

FORMULATION AND *IN VITRO* EVALUATION OF ESOMEPRAZOLE MAGNESIUM HYDROPHILIC MATRIX SR TABLET

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Abstract

In the present study an attempt has been taken to develop esomeprazole sustained release matrix tablet using hydroxypropyl methylcellulose (HPMC) polymer such as Methocel K4M CR by direct compression method. Various amount of Methocel K4M CR 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 granules were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, total porosity, and drug content. The prepared tablets were subjected to thickness, weight variation, hardness, friability measurements, drug content determination and in vitro release studies. The granules showed satisfactory flow properties, compressibility and drug content. All the tablet formulations complied with pharmacopoeial specifications for tested parameters. The dissolution study were conducted 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. From in vitro dissolution study, the formulation F-5 (40%) and F-6 (45%) met the official release pattern of esomeprazole for 10h period. The release mechanisms were explored and explained by Zero order, Higuchi, First order and Korsmeyer-Peppas equations. The release kinetics of formulation F-5 and F-6 very closely followed Higuchi kinetic order than first order and zero order kinetics. From Korsmeyer-Peppas equation it was found that the drug release followed both diffusion and erosion mechanism in all cases.

Key Words: Esomeprazole, Direct compression, Sustained release, Methocel K4M CR, Release Kinetics.

esomeprazol Magnesium Hidrofilik Matris SR Tablet Formülasyonu ve *In Vitro* Değerlendirilmesi

*Bu araştırmada, hidroksipropil metal selüloz polimeri (HPMC) olan "Methocel K4M CR" kullanılarak esomeprazol uzun etkili matris tablet geliştirilmesine ve doğrudan basım yöntemiyle hazırlanmasına çalışıldı. Matris tabletin toplam ağırlığının, sırasıyla %20, %25, %30, %35, %40, %45 ve %50'si oranında gecikmiş etkili salım araştırılmak üzere, "Methocel K4M CR" nin farklı miktarları, önerilen 7 formülasyonun (F1-F7) matris yapısının oluşturulması amacıyla kullanıldı. Granüller yığın açısı, vuruş dansitesi, basılabilirlik indisi, toplam porozite ve ilaç içeriği yönünden incelendi. Hazırlanan tabletlerde kalınlık, ağırlık sapması, sertlik, ufalanma-aşınma testleri, ilaç içeriği tayini ve in vitro salım çalışmaları gerçekleştirildi. Tablet formülasyonlarının tümü incelenen parametreler yönünden farmakope spesifikasyonları ile uyumlu bulundu. Disolüsyon çalışması ilk 2 saat için taklit edilmiş mide ortamında (pH 1.3), daha sonra ise 8 saat süre ile taklit edilmiş barsak ortamında (pH 6.8), USP II no'lu disolüsyon aparatı kullanılarak yapıldı. *In vitro* disolüsyon çalışması bulgularına göre, F5 (%40) ve F6 (%45) formülasyonları 10 saatlik süre içerisinde esomeprazolün farmakopedeki salım profiliyle uyumlu bulundu. Salım mekanizmaları, 0. derece, Higuchi, 1. derece ve Korsmeyer-Peppas kinetiklerine göre incelendi. F5 ve F6 formülasyonlarının salım kinetikleri 1. ve 0. dereceden çok Higushi kinetiğine uygun bulundu. Korsmeyer-Peppas bağıntısına göre tüm formülasyonlarda ilaç salımının difüzyon ve erozyon mekanizmalarına uygun olarak gerçekleştiği bulundu.*

Anahtar Kelimeler: Esomeprazol, Doğrudan basım, Uzatılmış salım, Methocel K4M CR, Salım kinetikleri.

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INTRODUCTION

Esomeprazole, the *S*-isomer of omeprazole, irreversibly inhibits the gastric parietal H⁺/K-ATPase enzyme involved in the production of hydrochloric acid in the stomach. It 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 using hydroxypropyl methylcellulose (HPMC). The polymers are hydrophilic in nature and can hold active ingredients firmly that depend on the concentration or ratio of the polymers used (2). 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 area for its ease, compliance, faster production, avoiding hydrolytic or oxidative reactions occurred during processing of dosage forms (3). Sustained or controlled drug delivery occurs while drug is 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 to 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 that each of them 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. Methocel K4M CR is hydrophilic polymer that becomes hydrated, swollen and facilitates diffusion of the drug (7).

EXPERIMENTAL

Materials

Esomeprazole magnesium (Cipla, India); hydroxypropyl methylcellulose-Methocel K4M Premium USP/EP (Dow Chemical Company, Midland, MI, USA); microcrystalline Cellulose (Avicel PH101) (Hanau Chemicals Ltd., Japan); polyvinyl pyrrolidone (Povidone K-30) (Hanau Chemicals Ltd., Japan); colloidal anhydrous silica (Aerosil 200) (Hanau Chemicals Ltd., Japan); magnesium stearate (Hanau Chemicals Ltd., Japan); hydrochloric acid (Merk, Germany); sodium hydroxide (Merk, Germany); ortho-phosphoric acid (Merk, Germany) were used.

Preparation of Tablets

The tablet was prepared by simple blending of active ingredient with polymers, filler, binder, lubricant and flow promoter followed by direct compression. 50 tablets were prepared for each proposed formulation. Properly weighed Methocel, Povidone K-30, Avicel PH 101, magnesium stearate, aerosil and the active ingredient were then taken in a photo film container and blended in a laboratory designed small drum blender machine for 30 minutes to ensure throughout mixing and phase homogenization (Table1). The mixture with a total mass of 300 mg including 20 mg

esomeprazole was manually fed into the die of a hydraulic press equipped with flat-faced punches of 8 mm in diameter to produce tablets. The compression force was kept constant at 200 MPa for 10 seconds.

Table 1: Composition of the investigated matrix tablets (all quantities are given in mg).

Proposed Formulation	Esomeprazole	Methocel K4M CR	Avicel	Povidone K-30	Magnesium stearate	Aerosil	Total Wt.
F-1	20	60	150	60	5	5	300
F-2	20	75	135	60	5	5	300
F-3	20	90	120	60	5	5	300
F-4	20	105	105	60	5	5	300
F-5	20	120	90	60	5	5	300
F-6	20	135	75	60	5	5	300
F-7	20	150	60	60	5	5	300

Analytical Validation of the Quantification Method

Analytical validation of spectrophotometric method used for the quantification of esomeprazole in dissolution studies was done by investigating the linearity and range, accuracy and precision values in terms of repeatability and intermediate according to ICH Guidelines Q2 (R1) (12). Linearity and range was studied at six points in a concentration range of 0.005-0.2 mg/mL. Accuracy was tested by repeating six experiments for the same concentration point in the same day. Precision was tested as repeatability and intermediate precision. Repeatability was done on three different concentrations from the calibration curve performing three measurements for each concentration and intermediate.

Preparation of dissolution medium

For dissolution study, 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 1.2): 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 ortho-phosphoric acid.

Physical evaluation of granules

The granules were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, total porosity, and drug content etc.

Physical evaluation of matrix tablet

The prepared tablets were subjected to thickness, weight variation, hardness, friability measurements, drug content determination and *in vitro* release studies.

In vitro dissolution study

Dissolution studies were conducted according to USP method (USP XXII) using apparatus II paddle at a speed of 75 rpm and the temperature was maintained at 37.0±0.5° 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 dissolution media. 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.

RESULTS AND DISCUSSION

In the present study an attempt has been taken to develop sustained release tablet of esomeprazole magnesium by direct compression method using Methocel K4M CR as rate retarding materials (Table 1). Methocel K4M CR was utilized in the proposed formulations F-1 to F-7 in order to evaluate the amount of polymer required to provide desired release rate for 12 hour period. Tablet matrices containing different percentage of hydroxypropyl methylcellulose-Methocel K4 M (20%, 25%, 30%, 35%, 40%, 45%, and 50% of total weight of tablet matrix) were placed in the dissolution media according to the design of study. The variable ranges of Methocel K4 M were chosen by considering physicochemical nature of the polymer in the physiological fluid and physicochemical properties of the drug. According to USP recommendation for an ideal sustained release dosage form like theophylline SR, the percent release in 1st hour should be not more than 30% and in 10th hour not less than 80% (USP 29th Edition, 2006)⁹. The percent release from all the respective polymer matrix systems were plotted against time to observe the drug release pattern. The tablets of all the formulations (F-1 to F-7) were free from all kinds of physical problems like hardness, thickness, friability, weight variation etc. The granules of proposed formulations (F-1 to F-7) were evaluated for loose bulk density (LBD), tapped bulk density (TBD), compressibility index, total porosity, angle of repose and drug content. The results of LBD and TBD ranged from 0.40 ± 0.05 to 0.50 ± 0.02 and 0.51 ± 0.03 to 0.70 ± 0.05 respectively. The results of compressibility index (%) ranged from 12.25 ± 0.01 to 17.78 ± 0.03 . Generally, compressibility index values up to 15% resulted well to excellent flow properties. The results of angle of repose ($^{\circ}$) ranged from 22.25 ± 0.02 to 24.15 ± 0.02 . The results of angle of repose ($< 30^{\circ}$) indicated good flow properties of granules. The percentage porosity values of the granules ranged from 23.0 ± 0.01 to 27.25 ± 0.06 %, indicating that the packing of the granules may range from close to loose packing and also further confirming that the particles are not of greatly different sizes. Generally, a percentage porosity value below 26% shows that the particles in the powder are of greatly different sizes and a value greater than 48% shows that particles in the powder are in uniform of aggregates or flocculates. The drug content in a weighed amount of granules of all formulations ranged from 98.25 ± 0.08 to 101.45 ± 0.04 %. All these results indicated that the granules possess satisfactory flow properties, compressibility and drug content.

The tablets of the proposed formulations (F-1 – F-7) were subjected to various evaluation tests like thickness, hardness, weight variation test and friability. The thickness of the tablets ranged from 2.05 ± 0.10 to 2.75 ± 0.03 mm. The hardness and percentage friability of the tablets of all the formulations ranged from 5.0 ± 0.02 to 6.1 ± 0.04 kg/cm² and 0.05 ± 0.04 to 0.50 ± 0.01 %, respectively. The average percentage deviation of 20 tablets of each formula was less than ± 5 %. Drug content among different batches of tablets ranged from 97.03 ± 0.05 to 101.65 ± 0.02 %. It was found that all the formulations showed uniform thickness. In a weight variation test, the pharmacopeial limit for

the percentage deviation for tablets was $\pm 0.5\%$. The average percent weight deviation of all tablet formulations was found to be within the pharmacopoeial limit. Good uniformity in drug content was found among different batches of the tablets, and the percentage of drug content was more than 97%. In this study, the percentage friability for all the formulations was below 1%, indicating that the friability was within the official limits. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness and friability.

From the dissolution study, it was found that the proposed formulation F-5 and F-6 exhibited official drug release pattern than other formulations for 12 hour period. Among these formulations, the rate and extent of drug release was decreased with increasing the amount of Methocel K4M CR (Table 2). This polymer has been well known to retard the drug release by swelling in aqueous media. A polymer's ability to retard the drug release rate is related to its viscosity. However, processing factors including particle size, hardness, porosity and compressibility index also affect the release rate of drug from tablets. The hydration rate of HPMC depends on the nature of the substituent like hydroxypropyl group content. Methocel K4M CR was used because it forms a strong viscous gel in contact with aqueous media, which may be useful in controlled delivery of drugs. The drug release data obtained were extrapolated by Zero order, Higuchi, First order and Korsmeyer-Peppas equations to know the mechanism of drug release from these formulations (Table 3). All the formulations did not follow Zero order release pattern (Figure 1). The log transformed data showed a fair linearity, with regression values between 0.92 and 0.97. The release rate of drug from the matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to the transport of drug from the dosage matrix into the *in vitro* study fluid depending on the concentration. As the gradient varies, the drug releases and the distance for diffusion is increased. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square-root kinetics or Higuchi's kinetics (8). In this experiment, the *in vitro* release profiles of drug from all these formulations could be best expressed by Higuchi's equation, as the plots showed high linearity (R^2 : 0.97 to 0.98). To confirm the diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation¹¹. The formulations showed good linearity (R^2 : 0.97 to 0.98), with slope (n) values ranging from 0.414 to 0.740, indicating that diffusion was the predominant mechanism of drug release from these formulations. When the data was plotted according to Korsmeyer-Peppas equation, the formulations F-5 and F-6 showed high linearity (R^2 : 0.99), with a comparatively high slope (n) values of >0.6 , which appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous diffusion. The relative complexity of these formulations and their components indicated that the drug release was controlled by more than one processes. Hence, diffusion coupled with erosion might be the mechanism for the drug release from Methocel K 4M CR based matrix tablet.

The proposed mechanism of Methocel K4M CR

The proposed drug release mechanism from Methocel K4M CR is as follows: hydration, swelling and diffusion of the drug particles. Methocel K4M CR is hydrophilic polymer first hydrated while get in contact with dissolution fluid and then swollen and allow gradual dissolution and diffusion of drug from the matrix.¹⁰

When those polymers are hydrated in contact with dissolution fluid, a number of porous channels are 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 The minimum percent i.e.40% Methocel K4M exhibited desired sustained release action. 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 is complicated than the dissolution 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. 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.

Table 2: Effect of Methocel K4M CR (F1-F7) on esomeprazole magnesium release in simulated gastrointestinal fluid and simulated intestinal fluid (Zero order plots)

Time (hours)	% of Release						
	F-1	F-2	F-3	F-4	F-5	F-6	F-7
0	0	0	0	0	0	0	0
1	41.24	40.68	36.85	30.8	30.88	25.81	25.19
2	45.9	45.35	40.68	42.12	35.83	30.27	29.16
3	55.05	49.85	45.18	45.79	44.29	36.91	33.48
4	59.87	50.85	50.18	47.28	43.25	40.04	39.12
5	60.53	55.02	55.18	53.77	49.05	45.82	42.61
6	65.85	60.85	57.68	55.6	55.79	47.98	44.42
7	70.17	63.18	65.02	65.75	61.72	55.26	51.39
8	71.82	75.35	76.02	75.74	72.31	65.87	53.2
9	86.8	80.52	79.18	76.91	75.95	71.16	55.83
10	90.79	89.68	85.35	81.90	78.09	73.32	68.11

Table 3: Kinetic modeling data of the formulations by using different percent of polymer Methocel K4M CR in simulated dissolution media.

Formulation Code	Zero Order			First Order			Higuchi		
	r ²	k	RMS	r ²	k	RMS	r ²	k	RMS
F-1	0.85	0.181	152.5	0.91	0.261	116.2	0.96	0.572	172.03
F-2	0.87	0.235	150.02	0.92	0.442	152.5	0.96	0.571	154.5
F-3	0.88	0.193	196.3	0.93	0.321	124.3	0.97	0.621	199.01
F-4	0.89	0.264	114.8	0.95	0.425	110.05	0.97	0.425	121.03
F-5	0.92	0.451	121.01	0.97	0.541	158.6	0.97	0.654	154.0
F-6	0.92	0.364	125.6	0.96	0.234	198.03	0.98	0.359	111.05
F-7	0.89	0.195	164.01	0.93	0.325	127.7	0.96	0.546	123.01

r² : Determination coefficient, K: Dissolution rate constant, RMS: Residual mean square

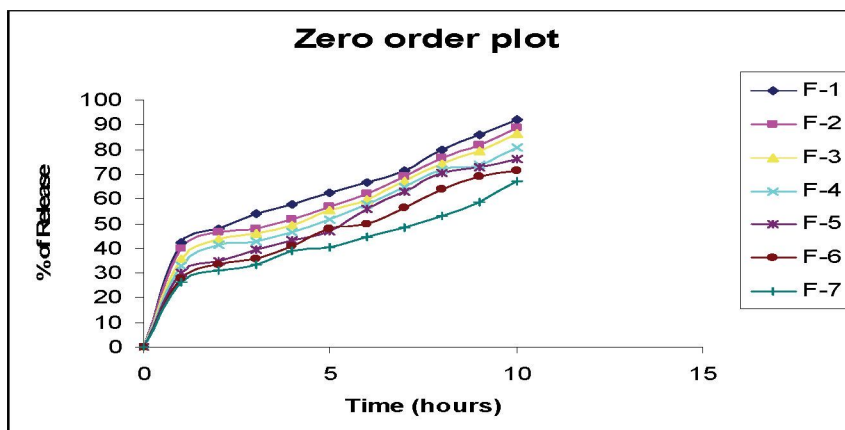


Fig.1a: Zero order plot of release kinetics of seven formulations (F-1 to F-7) of esomeprazole magnesium from Methocel K4M CR based matrix tablets

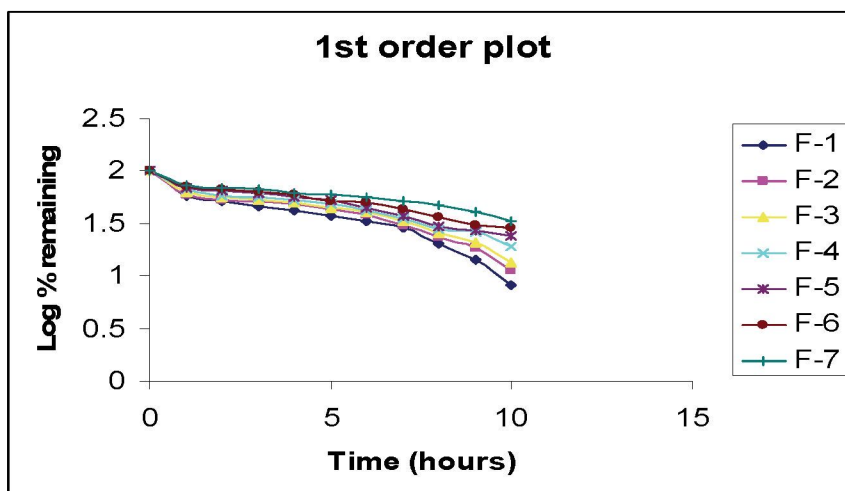


Fig.1b: First order plot of release kinetics of seven formulations (F-1 to F-7) of mesomeprazole magnesium from Methocel K4M CR based matrix tablets.

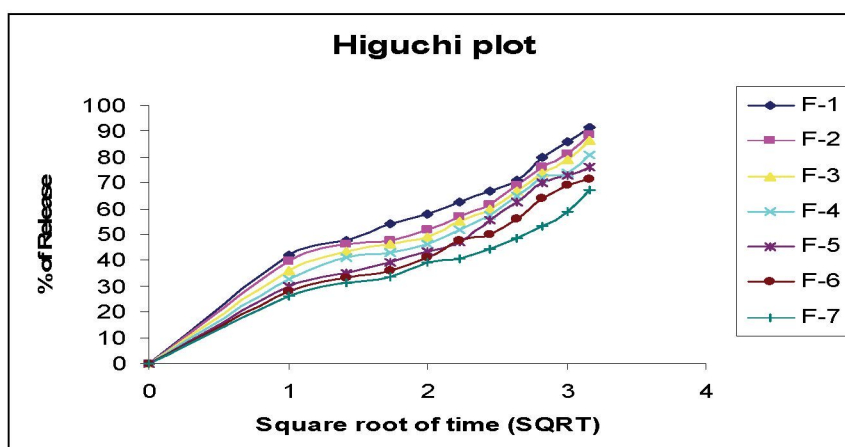


Fig1c: Higuchi plot of release kinetics of seven formulations (F-1 to F-7) of esomeprazole magnesium from Methocel K4M CR based matrix tablets.

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 K4M CR. From the study it was concluded that 40% Methocel K4M at least met the desired sustained release pattern. 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 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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