6.43	4.39	7.36	6.07	6.99	4.57
	AIC	57.66	54.02	62.02	54.39	64.71	60.87	63.67	55.21
Weibull	R^2	0.995	0.995	0.976	0.985	0.988	0.990	0.977	0.979
	β	0.811	0.732	0.745	0.716	0.674	0.613	0.602	0.637
	RMSE	1.72	1.11	3.91	2.42	2.43	2.80	3.80	3.25
	AIC	37.92	29.16	54.27	46.70	44.76	47.62	53.71	50.63
Korsmeyer-Peppas	R^2	0.990	0.987	0.998	0.993	0.981	0.996	0.990	0.990
	n	0.604	0.606	0.539	0.584	0.538	0.519	0.494	0.556
	RMSE	1.96	1.28	1.11	1.40	1.57	1.75	2.22	2.07
	AIC	40.45	32.00	29.03	33.70	36.02	38.22	42.94	41.60

characteristics of polymers, drug to polymer ratio and geometric of dosage form (Grassi and Grassi, 2005).

The release exponent (n) indicates of the mechanism the drug release. An exponent value of cylindrical geometric n = 0.45 indicates Fickian diffusion, n within 0.45-0.89 indicates the anomalous transport, n = 0.89 indicates case II transport and n more than 0.89 indicates super case II transport. Based on the n value all formula within 0.45-0.89, thus indicates the drug release mechanism was controlled by diffusion and relaxation of the polymer chain and imbibition of water causing polymer change from glassy to rubbery state. Methocel® K15M CR was the polymer resistant with erosion and XG rapidly hydration thus combination of both polymer controlled drug release manner followed zero-order release.

Drug kinetics release based on parameters on table II. Difference of formulation indicated different kinetics release. Selected kinetics model to describe the drug release based on goodness of fit (the highest of R^2) and least fit square (the lowest of AIC and RMSE) thus similarity between observed and predicted model (Motoulsky and Christopoulus, 2003). All formulas except Fabc were best fitted by Higuchi model and Fabc was best fitted by zero-order model. Shape curve parameter (β) of Weibull model indicates drug release with initial burst release ($\beta<1$) with the higher slope in initial time and followed by constant release. Hixson-Crowell model indicates the drug release occurs the surface of tablet diminish proportionally overtime (erosion). Highuci described drug release diffusion pass through the tortuosity of matrix followed fickian diffusion. Ideally, drug release from controlled release formulation with constant release rate (Costa and Lobo, 2001).

CONCLUSIONS

Floating lag time and drug release were affected by XG, effervescent components and hardness. Hardness was the most dominant

factor affected the floatation behavior. Increasing hardness and XG reduced the drug release at initial time and drug release. Increasing the sodium bicarbonate proportion increased the drug release and citric acid promoted initial burst release effect.

Based on superimposed contour plot optimum area was found in range XG 58-100mg, sodium bicarbonate 45-63mg, citric acid 7-25mg and hardness 70-98N.

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