In vitro Release Kinetic Study of Esomeprazole Magnesium from Methocel K15M and Methocel K100 LVCR Matrix Tablets

Bishyajit Kumar Biswas[1], Md. Safiqul Islam[1], Farida Begum[2] and Abu Shara Shamsur Rouf[1]

[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh
[2]Department of Clinical Pharmacy and Pharmacology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh

ABSTRACT: In the present study esomeprazole sustained release tablet matrix was prepared by utilizing different grades of hydroxypropyl methylcellulose (HPMC) polymers such as Methocel K15M & Methocel K100 LVCR by direct compression method. Different amount of Methocel K15M was used to develop matrix builder in the seven proposed formulations (F1-F7) for the study of release rate retardant effect at 20%, 25%, 30%, 35%, 40%, 45% and 50% of total weight of tablet matrix respectively. The dissolution study of Methocel K15M based tablet matrices of those proposed formulations were carried out in the simulated gastric medium (pH 1.3) for first two hours and then in the simulated intestinal medium (pH 6.8) for 8 hours using USP dissolution apparatus II. The formulation F-5 (40%) and F-6 (45%) met the optimum release rate of esomeprazole for 10h period of *in vitro* dissolution study. The release kinetics of formulation F-5 and F-6 very closely followed Higuchi kinetic order than first order and zero order kinetics. Similarly Methocel K100 LVCR was used to develop matrix builder in another seven proposed formulations (F8-F14). It was found that formulations F-11 (35%), F-12 (40%) and F-13 (45%) met the desired release rate of esomeprazole for 10h period. The release kinetics of formulation F-11, F-12 and F-13 followed Higuchi kinetic order. Between these two polymers, Methocel K100 LVCR showed better release retardant effect than Methocel K15M.

Key words: Esomeprazole, Direct compression, Controlled release, Methocel K15M and Methocel K100 LVCR

INTRODUCTION

Esomeprazole an *S*-isomer of omeprazole that acts as proton pump inhibitor, used to treat gastroesophageal reflux disease (GERD), erosive esophagitis, gastric ulcer etc.[1] Esomeprazole sustained release tablet matrix was prepared by direct compression method by utilizing different grades of Hydroxypropyl methylcellulose (HPMC) that were Methocel K15M and Methocel K100 LVCR. These polymers are hydrophilic in nature and can hold active ingredients firmly that depend on the concentration or ratio of the polymers used.[2]

Correspondence to: Abu Shara Shamsur Rouf
E-mail: rouf321@ yahoo.com

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Oral sustained release dosage form by direct compression technique is a very simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms.[3]

Sustained or controlled drug delivery occurs while embedded within a polymer that may be natural or semi-synthetic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predetermined fashion and released the drug at constant rate for desired time period.[4]

There are number of techniques applied in the formulation and manufacturing of sustained release dosage form. However, the matrix tablet by direct compression has attracted much attention due its technological simplicity in comparison with other controlled release systems. Direct compression method has been applied for preparation of tablet matrix that involved simple blending of all ingredients used in the formulations and then underwent direct compression. It required fewer unit operations, less machinery, reduced number of personnel and reduced processing time, increased product stability and faster production rate.[5]

A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept. Polymers that primarily forming insoluble or skeleton matrices are considered as the first category of retarding materials and are classified as plastic matrix systems. The second class represents hydrophobic and water-insoluble materials, which are potentially erodable and the third group exhibits hydrophilic properties.[6]

There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. The release of drug from the tablet matrix depends on the nature of polymer. Both Methocel K15M and Methocel K100 LVCR are hydrophilic polymers that become hydrated, swollen and facilitates to diffuse the drug.[7]

In the present study an attempt has been made to formulate esomeprazole magnesium as sustained release tablet matrix with the addition of release retarding polymers Methocel K15M and Methocel K100 LVCR in different ratios. The effect of viscosity grade and polymer loading on drug release were recorded and release kinetics was evaluated.

MATERIALS AND METHODS

Drug: Esomeprazole magnesium (Cipla, India); **Polymers:** Hydroxypropyl methylcellulose-Methocel K15M Premium USP/EP and Hydroxypropyl methylcellulose-Methocel K100 LVCR Premium USP/EP (Dow Chemical Company, Midland, MI, USA); **Other excipients:** Microcystalline Cellulose (Avicel-101) (Hanau Chemicals Ltd., Japan); Polyvinnyl Pyrrolidone (Povidone K-30) (Hanau Chemicals Ltd., Japan); Colloidal Anhydrous Silica (Aerosil 200) (Hanau Chemicals Ltd., Japan); Magnesium Stearate (Hanau Chemicals Ltd., Japan); **Solvents and reagents:** Hydrochloric acid (Merk, Germany); Sodium Hydroxide (Merk, Germany); Ortho-phosphoric acid (Merk, Germany); **Equipments:** Single Punch Tablet Press; Simadzu UV Spectrophometer; Digital pH meter; Electronic Hardness tester (Ereweka, Germany); Electrolab Tablet Dissolution Test machine (XXII); Sartorius Electronic Balance.

Preparation of dissolution medium. For dissolution simulated gastric medium (pH 1.3) and simulated intestinal medium (pH 6.8) were required. a) **Preparation of simulated gastric medium (0.1 N HCl pH 1.3)**: For 0.1N HCl, 11.4 ml of Hydrochloric acid (32% w/v) was diluted with sufficient water to produce 1000 ml. b) **Preparation of simulated intestinal medium (Buffer pH 6.8)**: 20 ml Sodium Hydroxide (25%) was diluted with 0.1 N Hydrochloric acid to 1000 ml adjusting pH 6.8 by addition of 1.2 ml *o*-phosphoric acid.

Preparation of matrix tablet. Drug, polymer and other excipients were weighed separately for 50 tablets per formulation as per proposed formulations. The proposed formulations were coded as F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8, F-9, F-10, F-11, F-12, F-13, F-14. The amounts of drug and excipients are expressed in milligram unit. Then active ingredient, microcrystalline cellulose, povidone K-30, polymer and aerosil were blended for 15 minutes and then magnesium stearate was added and further blended for another 1 minute. Blended mass was taken in the hopper and then die and punch were adjusted to get the desired weight of the tablet (300 mg). After compression the tablets were weighed and tablet weight was found 298 mg -308 mg. The tablets were prepared by direct compression; the types and amounts of polymers used are shown in Table 1.

***In vitro* dissolution study of the tablet matrix.** Dissolution studies were conducted according to USP method (USP XXII) using apparatus II paddle at a speed of 50 rpm and the temperature was maintained at 37.0±0.5^{o} C. The total duration of dissolution was 10 hours in which for the first 2 hours the tablet matrices were subjected to simulated gastric media (0.1 N HCl pH 1.3) and the later eight hours the tablet matrices were subjected to simulated intestinal media (Buffer pH 6.8). **Acid stage:** 900 ml of 0.1 N HCl was placed in each vessel and the apparatus was assembled. Six tablets from each formulation were weighed and placed in the baskets. The operation in the acid stage was carried out for 2 hours. After each hour 10 ml of sample solution was withdrawn and filtered. The released drug was assayed by using UV spectrophotometer at 276 nm. **Buffer stage:** After 2 hours operation in the acid stage, 20 ml NaOH (25%) was added to the previous fluid. The pH (6.8 ± 0.05) was adjusted with addition of 1.2 ml ortho-phosphoric acid. The operation was continued for 10 hours. After each one hour interval 10 ml of dissolution solution was sampled and filtered and the released drug assayed by using UV spectrophotometer at 305 nm. At each withdrawal 10 ml of fresh dissolution medium was added.

Table1. Esomeprazole, Methocel K15M, Methocel K100 LVCR and other excipients used in the proposed formulation F1 - F14

Proposed Formula-tion	Esome-prazole (mg)	Methocel K15M (mg)	Methocel K100 LVCR (mg)	Avicel (mg)	Povidone K-30 (mg)	Magnesium stearate (mg)	Aerosil (mg)	Total Wt. (mg)	Methocel K15M/ Methocel K100 LVCR (%)
F-1	20	60	-	150	60	5	5	300	20
F-2	20	75	-	135	60	5	5	300	25
F-3	20	90	-	120	60	5	5	300	30
F-4	20	105	-	105	60	5	5	300	35
F-5	20	120	-	90	60	5	5	300	40
F-6	20	135	-	75	60	5	5	300	45
F-7	20	150	-	60	60	5	5	300	50
F-8	20	-	60	150	60	5	5	300	20
F-9	20	-	75	135	60	5	5	300	25
F-10	20	-	90	120	60	5	5	300	30
F-11	20	-	105	105	60	5	5	300	35
F-12	20	-	120	90	60	5	5	300	40
F-13	20	-	135	75	60	5	5	300	45
F-14	20	-	150	60	60	5	5	300	50

Kinetic analysis of release data. The release of drug from sustained release dosage form is regulated by several processes. These are extraction or diffusion of drug from matrix and erosion of matrix, alternatively the drug may be dissolved in the matrix material and then released by diffusion through membrane. In some cases, drug may be released by osmotic process. Different kinetic equations (Zero order, First order, and Higuchi's equation) were applied to interpret the release rate from the tablet matrix. The best fit of higher correlation ($R^2 > 0.98$) was found with well-known Higuchi equation. Higuchi derived the rate of release of drugs dispersed in an inert matrix system.[8]

RESULTS AND DISCUSSION

In this study, two different grades of cellulose derivatives - Methocel K15M and Methocel K100 LVCR were used for the development of esomeprazole magnesium sustained release tablet matrix by direct compression method. The effect of Methocel K15M and Methocel K100 LVCR on esomeprazole magnesium sustained release dosage was assessed. Different percentage of hydroxypropyl methylcellulose-Methocel K15 M (20%, 25%, 30%, 35%, 40%, 45%, 50% of total weight of tablet matrix) and different percentage of hydroxypropyl methylcellulose-Methocel K100 LVCR (20%, 25%, 30%, 35%, 40%, 45%, 50% of total weight of tablet matrix) containing tablet matrices were placed in the dissolution media according to design of study. The percent release from all the respective polymer

matrix systems were plotted against time to observe the drug release pattern. It was seen that percent of drug release was increased by decreasing the amount of Methocel K15M and Methocel K1000 LVCR in the formulations (Table 2).

The polymer Methocel K15M was used alone with esomeprazole magnesium as the matrix builder in the proposed formulations F-1, F-2, F-3, F-4, F-5, F-6, F- 7 as 20%, 25%, 30%, 35%, 40%, 45%, 50% of the total weight of the tablet respectively (Table 1).The variable ranges of Methocel K15 M were selected by considering physicochemical behavior of the polymer in the physiological fluid and physicochemical properties of the drug. According to USP for an ideal sustained release dosage form like theophylline SR, percent release in 1st hour should be not more than 30% and in 10th hour not less than 80% (USP 29th Edition, 2006).[9]

Table 2. Effect of Methocel K15M (F1-F7) and Methocel K100 LVCR (F8-F14) on esomeprazole magnesium release in simulated gastrointestinal fluid and simulated intestinal fluid (Zero order plot)

Time (hours)	% of drug release													
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12	F-13	F-14
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	42.24	39.68	35.85	32.8	29.88	27.81	26.19	37.75	35.28	33.43	28.99	26.3	24.39	22.12
2	47.9	46.35	43.68	41.12	34.83	33.27	31.16	42.22	41.18	38.59	35.12	31.45	27.38	25.77
3	54.05	47.85	46.18	42.79	39.29	35.91	33.48	46.03	45.11	43.41	41.25	38.11	34.68	29.93
4	57.87	51.85	49.18	46.28	43.25	41.04	39.12	50.5	48.56	46.07	44.89	45.09	39.98	34.41
5	62.53	57.02	55.18	51.77	47.05	47.82	40.61	55.13	54.63	52.39	48.87	45.76	44.96	37.74
6	66.85	61.85	59.68	57.6	55.79	49.98	44.42	60.43	57.91	56.71	53.83	52.08	46.62	44.22
7	71.17	69.18	67.02	64.75	62.72	56.26	48.39	67.54	64.79	61.86	57.81	55.24	52.42	47.21
8	79.82	76.35	74.02	71.74	70.31	63.87	53.2	75.16	71.52	70.17	68.57	63.06	58.23	51.86
9	85.8	81.52	79.18	73.91	72.95	69.16	58.83	82.94	79.55	78.49	72.21	70.71	64.03	57.34
10	91.79	88.68	86.35	80.9	76.09	71.32	67.11	89.72	86.28	85.14	78.84	75.7	71.16	66.65

The release pattern of esomeprazole magnesium from the proposed formulation 5 (40% Methocel K15M), and proposed formulation 6 (45% Methocel K15M) met the desired sustained release pattern (Table 2). This indicated that at a minimum percent (40%) of Methocel K15 M the desired sustained release of esomeprazole was obtained by direct compression method which is evident from 1st hour to 10th hour *in vitro* dissolution studies. Again, Methocel K100 LVCR alone was used with esomeprazole magnesium as the matrix builder in the proposed formulations F-8, F-9, F-10, F-11, F-12, F-13, F-14 as 20%, 25%, 30%, 35%, 40%, 45%, 50% of the total weight of the tablet respectively (Table 1). The same variable ranges of Methocel K100 LVCR were selected on the basis of physicochemical behavior of the polymer in the physiological fluid and physicochemical properties of the drug. The drug release order in the proposed formulation F-11 (35% Methocel K100 LVCR), F-12 (40% Methocel K100 LVCR), and F-13 (45% Methocel K100 LVCR) met the desired sustained release action (Table2).

Determination of release mechanism from multiple coefficients. The drug release data of the proposed formulations F-1, F-2, F-3, F-4, F-5, F-6, F-7 were treated in different kinetics orders such as Zero Order Plot (Table 2, Fig.1), First Order Plot (Fig.1) and Higuchi Plot (Fig. 1) and their correlation coefficients were determined graphically to identify their release mechanism.

From Table 3 it was observed that proposed formulations F-1, F-2, F-3, F-4, F-5, F-6 & F-7 although followed first order and Higuchi release kinetics however, the release kinetics was very close to 1 in case of Higuchi plot than other kinetic orders that indicated Higuchi release kinetics was predominant here. In case of Methocel K100 LVCR the drug release data were treated in different kinetic orders (Fig. 2) such as zero order, first order and Higuchi release kinetics to assess the release mechanism of esomeprazole.

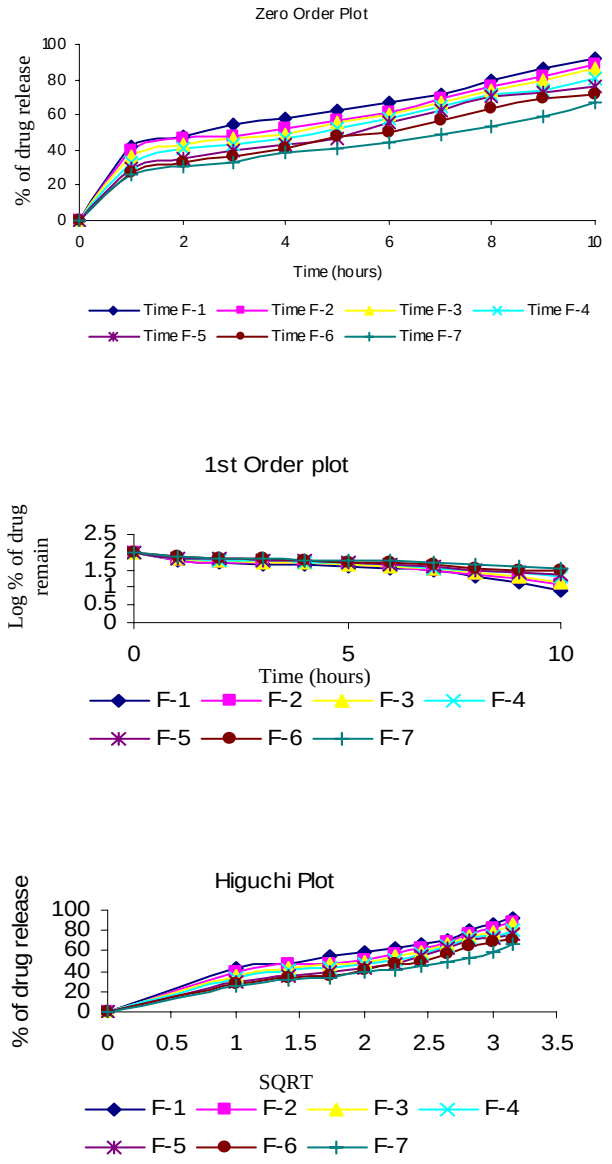

Figure 1. Effect of Methocel K15M on Esomeprazole magnesium from proposed formulations F1-F7 in simulated gastrointestinal fluid and intestinal fluid

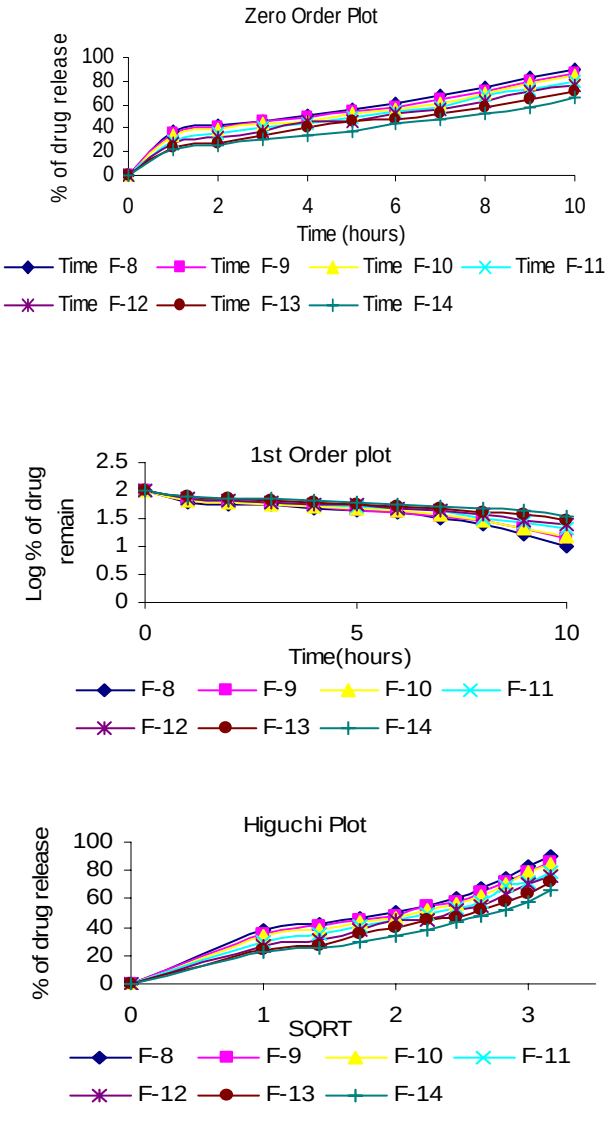

Figure 2. Effect of Methocel K100 LVCR on Esomeprazole magnesium from proposed formulations F8-F14 in simulated gastrointestinal fluid and intestinal fluid

From Table 3 it was observed that F-8, F-9, F-10, F-11, F-12, F-13, F-14 followed both first order and Higuchi release mechanism. It is also added that correlation coefficients of Higuchi were very close to 1 that reflected predominant Higuchi release mechanism. From the above discussion it can be predicted that Methocel K100 LVCR was better than Methocel K15M for esomeprazole magnesium sustained release tablet matrix. Methocel K100 LVCR at 35% can give expected sustained release by direct compression method and that may be better to combat against ulcer diseases more effectively.

The proposed mechanism of Methocel K15M and Methocel K100 LVCR. The proposed drug release mechanism of Methocel K15M and Methocel K100 LVCR are as follows-hydration, swollen and diffuse the drug particles.

Both Methocel K15M and Methocel K100 LVCR are hydrophilic polymers first hydrated while get in contact with dissolution fluid and then swollen and allow gradual dissolution and diffusion of drug from the matrix.[10]

Table 3. Multiple coefficients determination data by using different percent of polymer Methocel K15M and Methocel K100 LVCR in simulated dissolution media

Formulation code	Multiple coefficient of determination (r^2)		
	Zero order	First order	Higuchi
F-1	0.8537	0.9192	0.9673
F-2	0.8717	0.9233	0.9618
F-3	0.8898	0.9359	0.97
F-4	0.8961	0.9578	0.9754
F-5	0.9221	0.9706	0.9773
F-6	0.9202	0.9688	0.98
F-7	0.8961	0.9353	0.9655
F-8	0.8997	0.9085	0.9636
F-9	0.8983	0.9239	0.9678
F-10	0.9114	0.9226	0.9657
F-11	0.9194	0.9539	0.9777
F-12	0.9229	0.9589	0.9798
F-13	0.9397	0.9649	0.9804
F-14	0.9428	0.9544	0.9685

When those polymers get hydrated in contact with dissolution fluid, a number of porous channels were formed within the polymeric structure. Through that porous channels, fluid enter slowly and dissolve the drug on the basis of partition coefficient. The drug solution is then diffused or released from the matrix. The dissolution and diffusion of the drug molecule depend on rate and extent of polymer hydration, number of channel formation, amount of fluid enter into the porous channel, number of multilayer formation, partition coefficient of the drug.[11] From the study it is evident that Methocel K100 LVCR is quite better than Methocel K15M as rate retardant. The minimum percent i.e.40% Methocel K15M exhibited desired sustained release action whereas minimum only 35% Methocel K100 LVCR showed desired sustained release action whose molecular weight was higher than Methocel K15M. The release rate of the water soluble polymer depends on molecular weight; the larger the molecule, the stronger the forces holding the chains together.[12] More energy has to be expended to force the chain apart in the liquid.

The velocity of penetration (*S*) of a solvent into the bulk polymer obeys the relationship

$$S=kM^{-A}$$

Where M is the molecular weight, k and A being constants.

The dissolution process from the polymer matrix was complicated than from ordinary crystalline materials. It is frequently observed that swollen layer and gel layers form next to the diffusion layer.[13] We also observed that when the percent of polymer increased then the release of the drug was decreased and in case of 50% Methocel K100 LVCR polymer the release was 67% at 10^{th} hour. This was occurred due to multilayer formation in the tablet matrix. When the tablet matrix was hydrated then it became swollen and made channel to penetrate water into the matrix and dissolved the drug and finally diffused. Due to formation of multilayer, the pathway was not straight forward and drug release was retarded.

CONCLUSION

Esomeprazole is widely used against ulcer. Ulcerative diseases are very common where the patients take medicine regularly. Sustained release dosage form of esomeprazole can provide better patient compliance and prolonged action against ulcer disease. The half life of esomeprazole is 1.5 hour for oral dosage. Due to its rapid elimination and posology, this drug will be a suitable candidate if formulated into sustained release dosage forms. The present study was investigated in order to formulate esomeprazole magnesium sustained release with addition of release retarding polymer Methocel

K15M and Methocel K100 LVCR. From the study it was concluded that at least 40% Methocel K15M showed desired sustained release and at least 35% Methocel K100 LVCR met the desired sustained release action. Besides, Methocel K100 LVCR was better than Methocel K15M for esomeprazole magnesium sustained release tablet matrix by direct compression. We also observed that Higuchi release kinetics was predominant among all the release kinetics. The use of direct compression method may increase high production, performance, save valuable time in manufacturing plan, less involvement of labour, reduce cost and increase profit. The proposed formulations (F-5 and F-11) may be used for the development of esomeprazole sustained release matrix and meet the patient's demand in order to combat against ulcer more precisely.

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