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DRUG DEVELOPMENT AND OPTIMIZATION FORMULA OF RANITDIN HCl GASTRORETENTIVE MUCCOADHESIVE FLOATING SYSTEM TABLET

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Keywords:

Ranitidine HCl, floating-mucoadhesive, swelling index, Gastroretentive, Factorial Design

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ABSTRACT: Ranitidine hydrochloride (RHCl) is a histamine H2 receptor antagonist, it's widely in active duodenum ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis. Ranitidine HCl has a short biological half-life of drug 2 - 3 h, has 50% absolute bioavailability, colonic metabolism of ranitidine HCl was partly responsible for the poor bioavailability. Based on these, gastroretentive drug delivery system (GRDDS) using floating-mucoadhesive system dosage form of Ranitidine HCl has been developed that makes less frequent administering of the drug also improve bioavailability. Factorial design 2^3 was applied to optimize the formula of ranitidine HCl floating-mucoadhesive tablet by the varying level of polymer, it was chitosan 50 - 100 mg as a mucoadhesive agent, HPMC K4M 20 - 50 mg as a swelling agent, and drug release controlled, and sodium bicarbonate 20 - 40 mg as gas generating agent. The optimum formula determined by superimposed contour plot from various parameters: physical properties of granule, tablet, and drug release 6 h using a design expert ® program. Based on superimposed contour plot design expert ® obtained an optimum formula for the area in the range of chitosan 100 mg; HPMC K4M 50 mg; and Sodium bicarbonate 26, 25 mg.

INTRODUCTION: Ranitidine hydrochloride (RHCl) is a histamine H2 receptor antagonist, it's widely in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis. The recommended dosage of ranitidine HCl is 150 mg twice daily or 300 mg once daily. The effective treatment of erosive esophagitis requires administration of 150 mg ranitidine 4 times a day.

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Ranitidine HCl has a short biological half-life of drug 2 - 3 hours, has 50 - 60% absolute bioavailability, colonic metabolism of ranitidine HCl was partly responsible for the poor bioavailability of ranitidine from the colon. The gastroretentive drug delivery system is retained in the stomach and is useful for drugs that are poorly soluble or insoluble in gastric fluids. This system helps in continuously releasing the drug before it reaches the absorption, thus ensuring optimal bioavailability.

The density of the system can be reduced by incorporating a number of low-density fillers or polymers into the system such as hydroxyl cellulose, lactates or microcrystalline cellulose. The basic idea behind the development of such a system

is to maintain a constant level of drug in the blood plasma in spite of the fact that the drug does not undergo disintegration. The drug usually keeps floating in the gastric fluid and slowly dissolves at a predetermined rate to release the drug from the dosage form and maintain constant drug levels in the blood levels [1]. In this study, the components will be optimized is HPMC K4M, chitosan, sodium bicarbonate with range 20 - 50 mg; 50 - 100 mg; 20 - 40 mg. the response will be used for optimization such as compressibility index, hardness, friability, floating lag time, drug release rate.

MATERIALS AND METHODS: Ranitidine HCl was purchased from Kimia Farma, Tbk Indonesia. HPMC K4M was from Shanghai Honest Chem Co., Ltd. chitosan was from N & R Industries, INC. Isopropyl alcohol was from Merck KGaA, Darmastadt, Germany. PVP K-30 was from nanhang industrial co., ltd. Magnesium stearate, talcum, and citric acid were ordered from Bratachem, Indonesia.

Preparation of Ranitidine HCl Gastroretentive System Floating - Mucoadhesive Tablets: Ranitidine HCl gastroretentive system floating - mucoadhesive tablets was formulated by using combination two polymers and gas generating agent. HPMC K4M, chitosan, and sodium bicarbonate were optimized by using factorial design 2^3 and analyzed with design expert software 7.1.5. The low and the high level of each chitosan (-50 mg, +100 mg); HPMC K4M (-20 mg, +50 mg); and sodium bicarbonate (-20 mg, +40 mg). Each formula floating tablet contains 300 mg ranitidine HCl were prepared by a conventional wet granulation method according to the formula **Table 1**. The ingredients were weighed and mixed thoroughly. Granulation was done with a solution of PVP K-30 in sufficient isopropyl alcohol. The granule (14 meshes) was dried in a hot air oven at 40 ± 0.5 °C. The dried granule was filtered 18 meshes and mixed with magnesium stearate as a lubricant, talc as a glidant, and citric acid as gas generating agent [2].

TABLE 1: FACTORIAL DESIGN 2^3 FOR FORMULATION OF RANITIDINE HCL GASTRORETENTIVESYSTEM FLOATING-MUCOADHESIVE TABLETS

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Ranitidine HCl	300	300	300	300	300	300	300	300
Chitosan	50	50	50	50	100	100	100	100
HPMC K4M	20	20	50	50	20	20	50	50
Sodium Bicarbonate	20	40	20	40	20	40	20	40
Isopropylalcohol	QS	QS	QS	QS	QS	QS	QS	QS
PVP K-30	10	10	10	10	10	10	10	10
Talc	4	4	4	4	4	4	4	4
Magnesium Stearate	4	4	4	4	4	4	4	4
Citric Acid	70	70	70	70	70	70	70	70
Total Weight	478	498	508	528	528	548	558	578

Evaluation Studies of Ranitidine HCl Gastroretentive System Floating – Muccoadhesive:

Preformulation Parameters:

Bulk Density and Tapped Density: Bulk density (BD) and tapped density (TD) was determined. Weight accurately 20 g of granules was transferred in 100 ml graduated cylinder without compacting. Calculated the apparent bulk density in gram/ml by the following formula [3].

Bulk density = (weight of bulk) / (bulk volume)

Tapped density measured, weight accurately 20 g granules and transferred in 200 ml measured glass graduated cylinder of tap density tester. Calculated by formula [3].

Tapped Density = (weight of bulk) / (tapped volume)

Compressibility Index: The compressibility index of the granules was determined by Carr's compressibility index [2]. The formula for Carr's Index is as below:

Carr's Index (%) = ((TD-BD)) / TD × 100

Evaluation of Tablets:

Weight Variation Test: Twenty tablets of the formulation were selected at random, weight, average weight, coefficient of variation, and the standard deviation was calculated.

Hardness Test: Hardness of tablet was determined using hardness tester. A good formulation should have hardness value in a range of 8 - 13 kg/cm^2 [4].

Friability: Friability is the measure of tablet strength and measured with Roche friability tester. Twenty tablets were weight accurately and place in the tumbling apparatus that revolved at 25 rpm for 4 minutes [5]. The friability of the tablet was calculated according to the below:

$$\% \text{ Friability} = (\text{Initial weight-Final Weight}) / (\text{Initial Weight}) \times 100$$

Floating Lag Time and Floating Time: Floating lag time is the ability of tablet float on the surface of the medium. The tablet was placed in 250 ml beaker glass containing 0.1 N HCl, pH 1.2 at 37 ± 0.5 °C [6]. The time required for the tablet rise to the surface of medium and float was determined as floating lag time. Floating time is the duration of time the dosage form to constantly remain on the surface of medium [6].

***In-vitro* Drug Release Study:** The release of ranitidine HCl from the floating tablet was determining using dissolution tester apparatus type II (paddle). The dissolution was performed using 900 ml of 0,1N HCl at 37 ± 0.5 °C and 75 rpm. At predetermine time intervals 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300, dan 360 min, 5.0 ml of the sample were withdrawn by means of a syringe filtered, the volume withdrawn at each interval was replace with same quantity of fresh dissolution medium. The sample was analyzed for the drug release by measuring the absorbance at 315 nm using UV Visible spectrophotometer [7].

RESULT AND DISCUSSIONS: Gastroretentive floating tablets of ranitidine HCl were prepared and optimized by 23 factorial design using software design expert software 7.1.5. In order to select optimum formulas and also to achieve the desired prolonged release of drug from the dosage form (by retaining drug at gastric environment). The three-factor parameters involved in the development of formulation are, the concentration of HPMC K4M polymer, chitosan polymer, and sodium bicarbonate as the independent variable (X1, X2, X3), and the response factor such as compressibility index, friability, hardness, floating lag time, *in-vitro* drug release. Totally eight formulation **Table 1** of sustained-release tablet dosage form were prepared by wet granulation method

TABLE 2: RESULT PREFORMULATION PARAMETERS OF RANITIDINE HCL GASTRORETENTIVESYSTEM FLOATING – MUCOADHESIVE TABLETS

Formulas	Carr's Index (%)	Hausner's Ratio	Flow Property
F1	0.194 ± 0.043	1.140 ± 0.030	Excellent
F2	0.079 ± 0.041	1.061 ± 0.031	Excellent
F3	0.270 ± 0.018	1.281 ± 0.017	Excellent
F4	0.242 ± 0.034	1.270 ± 0.033	Excellent
F5	0.131 ± 0.031	1.160 ± 0.037	Excellent
F6	0.199 ± 0.016	1.208 ± 0.015	Excellent
F7	0.259 ± 0.045	1.283 ± 0.044	Excellent
F8	0.189 ± 0.012	1.278 ± 0.013	Excellent

The prepared tablets of all the formulations were evaluated for pre-compression parameters like bulk density, tapped density and compressibility index and physical characters like tablet hardness, friability, weight variation, floating lag time, total floating time, *in-vitro* drug release. The main aim was to control the release of drug up to 6 h. All formulation showed good Carr's index and Hausner ratio **Table 2**. Carr's index ranged from 0.079 ± 0.041 to 0.270 ± 0.018 and the Hausner ratio ranged from 1.061 ± 0.031 to 1.283 ± 0.044. The shape of tablets of all formulations remained off white yellow, smooth, flat-faced circular with no visible cracks

TABLE 3: RESULT EVALUATION TABLET OF RANITIDINE HCl GASTRORETENTIVE SYSTEM FLOATING – MUCOADHESIVE TABLETS

Formulas	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Floating Lag Time (sec)	Floating Duration Time (hr)	K Zero Order (mg/menit)
F1	7.52 ± 1.37	0.47 ± 0.0015	478.15 ± 0.17	313.00 ± 11.53	6 jam	0.168
F2	8.05 ± 1.34	0.33 ± 0.0021	498.15 ± 0.15	90.67 ± 5.03	6 jam	0.097
F3	7.84 ± 1.08	0.31 ± 0.0022	508.15 ± 0.17	94.33 ± 8.50	>24 jam	0.166
F4	7.56 ± 1.67	0.47 ± 0.0016	528.25 ± 0.17	52.67 ± 4.51	>24 jam	0.160
F5	7.04 ± 0.73	0.35 ± 0.0019	528.10 ± 0.10	210.00 ± 9.54	12 jam	0.153
F6	7.02 ± 0.60	0.30 ± 0.0024	548.15 ± 0.11	110.00 ± 9.17	12 hour	0.140
F7	7.56 ± 1.67	0.28 ± 0.0016	558.25 ± 0.14	163.33 ± 5.86	>24 jam	0.234
F8	7.56 ± 1.67	0.44 ± 0.0016	578.25 ± 0.11	72.67 ± 6.81	>24 jam	0.179

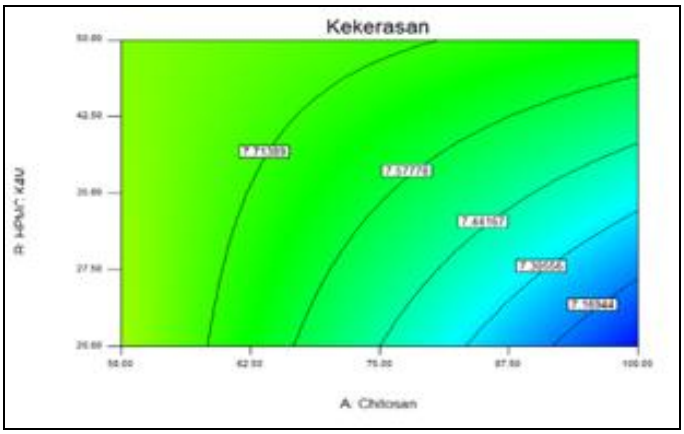

FIG. 1: TABLET HARDNESS OF FACTORIAL DESIGN CONTOUR PLOT

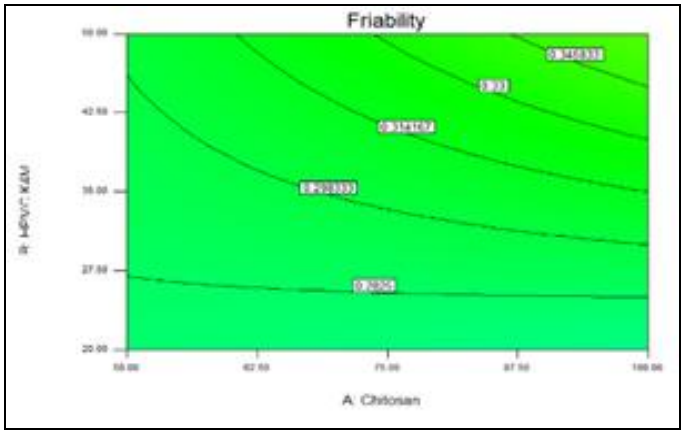

FIG. 2: TABLET FRIABILITY OF FACTORIAL DESIGN CONTOUR PLOT

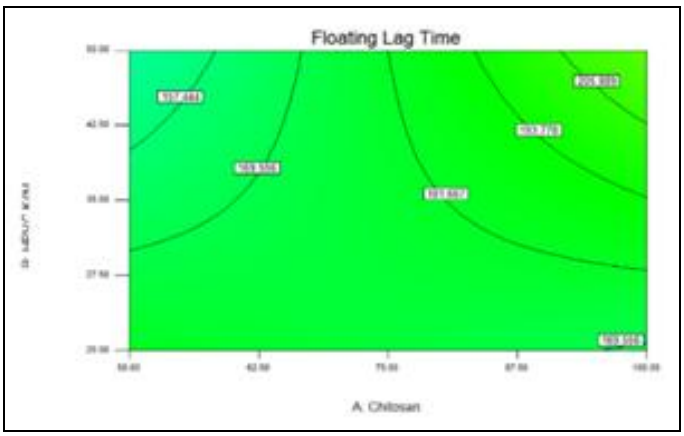

FIG. 3: TABLET FLOATING LAG TIME OF FACTORIAL DESIGN CONTOUR PLOT

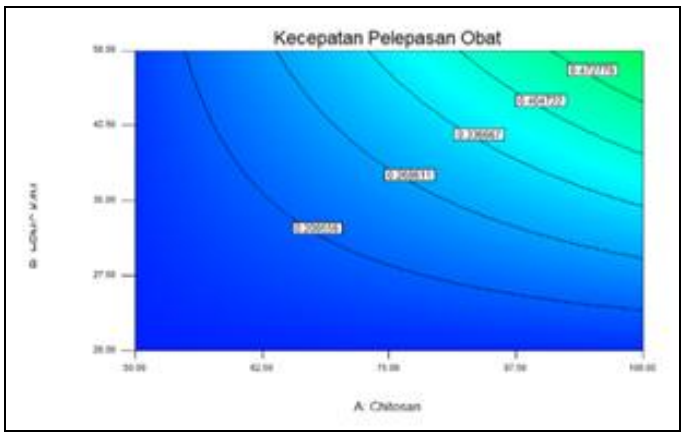

FIG. 4: DRUG RELEASE RATE OF FACTORIAL DESIGN CONTOUR PLOT

The hardness of the tablets was measured by monsanto tester (Thermo Lab, Mumbai, India) and was in between 7.02 ± 0.60 to 8.05 ± 1.34 kg/cm^2. The equation of factorial design for hardness obtained Y = 7.59-0.25(A) + 0.15(B) + 0.037(C) + 0, 16(A) (B) – 0.062(A) (C)-9, 12(B) (C) + 0, 096(A) (B) (C).

Based on the tablet hardness contour plot **Table 3, Fig. 1** and the equation show each component and their interactions have a significant effect on tablet hardness. HPMC K4M, and Sodium bicarbonate increase effect of hardness tablet, it shows indicated by the coefficient on the equation factorial design, but chitosan give decrease effect the value tablet hardness, it is seen minus coefficient on the equation factorial design. Interaction between components in the formula can increase the value tablet hardness although not significant because its value is less than the HPMC K4M coefficient. With coefficient value indicates that more the amount of HPMC K4M on formula can increase tablet hardness [8] because HPMC K4M can also as a binder on the tablet particles so that particles bonds can make stronger [9]. The tablet friability was found below 1% indicating good mechanical resistance. The equation of factorial design for friability of tablet obtained Y = 0.30 + 0.012(A) + 0.030(B) + 0.025(C) + 0.018(A) (B) + 0.033(A) (C) + 0.095(B) (C) - 0.014(A) (B) (C).

Based on the equations and contour plots **Table 3, Fig. 2** friability of tablets shows all component can increase the friability of tablets, but interaction three-component can decrease friability of tablet, it shows the value of the negative's coefficient. Floating capability or floating time is the start time of floating tablet (Floating lag time). Sodium bicarbonate and citric acid added on formulas as a gas generating agent. On contact with dissolution medium (0.1N HCl), carbon dioxide gas was generated. It was observed that the gas generated is trapped and protected within gel formed by hydration of polymer (HPMC K4M and chitosan), thus decreasing the density of the tablet below 1 and the tablet becomes buoyant.

The floating time can be seen in **Table 3** and the analysis can show in **Fig. 3**. The equation of factorial design for floating lag time is Y = 178.33+14.83(A) + 3. 33 (B) + 17.92 (C) + 21.50 (A) (B) + 99.42 (A) (C) + 28. 42(B) (C) - 31.42 (A) (B) (C). Base on equation shows, chitosan, HPMC K4M and sodium bicarbonate increase floating lag time of tablet. Interaction between chitosan, HPMC K4M, and sodium bicarbonate have a negative coefficient, its means the interaction will decrease the floating time. The combination of these 3 components will form an effervescent system. The gas formed by the reaction of citric acid and sodium bicarbonate increase up floating a part of that gas formed will be also be trapped inside HPMC K4M gel structure so will further simplifying the floating process [10]. Based on the release rate data of ranitidine HCl floating in **Table 3** and the analysis is illustrated in the contour plot as shown in **Fig. 4**. Based on release rate data of ranitidine HCl (mg/minutes) is obtained factorial design equation as follow: Y = 0. 25 + 0.098 (A) + 0.11(B) + 0.065 (C) + 0.090 (A) (B) + 0. 084 (A) (C) + 0.086(B) (C) + 0.070(A) (B) (C). The release rate of ranitidine HCl depended by each component as well as interactions between components. Each component like chitosan, HPMC K4M, and sodium bicarbonate increase drug release rate of ranitidine HCl. HPMC K4M as the hydrophilic matrix will be forming a gel when interacting with the medium. A large amount of HPMC K4M increase forming a gel and make of tablet thick so that the amount of drugless. The higher content of chitosan affected the extent of drug release whereas the type and quantity of HPMC K4M in the matrix affected the pattern of drug release. Sodium bicarbonate and citric acid that form CO_2 gas when reacting with the medium can make form a cannel (pore) on the matrix so that the amount of the drug can release more. A large amount of sodium bicarbonate than the pore that formed more and makes it increase drug release rate [10].

TABLE 4: RESPOND AND IMPORTANCE CRITERIA PARAMETER

Respon	Goal	Max point	Min. Point	Bobot
Compressibility Index	In Range	0.278%	0.077%	+++
Hardness	Maximize	8.3 kg/cm^2	7 kg/cm^2	+++
Friability	Minimize	0.55%	0.1%	+++
Floating Lag Time	Minimize	346 second	38 second	+++
Drug Release Rate Zero Order	Maximize	1.181 mg/minute	0.097 mg/minute	+++++

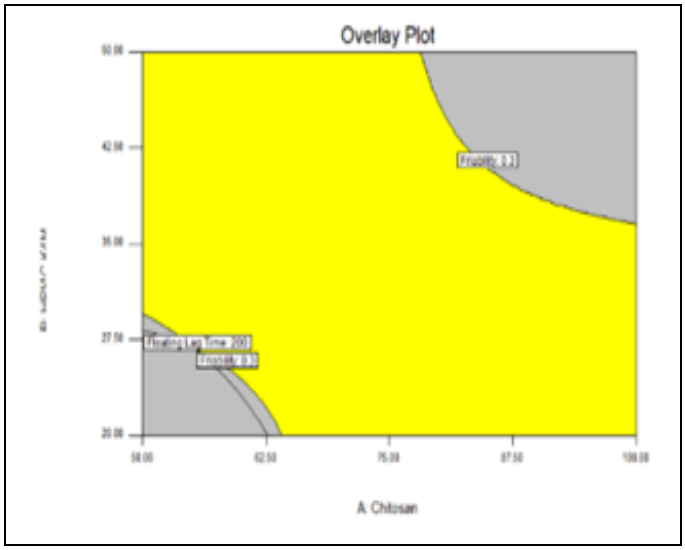

FIG. 5: SUPERIMPOSED CONTOUR PLOT OF FACTORIAL DESIGN VARIOUS PARAMETERS COMPRESSIBILITY INDEX, HARDNESS, FRIABILITY, FLOATING LAG TIME, DRUG RELEASE RATE

The optimum formula determined by superimposed contour plot using design expert ® program with various parameters, such as compressibility index, hardness, friability, floating lag time, drug release rate. Form the superimposed graph **Fig. 5** obtained an optimum area in the comparison chitosan 100 mg, HPMC K4M 50 mg, and sodium bicarbonate 27, 10 mg. In the area when produced will give the physical properties of granules and tablets such as expected criteria corresponding to criteria/goal seat as in **Table 4.**

CONCLUSION: The optimum formula area was obtained in the chitosan 100 mg, HPMC K4M 50 mg, and sodium bicarbonate 27.10 mg.

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REFERENCES:

1. Rathore J and Parmar HK: Formulation and evaluation floating tablets of norfloxacin. International Journal of Pharma Sciences and Research 2015; 6(01): 23-27.
2. Sarangapani S and Rajappan M: Lansoprazole release from a floating dosage form based on the natural polymer of *Delonix regia*. International Journal of Pharm Tech Research 2012; 4(3): 1084-95.
3. Tekade BW, Jadhao UT, Patil SG and Patil VR: Formulation and *in-vitro* evaluation of floating tablets of cefpodoxime proxetil. International Journal of Current Pharmaceutical Research 2017; 9(6): 18-22.
4. Ekade BW and Thakare VM: Optimization and *in-vitro* evaluation of verapamil hydrochloride floating bilayer tablet. Pharma Innovation J 2014; 3: 48-56.
5. Tekade BW and Thakare VM: Optimization and *In-vitro* evaluation of verapamil hydrochloride floating bilayer tablet. Pharma Innovation J 2014; 3: 48-56.
6. Sandeep M, Sai KV, Sudheer B, Ershad S, Adithya K and Srinivas M: Preparation and evaluation of chrono pharmaceutical drug delivery of lansoprazole. Research and Review-Journal of Pharmacy and Pharmaceutical Sciences 2013; 2(4): 45-54.
7. Fouladi F and dan Mortazavi SA: Preparation and *in-vitro* evaluation of gastroretentive bupropion hydrochloride tablets. Trop J Pharm Res 2012; 11 (3): 351-59.
8. Sulaiman TNS, Fudholi A and Nugroho AK: Optimasi formula tablet gastroretentive ranitidine HCl dengan system floating. Majalah Farmasi Indonesia 2011; 22(2): 106-14.
9. Ingale RD, Thakare VM, Tekade BW and Patil VR: Development and evaluation of ranitidine hydrochloride floating. International Journal of Pharmaceutical Sciences and Reserch 2014; 5(1): 269-74.
10. Rashati D, mursidatur RS and Formulasi UF: Tablet floating teofilin dengan matrik hpmc. Jurnal Ilmiah Kesehatan 2016; 1(1): 13-19.
11. Asif M, Yasir M, Bhattacharya A and Bajpai M: Formulation and evaluation of gastroretentive dosage form for fluvastatin sodium. Pharm Globale (IJCP) 2010; 4(08): 1-4.
12. Rajesh bhai THK, Senthil A, singh GC, Jyotindra P and Narayanswamy VB: Formulation and evaluation of gastroretentive floating tablets of gliclazide. IJRAP 2011; 2(4): 1368-73.
13. Indonesian Pharmacopea.. *Farmakope* Indonesia Edisi V. Jakarta: Departemen Kesehatan Republik Indonesia 2014.

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