International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Research Article **CODEN: IJPNL6**

FORMULATION AND EVALUATION OF FLOATING CAPSULES OF PROPRANOLOL HCl USING MODIFIED PULSINCAP TECHNIQUE

*GSN Koteswara Rao[1], KV Ramana Murthy[2], GSV Subrahmanyam[3]

[1]Viswanadha Institute of Pharmaceutical Sciences, Anandapuram, Visakhapatnam, A.P.
[2]AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, A.P.
[3]Unichem Laboratories, Goa.

***Corresponding author e-mail:** eswarmpharm@gmail.com

ABSTRACT

In our present investigation an attempt was made to apply modified pulsincap technique to develop floating capsules of propranolol HCl using PEO WSR 301. The formulation mixture was hand filled into the hardened body (formaldehyde exposed) and covered with unhardened cap. All the formulations with varying ratios of drug:polymer and varying time periods of exposure to formaldehyde vapors were evaluated for residual formaldehyde content, weight variation, drug content, *in-vitro* buoyancy, drug release pattern, compatibility studies etc. The formulations F2.3 with drug-polymer ratio of 1:0.75 prepared by using 2 h exposed capsule body was found as the optimized formulation as it has satisfied the buoyancy characteristics, shown controlled release of 100% in 12 h as per USP criteria and utilized less polymer concentration among all formulations in addition to all other parameters assessed. Hence modified pulsincap technique can be successfully used for the development of floating capsules of propranolol HCl using PEO WSR 301.

Keywords: floating capsules, modified pulsincap, formaldehyde vapors, propranolol HCl, PEO WSR 301.

INTRODUCTION

Gastric floating drug delivery systems (GFDDS) are suitable for any of the drugs whose absorption window is in stomach or upper parts of small intestine, whose solubility is more in acidic environment or less in alkaline environment, whose stability is less in alkaline environment, whose site of action is stomach or upper gastrointestinal tract (GIT). [1,2]

Propranolol HCl is a synthetic, non-selective beta-adrenergic receptor-blocking agent widely used in the management of hypertension. It has low bioavailability and shorter elimination half life (2 to 6 hours) due to its narrow absorption window in the upper parts of the gastro intestinal tract.[3] Thus a controlled release dosage form of propranolol HCl that release the drug in stomach is desirable for the improvement of bioavailability, therapeutic efficacy of the drug and possible reduction of dose.

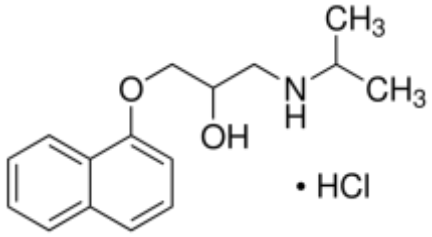

Fig. 1: Structure of propranolol HCl

Polyethylene oxide (PEO) is a biocompatible matrix-forming polymer, which is marketed as "POLYOX ™" retards the release rate of drug/s. PEO is widely used in pharmaceutical formulations like controlled release dosage forms. In the present investigation modified pulsincap technique is used to prepare the oral controlled release floating capsules of propranolol HCl that release the drug for a period of 12 h. In modified pulsincap technique, empty hard gelatin capsule bodies are hardened and made water insoluble by exposing to formaldehyde (HCHO)

vapours in presence of potassium permanganate where the amino acid molecules of gelatin gets cross linked with the HCHO vapours[4]. The rationale of the present investigation is to check the applicability of modified Pulsincap technique in the development of controlled release floating capsules using propranolol HCl as model drug.

MATERIALS AND METHODS

Propranolol HCl and PEO WSR 301 were obtained as gift samples from Sun Pharma and Unichem Labs respectively. Lactose was purchased from Loba Chemie Pvt. Ltd., whereas formaldehyde A.R., magnesium stearate and hydrochloric acid were purchased from Qualigens Fine Chemicals Pvt. Ltd.

Preparation of cross linked empty gelatin capsules[3-7]: Hard gelatin capsules of size-1 were taken and their bodies were separated from the caps. 25 ml of formalin (37% formaldehyde solution) was taken into the bottom of a desiccator and 0.5 g of potassium permanganate was added to generate the fumes. A wire mesh was kept above the solution to place capsule bodies on it for exposure. The capsule bodies were allowed to react with formaldehyde vapours for different time intervals of 1 h and 2 h. Then they were collected and kept in a hot air oven at 50^0C for 30 min to complete the reaction between formaldehyde and gelatin. Then these capsule bodies were taken out, kept for air drying to remove residual formaldehyde and stored in a polythene bag.

Chromotropic acid method for estimation of residual formaldehyde[8]: As per the method developed by D.A. Mac Fadyen, the residual formaldehyde in exposed capsules was estimated by chromotropic acid method for which the reagents used are formaldehyde solution A.R., sulphuric acid solution and chromotropic acid reagent. Chromotropic acid reagent was prepared by dissolving 0.2 g of chromotropic acid in 20 ml distilled water, filtering to remove insoluble sulphones and adding 80 ml H_2SO_4 solution to make up the volume upto 100 ml. The reagent was stored in stoppered bottle and protected from light. It was used within a week.

Procedure: Formaldehyde A.R. was suitably diluted with distilled water to obtain series of dilutions containing 0.76, 1.52, 3.8, 7.6 and 12.66 µg of formaldehyde per ml of dilution. To 1 ml of each dilution in a stopppered test tube, 9 ml of chromotropic acid reagent was added, mixed and heated in a boiling water bath for 30 min. The purple colored solution was cooled and color was measured in UV-Visible spectrophotometer at 570 nm against a reagent blank obtained by heating a mixture of 9 ml of chromotropic acid reagent with 1 ml of distilled water. The limit for free formaldehyde according to FDA is 0.002%.[9,10]

Calibration curve of propranolol HCl: Dilutions for stock solution (1 mg/ml) were made to obtain concentrations of 20, 40, 60, 80 and 100 mcg/ml in 0.1 N HCl and the absorbance was estimated at 319 nm. The calibration curve was developed based on the absorbance values as shown in fig. 2.

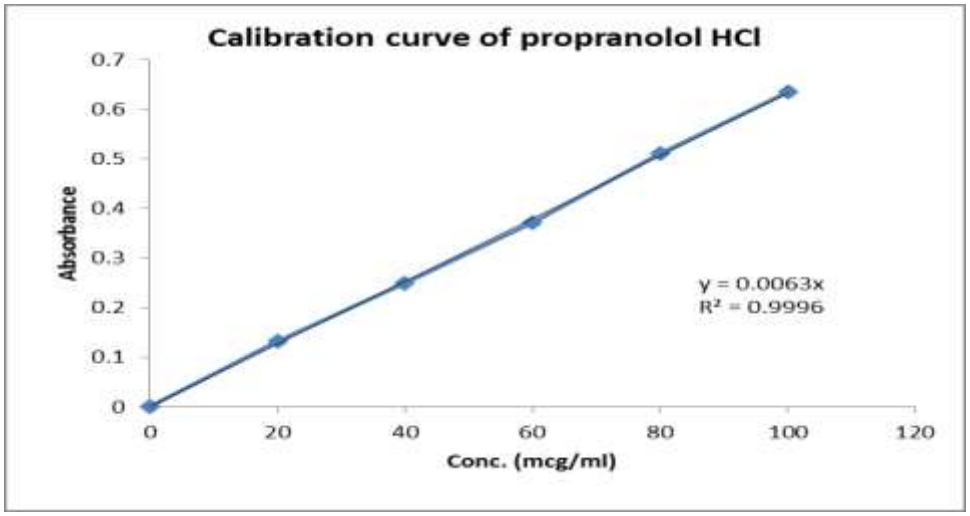

Fig. 2: Calibration curve of propranolol HCl

Formulation

Preparation of floating capsules of propranolol HCl using modified pulsincaps: As per the formulae given in table-1 and table-2, all the ingredients sufficient for a batch were weighed, geometrically mixed and hand filled in to the hardened capsule bodies, locked with unhardened cap.

Table 1: Formula of floating capsules of propranolol HCl (1 h exposed)

Ingredients (mg/capsule)	F1.1	F1.2	F1.3	F1.4	F1.5
Propranolol HCl	80	80	80	80	80
PEO WSR 301	20	40	60	80	100
Lactose	98	78	58	38	18
Magnesium stearate	2	2	2	2	2
Total weight	200	200	200	200	200

Table 2: Formula of floating capsules of propranolol HCl (2 h exposed)

Ingredients (mg/capsule)	F2.1	F2.2	F2.3	F2.4	F2.5
Propranolol HCl	80	80	80	80	80
PEO WSR 301	20	40	60	80	100
Lactose	98	78	58	38	18
Magnesium stearate	2	2	2	2	2
Total weight	200	200	200	200	200

Evaluation tests[11]

Evaluation of empty gelatin capsules: Both the treated and untreated capsules were tested and compared for weight variation, lockability, stickiness, color, shape and solubility (in distilled water and 0.1 N HCl) by randomly selecting ten capsules from each section.

Evaluation of controlled release floating capsules of propranolol HCl[12,13]: The formulated capsules were evaluated for *in-vitro* buoyancy studies like floating lag time, total floating time, weight variation, estimation of drug content and *in-vitro* dissolution studies. Compatibility studies were conducted using IR spectroscopy of pure samples of formulation ingredients and the whole mixture.

In-vitro buoyancy studies: All the prepared floating capsules of propranolol HCl both 1 h and 2 h exposed were subjected to *in-vitro* buoyancy test. The time required for the capsule to rise to the surface of the medium and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the floating time. The floating lag time and the floating time were determined in 1 litre glass beaker containing 900 ml of 0.1 N HCl.

Weight variation test: According to I.P., an intact capsule was weighed and then it was opened without losing any part of the shell. The contents were removed as completely as possible and shell was reweighed. The difference between the weighings gave the weight of the contents. This procedure was repeated for another 19 capsules. The average weight and % deviation of individual capsules from average weight was determined.

Estimation of drug content: From each batch, 5 capsules were randomly collected and the formulation mixture was separated. The powder mixture equivalent to 100 mg of propranolol HCl was weighed and transferred to 100 ml volumetric flask. It was dissolved in small quantity of methanol with vigorous shaking on a mechanical shaker and filtered into a 50 ml volumetric flask through 0.45 μm millipore nylon filter disc and the filtrate was made up to the mark with 0.1N HCl. Further appropriate dilutions were made and the absorbance was measured at 319 nm against blank (0.1N HCl).

In-vitro dissolution studies: *In-vitro* release of propranolol HCl from the prepared floating capsules

was studied using type-2 USP XXIV dissolution rate test apparatus (Model: DISSO 2000, M/s. LABINDIA) employing the paddle stirrer. The dissolution medium used was 900 ml of 0.1N HCl maintained at a temperature of 37±0.5º C and the paddle was rotated at 50 rpm for 12 h. After 0.5 h sample, at each interval of 1 h, 5 ml samples were withdrawn by means of a syringe fitted with a prefilter and immediately replaced with 5 ml of fresh medium. The absorbance of the samples was measured at 319 nm after suitable dilution with the medium using Elico SL-159 UV Spectrophotometer.

Drug release kinetics[14-18]: As a model-dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, Higuchi, Hixson-Crowell erosion and Korsmeyer-Peppas equations. The order of drug release from matrix systems was described by using zero-order or first-orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi diffusion, Hixson-Crowell erosion and Korsmeyer-Peppas equations.

Drug-polymer interaction studies by Fourier transform infrared spectroscopy: Infrared spectral analysis of pure samples of propranolol HCl, PEO WSR 303, lactose, magnesium stearate and optimized formulation were done using Fourier transform infrared spectrophotometer (Shimadzu model 8300). The IR spectra were done against KBr background.

RESULTS AND DISCUSSION

Estimation of free formaldehyde content: The limit for residual formaldehyde according to FDA is 0.002% and the formaldehyde exposed hard gelatin capsule bodies passed the chromotropic acid test as the value obtained is less than the standard limit.

Evaluation tests for empty gelatin capsules: All the empty capsules were lockable type, odourless, soft and slightly sticky when touched with finger. After formaldehyde vapour treatment, there were no significant changes in the capsules except for the slight stickiness. There was no significant change in colour and shape after formaldehyde vapour treatment. The individual weights of each capsule were quite uniform and cross linking did not show any significant change in weight. Untreated bodies dissolved in 15 min where as treated bodies remained intact even after 14 hrs. However untreated cap was dissolved in 15 min.

Evaluation of floating capsules of propranolol HCl
In-vitro buoyancy studies: The polymer present in the formulation swollen in the presence of fluid and formed mesh like structure entrapping the drug enabling its slow release. This also provided buoyancy to the capsule. All the prepared modified pulsincaps floated on the surface immediately upon their addition to the 0.1N HCl indicating no floating lag time. The floating time of the prepared modified pulsincaps was found to be in the range of 4-12 h as shown in table-3 in accordance with the complete release of drug. The results indicated that floating time was increased with increase in the polymer concentration.

Table 3: Floating time of propranolol HCl capsules

Formulation	Floating time (h)
F1.1	4
F1.2	7
F1.3	9
F1.4	12
F1.5	12
F2.1	5
F2.2	10
F2.3	12
F2.4	>14
F2.5	>14

Weight variation test: All the prepared modified pulsincap formulations complied with the compendial standards for uniformity of weight.

Estimation of drug content: The drug content estimated was found to be in the range of 98% to 102% of the stated amount of propranolol HCl and was within the standard limit of ±5 % variation.

In-vitro dissolution studies: The dissolution profiles of propranolol HCl from 1 h exposed modified pulsincaps were shown in fig. 3. More than 99.9% of the drug was released from F1.1, F1.2, F1.3, F1.4 and F1.5 in 4, 7, 9, 12 and 12 h respectively. The dissolution profiles of propranolol HCl from 2 h exposed modified pulsincaps were shown in fig. 4. A complete release of 100% drug from F2.1, F2.2 and F2.3 was found to be in 5, 10 and 12 h respectively. Formulations F2.4 and F2.5 were unable to release complete drug in 12 h. From the dissolution studies it was revealed that the drug release was decreased with increasing concentrations of polymer PEO WSR 301. The studies indicated that retardation of drug release from 2 h exposed capsules was more compared to 1 hr exposed capsules which may be due to excessive cross-linkage of the gelatin molecules initiated by the formaldehyde vapors. Among all the prepared formulations, F1.4 (drug:polymer 1:1) and F2.3 (drug:polymer 1:0.75) released the drug over a period of 12 h with sufficient buoyancy characteristics satisfying the USP criteria of drug release for a controlled release product. Since the formulation, F2.3 consumed less quantity of polymer, it was considered as best formulation.

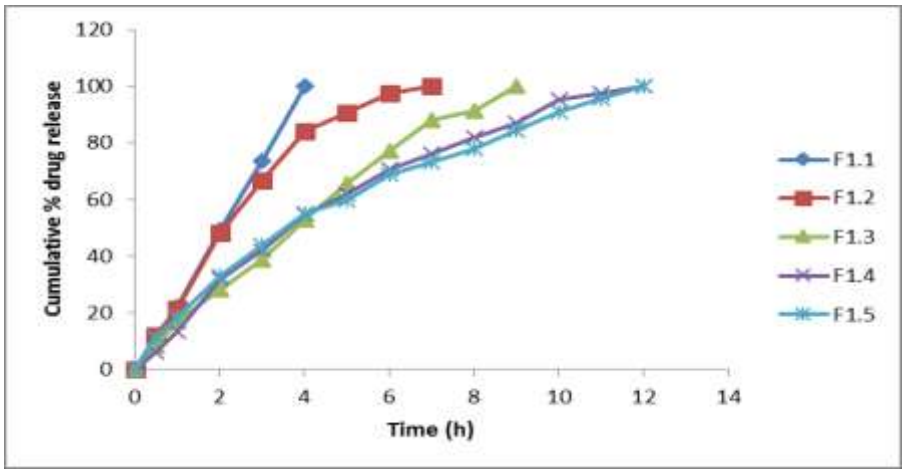

Fig. 3: Dissolution profile of floating capsules of propranolol HCl (1 h exposed): F1.1 to F1.5

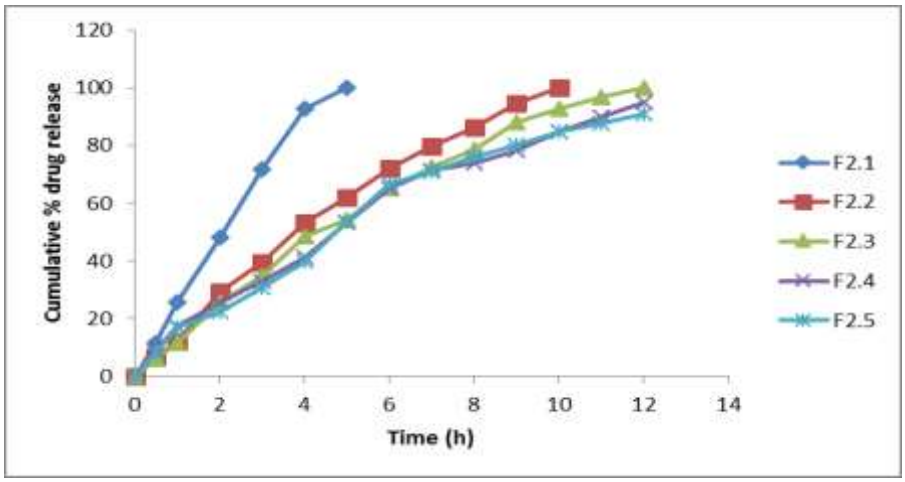

Fig. 4: Dissolution profile of floating capsules of propranolol HCl (2 h exposed): F2.1 to F2.5

Drug release kinetics: The best formulation F2.3 (drug:polymer 1:0.75) that controlled the release of drug over a period of 12 h was further analyzed for drug release kinetics. The correlation coefficient values as given in table-5 revealed that the best formulation, F2.3 is following zero order release kinetics with non-fickian (anomalous) diffusion mechanism.

Table 5: Correlation coefficient values of best formulation, F2.3

Formulation	r-value				n-value
	Zero order	First order	Higuchi	Erosion	Peppas
F2.3	0.976	0.913	0.937	0.921	0.674

FTIR analysis: FTIR spectra of Propranolol HCl showed a characteristic secondary amine –N-H stretch at 3280 cm^{-1}, C-H stretch at 2964 cm^{-1}, Aryl C=C stretch at 1579 cm^{-1}, Aryl O-CH_2 asymmetric stretch at 1240 cm^{-1}, Aryl O-CH_2 symmetric stretch at 1030 cm^{-1} and peak at 798 cm^{-1} due to alpha – substituted naphthalene. PEO WSR 301 showed characteristic peaks at 2919, 2851, 1019 and 961 cm^{-1}. The major peaks for the pure drug and the polymer were well in support with the theoretical prediction with respect to the functional groups as given above. The mixture of drug and polymer did not produce any major shift in principal peaks of propranolol HCl and also the presence of one ingredient did not produce shift in the peaks of other ingredient. This indicated that there is no interaction among drug and polymer used in the study. Hence FTIR spectral analysis proved the compatibility of the drug and polymer used in the study.

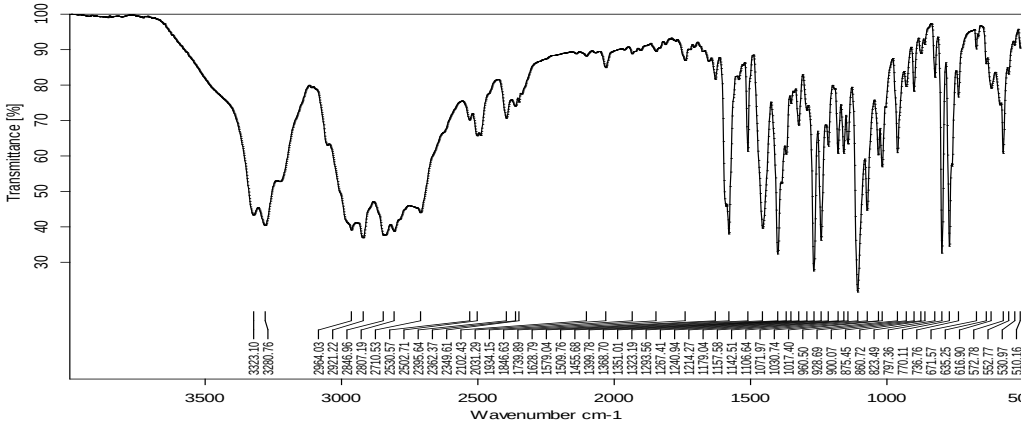

Fig. 5: FTIR spectra of pure drug, propranolol HCl

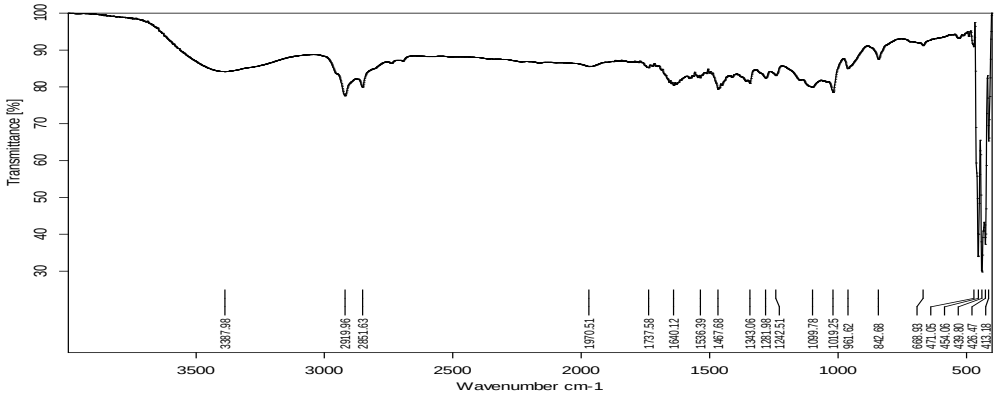

Fig. 6: FTIR spectra of polymer, PEO WSR 301

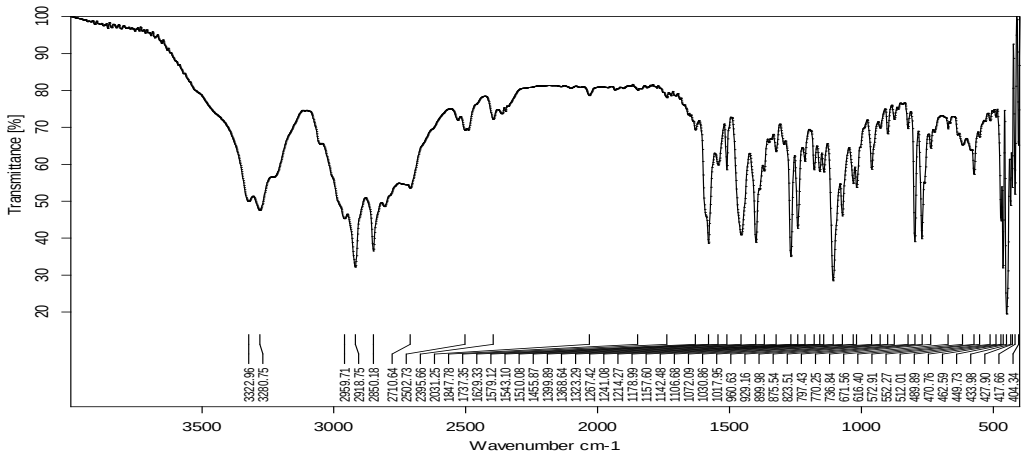

Fig. 7: FTIR spectra of best formulation, F2.3 (drug+polymer)

CONCLUSION

Among all the prepared formulations, one with drug:polymer ratio of 1:0.75 made with 2 h exposed capsule body coded as F2.3 has satisfied the floating characteristics, 12 h controlled release criteria as per USP and contained the less quantity of polymer. The present investigation revealed that PEO WSR 301 can be successfully used in the preparation of oral controlled release gastric floating capsules of propranolol HCl using modified pulsincap technique. It was also proved that 1 h and 2 h exposure to formaldehyde vapors is able to maintain the intact nature of capsule body for 12 h. No work has been reported till date on the design of floating capsules of propranolol HCl following modified Pulsincap technique using the polymer, PEO WSR 301. Hence this makes a significant contribution for the development of propranolol HCl GFDDS.

ACKNOWLEDGEMENT

The authors acknowledge Andhra University College of Pharmaceutical Sciences and Viswanadha Institute of Pharmaceutical Sciences, Visakhapatnam for providing necessary facilities.

REFERENCES

1. Shweta Arora, Javed Ali, Alka Ahuja, Roop K Khar, Sanjula Baboota. *AAPS PharmSciTech*, 2005; 6(3): 372-90.
2. Deshpande AA, Shah NH, Rhodes CT, Malick W. *Drug Dev Ind Pharm*, 1996; 22: 531-9.
3. Huang YB, Tsai YH, Yang WC, Chang JS, Wu PC, Takayama K. *Eur J Pharm Biopharm*. 2004; 58: 607-14.
4. Seshasayana A, Sreenivasa Rao B, Prasanna Raju Y, Cheruvu PS Narayan, Ramana Murthy KV. *Indian J Pharm Sci*, 2001, 63(4): 337-9.
5. Sindhu Abraham, MS Srinath. *Indian J Pharm Sci*, 2007; 69(1): 24-7.
6. Swati C Jagdale, Pravin S Phule, Gajanan J Chavan. *Int J Pharm Pharm Sci*, 2014; 6(5): 48-52.
7. Sharma GS, Srikanth MV, Sunil S, Ramana Murthy KV. *Int J Pharm Pharm Sci*, 2012; 4(3): 618-24.
8. D. A. MacFadyen. Estimation of formaldehyde in biological mixtures. *J Bio Chem*, 1945; 158(1): 107–33.
9. Nagaraja G, Sunil Agarwal, Dinesh Shenoy, Paramjeet Singh Minhas, Yogesh D. B., Fazil Baig. *J Chem Pharm Res*, 2013; 5(6): 76-87.

10. V.S. Mastiholimath, P.M. Dandagi, S. Samata Jain, A.P. Gadad, A.R. Kulkarni. *Int J Pharm*, 2007; 328(1): 49-56.
11. Khan Abdul Waris, Ahmed Mohammed Gulzar, B Ramesh. *Int Res J Pharm*, 2011; 2(1): 249-55.
12. Rosa M, Zia H, Rhodes T. *Int J Pharm*, 1994; 105: 65-70.
13. Indian Pharmacopoeia, Govt. of India, Ministry of Health and Family Welfare, The Indian Pharmacopoeia Commission, Ghaziabad, India, 182, 2007.
14. Lazarus J, Cooper J. *J Pharm Sci*, 1961; 50: 715-32.
15. Wagner JG. *J Pharm Sci*, 1967; 58:1253-7.
16. Higuchi T. *J Pharm Sci*, 1963; 52:1145-9.
17. Korsmeyer RW, Gurney R, Doelker E, Buri P, Peppas NA. *J Pharm Sci*, 1983; 15: 25-35.
18. Ritger P L, Peppas N A. *J Cont Release*, 1987; 5: 37-42.