

FACTORS INFLUENCING DRUG RELEASE CHARACTERISTIC FROM HYDROPHILIC POLYMER MATRIX TABLET

A GOYAL[†], P SHUKLA AND A K SRIVASTAVA

The aim of this work was to investigate the factors influencing the release characteristics of drug substances from hydrophilic polymer matrix tablet using various hydrophilic polymers such as Polyethylene oxide (PEO), Hydroxyethyl cellulose (HEC) and Xanthan gum (XG). The fabricated tablets were evaluated for physical characteristics like hardness, weight variation, friability and drug content. The effect of addition of diluent, on the drug release was also studied. The swelling studies were conducted for 6 hrs in 0.1 N HCl and phosphate buffer respectively whereas In vitro releases of drug were conducted by buffer change method. All the physical characteristics of the fabricated tablets were found to be within acceptable limits. It was found that the polymers could retard the release of drugs in both simulated gastric fluid (SGF) and simulated intestinal fluid (SIF), but at different levels. Results indicated that drug release characteristics from polymer matrix tablet follow Higuchi square root time kinetics and the mechanism of drug release was diffusion and relaxation.

Keywords : hydrophilic polymers, matrix tablet, polyethylene oxide, hydroxyethyl cellulose, xanthan gum, Higuchi square root time kinetics.

INTRODUCTION

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages¹. Sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration²⁻³. The use of polymers in controlling the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms. Sustained release can be achieved by formulating drugs as matrix devices using HPMC, Sodium CMC and other swellable polymer.^{4,6} Also the matrix tablets are easy to prepare and they are cost effective and exhibit predictable release behavior⁷.

Hydrophilic polymers with high gelling capacity are of particular interest in the field of controlled release. On coming in contact with aqueous medium they hydrate at solid-liquid interface and form a viscous layer which retards the release of the drug.^{8,9}

In this study various hydrophilic polymers such as Xanthan gum (XG) and Hydroxy Ethyl cellulose (HEC) were blended with PEO to form a sustained release matrix tablet. The aims of the present study were to investigate the role of hydrophilic polymers in sustaining the release of drugs in tablet dosage form, and to study the effects of pH, proportion of polymers, diluent and drug solubility on drug dissolution characteristics. The release kinetics and mechanism of drug release were also investigated by using various release kinetics model equations.

MATERIALS AND METHODS

Material used were hydroxyl ethyl cellulose (HEC), Polyethylene oxide (PEO) polyox WSR303 N, Xanthan Gum (Xnatural[®] 75), Microcrystalline Cellulose (Avicel PH 101) (Gift samples from Ranbaxy laboratories), hydrogenated vegetable oil (Lubritab) (Gift samples from Panacea Biotech), Metoprolol Succinate (Gift sample from Polydrug Laboratories) and Potassium dihydrogen orthophosphate (Central Drug House).

Manufacturing methods

The fabrication of matrix tablets was done using direct compression method

Direct compression method

All the excipients except polyethylene oxide were passed through sieve no 40 and Polyethylene Oxide was passed through sieve no. 25. Drug polymers and diluents were mixed by geometric dilution. After that lubricant (lubritab) was put and blended for five minutes and the mixture was compressed using concave punches of 8mm in diameter (Table-1)

Evaluation

All the batches were evaluated for weight variation, hardness, friability, thickness and drug content as per USP XXIV monograph. The weight variation was determined by taking 20 tablets using an electronic balance. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester (MHT-20, Campbell Electronics, Mumbai, India). Friability was determined by testing 10 tablets in a friability tester (FTA-20, Campbell Electronics) for 4 minutes at 25 rpm.

***Corresponding author:** [†] Department of Pharmaceutics, I.T., Banaras Hindu University, Varanasi, U.P.
e-mail: aankitsbhu@rediffmail.com

TABLE- 1 Formula for preparing matrix tablets.

Batch code	Drug		Polymers			Diluents	
	MS	TH	PEO	XG	HEC	MCC	DCP
A1	47.5	-	165	95	-	-	45
A2	47.5	-	165	-	95	-	45
A3	47.5	-	260	-	-	-	45
A4	-	47.5	165	-	95	-	45
A5	47.5	-	165	-	95	45	-
A6	47.5	-	120	-	95	137.5	-
A7	47.5	-	75	-	95	182.5	-

TABLE- 2 Formula for investigating the kinetics

Function	Equation
Zero order	% diss= Kt
First order	% diss=100 { 1- e ^{-kt} }
Higuchi	% diss = Kt ^{0.5}
Korsenmeyer-Peppas	% diss= Kt ⁿ

Swelling studies

Swelling studies were carried out for all the formulations (in triplicate for each batch). Three metallic baskets were weighed with a matrix tablet of each formulation, and placed into 1000mL of either SGF or SIF at 37 ± 0.5°C. At hourly intervals, the previously weighed baskets containing the tablet were removed, gently wiped with a tissue to remove surface water, reweighed, and then placed back into the vessel as quickly as possible. The mean weights were determined for each formulation, and the degree of Swelling (S) was calculated at each time point according to the relationship.¹⁰

$$S = (W_s - W_d) \times 100 / W_d$$

TABLE- 3 Physical characteristics (±S.D) of matrix tablets

Batch code	Average weight (mg)± SD	Thickness (mm) ± SD	Hardness (kg/cm ²) ± SD	Percent friability (%)	Percent drug content
A1	401 ± 3.43	4.59±0.02	6.4±0.8	0.38	100.1216
A2	404±2.44	4.48±0.04	5.8±0.7	0.29	99.1534
A3	409±2.36	4.51±0.07	6.6±0.6	0.27	99.5632
A4	411±3.17	4.41±0.07	6.6±0.4	0.19	100.02563
A5	409±4.01	4.51±0.04	6.3±0.2	0.22	99.2345
A6	408±3.52	4.43±0.07	6.9±0.4	0.21	100.4562
A7	409± 2.1	4.47±0.23	5.9±0.3	0.27	100.2536

TABLE- 4 Drug release kinetics from different matrix tablets (using Higuchi, zero order and first order release)

Batch code	Higuchi model		Zero order release		First order release	
	K	r ²	K	r ²	K	r ²
A1	26.77	0.9831	8.6982	0.9755	0.0981	0.9757
A2	24.49	0.9822	7.916	0.9710	0.274	0.974
A3	23.07	0.9827	7.4919	0.9741	0.263	0.9733
A4	22.08	0.9848	7.155	0.9718	0.292	0.9634
A5	21.04	0.9858	6.8239	0.9752	0.269	0.976
A6	19.568	0.9776	6.4581	0.9707	0.303	0.9545
A7	20.808	0.9880	6.895	0.9660	0.278	0.9456

Where W_d and W_s are the dry and swollen matrix weights, respectively, at immersion time (t) in the buffer.

DISSOLUTION STUDY

Release Rate Studies

Release rate for all the designed formulations was studied (in triplicate for each batch) for 8 hours using USP XXIV dissolution apparatus type II (paddle type), in 500 mL of 0.1N HCl and pH 6.8 phosphate buffer at $37.5^\circ\text{C} \pm 0.5^\circ\text{C}$. The stirring speed was set at 50 rpm. At predetermined time intervals, a 5 mL sample was withdrawn and replaced with fresh dissolution medium. After appropriate dilution the samples were analyzed using UV/VISIBLE spectrophotometer at 275nm and cumulative percentage of the drug released was than calculated.

Mathematical modeling

The release profile of the drug obtained was analysed using different kinetic models (Table-2) such as zero order, first order, Higuchi and Korsmeyer- Peppas model in order to evaluate the release mechanism from the matrices.

RESULTS AND DISCUSSION

Physical characterization

The variation in the thickness, weight, hardness and drug content uniformity values of all the fabricated tablets in reference to average values for each parameter, were found within the official limits (Table 3).

Swelling Studies

The mechanism of drug release from hydrophilic polymeric matrices involves solvent penetration, hydration

TABLE- 5 Determination of drug release mechanism using Peppas exponential model equation.

Batches	n
A1	0.6741
A2	0.6652
A3	0.6223
A4	0.6277
A5	0.6215
A6	0.6985
A7	0.6643

and swelling of the polymer, diffusion of the dissolved drug in the matrix, and erosion of the gel layer. Initially, the diffusion coefficient of drug in the dehydrated polymer matrix is low; it increases significantly as the polymer matrix imbibes more and more water and forms a gel, as time progresses. The hydration rate of the polymer matrix, and thereby the gel formation depends significantly on polymer proportion, viscosity, and to a lesser degree on polymer particle size.⁹ Swelling studies were conducted at two pH conditions acidic pH 0.1N HCl and pH 6.8 buffer and the effect of pH and time was studied in the batches. Effect of pH and different polymers on swelling of PEO matrix tablets

Amongst the batches A1,A2 and A3 batch A2 showed

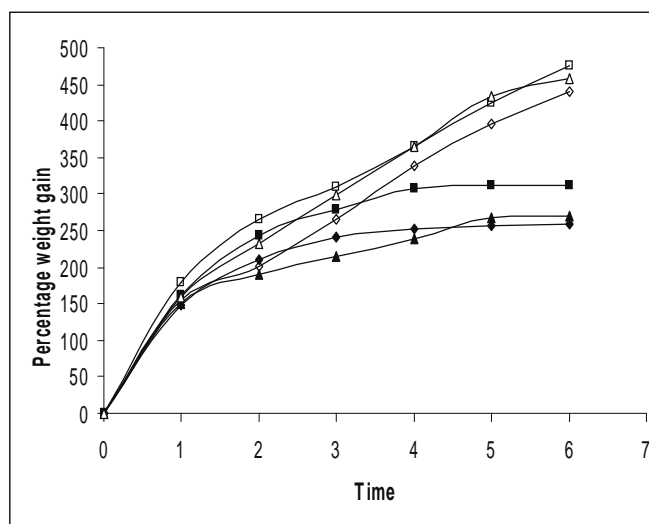


FIGURE 1. The water uptake study of batches A1, A2 and A3 in acidic pH (-?-), (-?-), (-?-) as well as in alkaline pH (-?-), (-?-), (-?) using USP XXIV dissolution apparatus at 50 rpm.

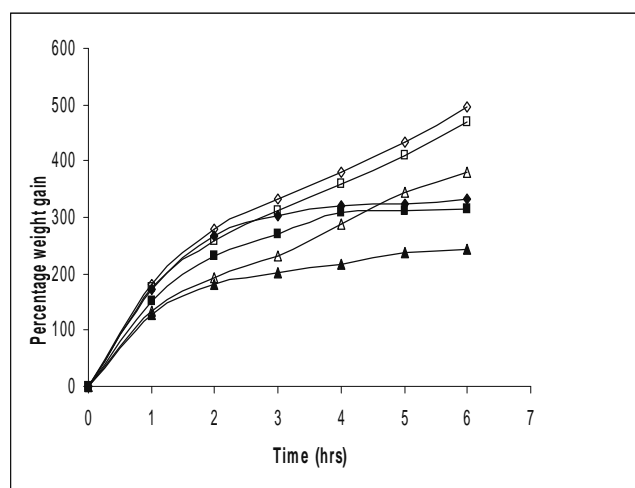


FIGURE 2. The water uptake study of batches A5, A6 and A7 in acidic pH (-?-), (-?-), (-?-) as well as in alkaline pH (-?-), (-?-), (-?-), using USP XXIV dissolution apparatus at 50 rpm.

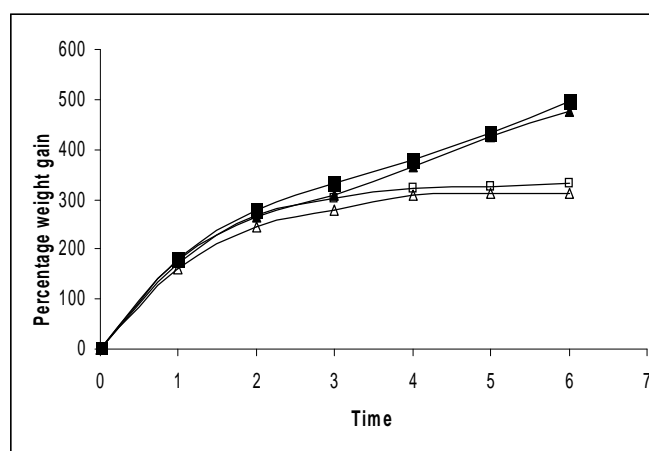


FIGURE 3. The water uptake study of batches A5 and A2 in acidic pH (-?-), (-?-) as well as in alkaline pH (-?-), (-?-), using USP XXIV dissolution apparatus at 50 rpm.

around 475% weight gain in pH 6.8 buffer and 327% weight gain in pH 0.1N HCl. It showed that the tablet swelled more rapidly in alkaline medium as compared to acidic pH. Batch A3 showed 457 % weight gain in pH 6.8 and 271% weight gain in 0.1N HCl whereas batch A1 showed 440% weight gain in pH 6.8 and 257% weight gain in 0.1N HCl.(Fig-1) From this it could be concluded that all the three batches showed pH dependent swelling. Effect of different amount of PEO on swelling behavior Amongst the batches A5, A6 and A7 at pH 6.8, the percentage weight gain was 497, 469 and 379 respectively (at 6th hr.) At 0.1 N HCl the percentage gain (at 6th hr) for the same batches was found to be 333, 316 and 243 respectively (Fig-2). The decrease in the percentage gain may be due to decrease in the amount of polymer as swelling is a function of amount of polymer present.

Effect of different diluents on swelling behavior

In alkaline pH batch A5 containing MCC as diluent showed more weight gain (497%) as compared to A2 (475%) after 6 hrs which may be due to hydrophilic behavior of MCC as compared to DCP. Same is true for weight gain in 0.1N HCl for A2 which showed the decrease in percentage weight gain after 6 hrs indicating the dissolution of DCP by acidic media. In case of A5 percentage weight gain was less as compared to that in pH 6.8 (Fig-3).

Effect of different drug solubility on swelling behavior

At pH 6.8 swelling or % weight gain of batch A4 at 6th hour was less as compared with batch A2 (Fig-4). In case of swelling in 0.1N HCl, weight gain was almost same for both the batches up to the 4th hour after which the weight gain of batch A2 increased more as compared to other batch. It may be due to the increase in solubility of Metoprolol Succinate as compared to the Tramadolol.

In Vitro Dissolution Studies

The plot of cumulative percentage released v/s time for matrix-embedded CR tablets prepared using different proportions of polymers (by buffer change method) is shown in Fig-5.

From the graph it could be concluded that the release of drug was found to be more in the gastric pH (burst release) as compared to the intestinal pH. The reason behind it may be inferred from the swelling studies of the polymers. As the percentage weight increase of each polymer was found to be more in the intestinal pH it may have sustained the release of the drug. Also, as shown by water uptake studies the release profile of batch A5 exhibited significant sustaining effect on drug release.

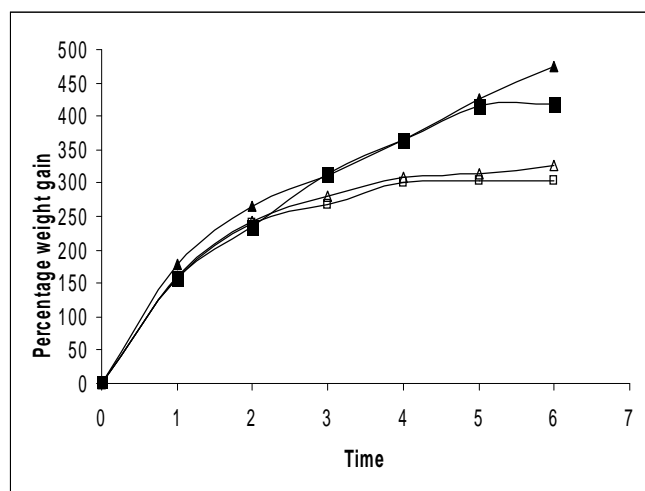


FIGURE 4. The water uptake study of batches A2 and A4 in acidic pH (-?-), (-?-) as well as in alkaline pH (-?-), (-?-) using USP XXIV dissolution apparatus at 50 rpm.

Drug release mechanisms

In order to investigate the release mechanism, the data were fitted to models¹¹ representing zero-order, first-order and Higuchi's square root of time. From the table, it is concluded that all the fabricated tablets followed Higuchi release kinetics (Table 4).

Further, to understand the drug release mechanism, the data were fitted to Peppas exponential equation $Mt/M\infty = Kt^n$, where $Mt/M\infty$ is the fractional drug release into the dissolution medium, K is a constant which incorporates the properties of the macromolecular polymeric system and drug and n is the diffusional exponent, which characterizes the drug transport mechanism¹². When $n = 0.5$, it indicates quasi-Fickian diffusion mechanism. For $n > 0.5$, an anomalous non-Fickian diffusion and the special case of $n = 1$ that has gained importance due to its potential application in the development of swelling controlled drug delivery systems with zero-order kinetics indicate pseudo-case-II transport mechanism.¹³ In the present study also it was observed (Table 5) that all the fabricated tablets followed non-Fickian diffusion mechanism, which indicates the drug release through diffusion and relaxation.

CONCLUSION

From the study it was concluded that the best sustained release tablet could be produced using PEO along with HEC as hydrophilic controlling polymer. Also it was found that amongst diluents, MCC swelled more in comparison with DCP and played an important role in retardation of drug release. The pH of dissolution media and the

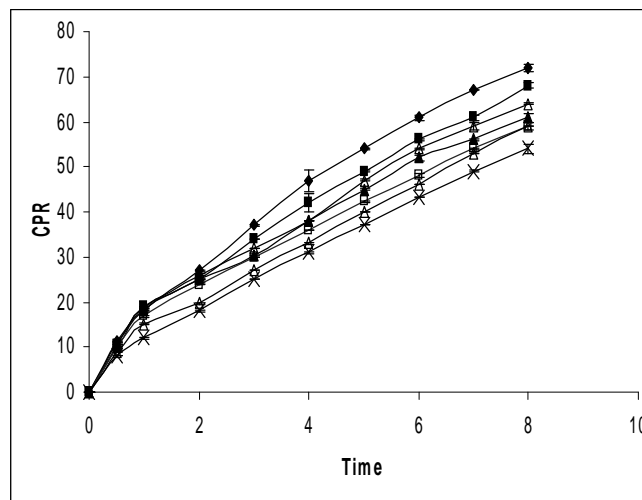


FIGURE 5. In vitro drug release profile of fabricated matrix tablets from batches A1 (-?), A2 (-+), A3 (-?-), A4 (-?-), A5 (-x-), A6 (-?-) and A7 (-?-) USP XXIV dissolution apparatus at 50 rpm. Bars represent \pm S.D. (n = 3).

solubility of the drug in dissolution media also affect the release characteristics from hydrophilic polymers. Thus, it was concluded that the potential controlled and sustained release matrix tablets could be prepared using optimized amount of hydrophilic polymers such as PEO and HEC along with diluent MCC.

ACKNOWLEDGEMENT

The authors are grateful to Poly drug laboratories (Pune, India), Lupin research park (Pune, India) and Ranbaxy Laboratories (New Delhi, India) for generous gift samples of drug and various polymers. The authors wish to thank University Grants Commission (New Delhi, India), for funding the project.

REFERENCES

1. Chien YW. Novel drug delivery systems. In: Chien YW, ed. Oral Drug Delivery and Delivery Systems. New York, NY: Marcel Dekker; 1992:139-196.
2. Turner S, Federici C, Hite M, Fassihi R. Formulation development and human in vitro-in vivo correlation for a novel, monolithic controlled-release matrix system of high load and highly water soluble drug Niacin. Drug Dev Ind Pharm 2004;30(8): 797-807.
3. Fernandes CM, Ramos P, Amilcar CF, Veiga FB. Hydrophilic and hydrophobic cyclodextrins in a new sustained release oral formulation of Nicardipine: In vitro evaluation and bioavailability studies in rabbits. J.Control.Release 2003;88(1):127-134.
4. Carstensen, J. T.. Pharmaceutics of solids and solid dosage forms, John Wiley and Sons, New York. 1977 p. 100.
5. Mockel, J. E., Lippold, B. C.. Zero-order drug release from hydrocolloid matrices. Pharm. Res. 1993;10: 1066-1070.

6. Swarbrick, J. Advances in controlled drug delivery. S. T. P. Pharma. 1996;6:53-56.
7. Mishra, B., Seenra, J., Singh, S., Sankar, C. Development and characterization of matrix tablets of ketorolac tromethamine. Indian Pharm. 2003;2:86-89.
8. Chirico S, Dalmoro A, Lamberti G, Russo G, Titomanlio G. Analysis and modeling of swelling and erosion behavior for pure HPMC tablet. J.Pharm.Sci 2007;122:181-188.
9. Vazquez MJ, Casalderrey M, Gomej-Amoza JG, Martinez-Pacheco R, Concheiro A. Atenolol release from hydrophilic matrix tablets with hydroxypropylmethylcellulose (HPMC) mixtures as gelling agent: effects of the viscosity of HTML mixture. Eur.J.Pharm.Sci.1996;4:39-48.
10. Efentakis M, Vlachou M, Choulis NH. Effects of excipients on swelling and drug release from compressed matrices. Drug Development and Industrial Pharmacy, 1997;23(1):107-112.
11. Sankar, C., Rani, M., Srivastava, A.K., Mishra, B. Chitosan based pentazocine microspheres for intranasal systemic delivery—development and biopharmaceutical evaluation. Pharmazie. 2001;56: 223-226.
12. Agarwal, V., Mishra, B. Design, development and biopharmaceutical properties of buccoadhesive compacts of pentazocine. Drug. Dev. Ind. Pharm. 1999;25: 701-709.
13. Lucy, W. S. C., Paul, W. S. H., Wong, F. L. Relationship between polymer viscosity and drug release from a matrix system. Pharm. Res. 1992;9:1510-1512.