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In-Vitro Evaluation of Oral Sustain Release Drug Delivery System for Ranolazine Using Hypromellose 50

Md. Shozan Mondal[1*], Md.Tauhidul Islam[1], Md. Ariful Islam[2], Sharif MD. Abuzar[1]

[1.] Department of Pharmacy, University of Asia Pacific, Dhanmondi, Dhaka-1209, Bangladesh

[2.] BRAC University, 66 Mohakhali, Dhaka-1212, Bangladesh

*Corresponding Author's E-mail: shozan_uap15@yahoo.com Tel: +8801670238605

ABSTRACT

In the present study an attempt has been made to evaluate the effect of HYPROMELLOSE 50 polymer on the release profile of drug from matrix system. Ranolazine, an anti-anginal agent was used as model drug to evaluate their release characteristics from different formulations. Matrix tablets of Ranolazine were prepared by wet granulation process using HYPROMELLOSE 50. Release kinetics of Ranolazine from these controlled sustain release matrice at 0.1 N HCl using USP paddle method with sinker was conducted for 12 hours and examined. Statistically significant differences were found among the drug release profile from different formulations of polymeric matrices. Higher polymer content (30%) in the matrix decreased the rate of the drug due to increased tortuosity and decreased porosity. At lower polymeric level (5%), the rate of drug release was elevated. The release mechanism was explored and explained with zero order, first order, Higuchi and Korsmeyer equation. The result generated in this study showed that the profile and kinetics of drug release were functions of polymer quantity and physico-chemical properties of drug. A controlled plasma level profile of Ranolazine drug can be obtained by modulation of polymer content in the matrix.

Keywords: *Ranolazine, Sustain Release, Hypromellose 50, In-Vitro Evaluation*

INTRODUCTION

Research and development of drug delivery systems are increasing at a rapid pace throughout the world. This worldwide trend will intensify in the next decade as cuts in public health expenses demand lower costs and higher efficacy. The fundamental target of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration for a definite period of time. Depending on the route of administration, a conventional dosage form of the drug e.g. solution, suspension, capsule, tablet etc produce a drug blood level time profile which does not maintain within the therapeutic range for extended period of time (Amidon et al., 2000)[1]. The short duration of action is due to the inability of the conventional dosage forms to control temporal delivery (Armand et at., 1987) [2]. If any attempt is made to maintain drug blood level in the therapeutic range for longer periods by, for example increasing the dose of an intravenous injection, toxic levels may be produced at any time (Rohrs et al., 2003)[3]. An alternative is to administer the drug repetitively using a constant dosing interval as in multiple dosing therapies (Ballard et al., 1978)[4]. In this case drug blood level reached and the time required reaching that level depends on the dose and the dosing interval (Capan et al., 1989) [5]. In recent years considerable attention has been focused on the development of new drug delivery systems. Recognition

of the possibility of re-patenting successful drugs by applying the concepts and techniques of controlled release drug delivery systems (Cavalla et al., 2003)[6], coupled with the increasing expense in bringing new drug entities to market, has encouraged the development of new drug delivery systems (Catellani et al., 1988)[7].

Hydroxypropyl methylcellulose (HPMC) is a dominant vehicle used for the preparation of oral controlled drug delivery systems. The matrix tablets were prepared using Hydroxypropyl methylcellulose (HPMC). Physical properties (hardness, thickness and diameter) and release kinetics of those matrix tablets were studied. The dissolution was carried out in 'eight pocket tablet dissolution tester (USP Apparatus II) at pH 1.20. Comparisons are made of the effect of different amount of Hydroxypropyl methylcellulose (HPMC) on the physical properties as well as zero order, Higuchi, first order and Korsmeyer release kinetics of Ranolazine tablet matrices.

MATERIALS AND METHODS:

Materials

Drug: Ranolazine (Ranbaxy, India).
Polymer: HYPROMELLOSE 50 (Shin-Etsu, Japan)

Excipients: Lactose (Lactose Company, New Zealand)

Microcrystalline cellulose (Ming Tai Chemical co.Ltd, Taoyuan Hsien, Taiwan)

Magnesium Stearate (Dr. Paul Lohmann GmbH KG, Germany)

Colloidal Silicon dioxide (Cabot India Ltd, Mumbai).

Reagent: Hydrochloric acid (Merck, Germany)

Methods of Study:

Preparation of Matrix Tablet

Tablets were prepared by wet granulation process. In all cases the amount of the active ingredient is 500 mg and the total weight of the tablet is 1000 mg. During granulation sodium hydroxide pellets is dissolve into purified water and then this solution is used as granulating solvent. Matrix-forming agents, lactose, microcrystalline cellulose, sodium hydroxide pellets, magnesium stearate, aerosil and the active ingredient were weighed properly. Firstly active ingredient, lactose and microcrystalline cellulose are mixed for 10 minutes properly. Then granulating solvent is added and mixed properly to get soft granules.

HYPROMELLOSE 50 and NaOH pellets were added into water to make solution. Then the soft mass is dried in laboratory oven for a certain period to evaporate excess moisture. Dried granules are sieved through 20 mesh SS screen to get compressible particle. Lubricants are added during blending part. During blending total mass is taken in a photo film container and blended in a laboratory designed small drum blender machine for about 30 minutes. Particular attention has been given to ensure thorough mixing and phase homogenization.

The appropriate amounts of the mixture were accurately weighed in an electronic balance for the preparation of each tablet and finally compressed using Manesty D type 16 station compression machine with a 19.00 x 8.80 mm concave, plain faced punch and die set. The compression force was 1.5 ton. Before compression, the surfaces of the die and punch were lubricated with purified talc (Batycky et al., 1997) [8]. All the preparations were stored in airtight containers at room temperature for further study.

Table-1: List of equipments used in the preparation of matrix tablets

Name	Source	Country of origin
Electric balance	Sartorius	Germany
	OHAUS LS 200	Switzerland
Sieve	Endecotts test sieve	UK
Blender	Laboratory designed small drum blender	India
Compression machine	Manesty D type	UK

Table-2: Formulation of Ranolazine tablet containing HYPROMELLOSE 50 matrices

Formulation Code	Weight (mg) / Tablet							
	Hypro mellose 50	Ranolazine	Lactose	Avicel pH 101	NaOH	Aerosil	Mg - stearate	Total
RHPMC50F1	50	500	250	181	4	5	5	1000
RHPMC50F2	100	500	200	181	4	5	5	1000
RHPMC50F3	150	500	150	181	4	5	5	1000
RHPMC50F4	200	500	100	181	4	5	5	1000
RHPMC50F5	250	500	50	181	4	5	5	1000
RHPMC50F6	300	500	0	181	4	5	5	1000

Characterization of Ranolazine Sustain Release Tablets

The ability of a tablet to withstand mechanical handling and transport has been evaluated by various types of tests: abrasion, bending, indentation, hardness, diametral crushing. However, the data from these tests seldom can be correlated in a precise manner (Fell et al., 1970) [9]. Hardness depends on the weight of material and the space between the upper and lower punches at the moment of compression (Alderman et al., 1984) [10]. If the volume of material or the distance between punches varies, hardness is likewise inconsistent.

A hardness test was carried out on 10 matrix tablets from each formulation using electronic hardness tester (ERWEKA, TBH 300, GmbH, Germany) at the Quality Assurance Department of Eskayef Bangladesh Limited. The hardness of matrix tablets was measured in Kp.

***In-Vitro* Dissolution Study of Ranolazine Sustain Release Tablets**

Dissolution Test

Dissolution Set Up: "The Rotating Paddle Method" consists of a paddle held by a motor shaft. The sinker is used to hold the sample immersed into the dissolution medium. The entire flask is immersed in a constant – temperature bath set at 37°c. The temperature range is maintained at 37°c ± 0.5°c. The rotating speed and the position of the basket must meet specific requirements set forth in the current USP (Gao et al., 1996) [11].

Dissolution Medium: All dissolution studies were carried out for sustain release Ranolazine formulations according to USP XII. 0.1N HCl is used as dissolution medium. The amount of drug dissolved in the medium was determined by UV spectrophotometer at 271 nm.

Preparation of dissolution medium for 0.1N HCl solution, 11 ml of hydrochloric acid (35 % w/v) was diluted to 1000 ml with purified water.

Table-3: List of equipments used to evaluate the chemical characterization of matrix tablet

No.	Equipments	Source	Country of Origin
1	Dissolution tester USP XXII	ERWEKA Model DT-700	Germany
2	UV- Spectrophotometer	UV – 1601 PC SHIMADZU	Japan
3	P^H meter	HANNA P^H 210	Portugal
4	Distill Water Plant	SMIC	China
5	Vortex Mixer	Guangho Ltd.	China
6	Safety Pipette Filler	Saffron	England
7	Dryer	LEEC Ltd.	England
8	Filter	Copley Instruments.	England
9	Electronic Balance	Sartorious	Germany
10	Hardness tester	ERWEKA, TBH 300	Germany

Dissolution Procedure

Dissolution studies were conducted in paddle method in the metallic drive shaft rotated at a speed of 100 rpm and the temperature was maintained at 37°c ± 0.5°C. As the tablets have floating tendency, sinker is used to keep immersed into the medium.

This operation was continued for 12 hours. At every 1-hour interval samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh dissolution medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 271 nm for Ranolazine by an UV spectrophotometer (Shimadzu, Japan). The amounts of drug present in the samples were calculated with the help of straight-line equation obtained from the calibration curves for respective drug. The dissolution study was continued for 12 hours to get a

simulated picture of the drug release in the in-vivo condition and drug dissolved at specified time periods was plotted as percent release versus time (hours) curve. This drug release profile was fitted into several mathematical models to get an idea of the release mechanism of the drug from the dosage form.

CHARACTERIZATION OF RELEASE KINETICS:

To detail the release kinetics, data obtained form in vitro drug release study were tested with the following mathematical model.

Zero order equation

The equation assumes that the cumulative amount of drug release is directly related to time. The equation may be as follows (Ranga et al., 1988) [12]:

$C = K0\ t$---------- (1)

Where, K0 is the zero order rate constant expressed in unit concentration/time and t is the time in hour. A graph of concentration vs time would yield a straight line with a slope equal to K0 and intercept the origin of the axes.

First order equation

The release behavior of first order equation is expressed as log cumulative percentage of drug remaining vs time. The equation may be as follows

$\text{Log } C = \text{Log } C0 - kt / 2.303$ ---------- (2)

Where,

C = The amount of drug un-dissolved at t time, C0 = Drug concentration at t = 0 k = Corresponding release rate constant.

Higuchi square root law

The Higuchi release model describes the cumulative percentage of drug release vs square root of time (Higuchi et al., 1963). The equation may be as follows (Higuchi, 1961) [13]:

$Q = K\sqrt{t}$ ---------- (3)

Where, Q = the amount of drug dissolved at time t. K is the constant reflecting the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Hixson-Crowell cube root law

It is the law that represents idea about the evaluation of drug release pattern changes with the surface area and the diameter of the particles/tablets. It is mentioned as the cube root of the percentage of drug remaining in the matrix vs time. The equation may be as follows:

$Q0^{1/3} - Qt^{1/3} = kHC \times t$---------- (4)

Where,

Q0 = Initial amount of the drug in the tablets.

Qt = The amount of drug release in time‘t’.

kHC = The rate constant for the Hixson-Crowell cube root law.

Korsmeyer–Peppas equation

Korsmeyer et al developed a simple, semi-empirical model relating exponentially the drug release to the elapsed time (Korsmeyer et al., 1983) [14] .The equation may be as follows:

$Q/Q0 = Ktn$ ---------- (5)

Where,

Q/Q0 = The fraction of drug released at time‘t’, k = Constant comprising the structural geometric

Characteristics, n = The diffusion exponent that depends on the release mechanism.

If $n \leq 0.5$, the release mechanism follows a Fickian diffusion, and if $0.5<n<1$, the release follows a non-Fickian diffusion or anomalous transport (Peppas, 1985). The drug release follows zero order drug release and case II transport if n=1. But when n>1, then the release mechanism is super case II transport. This model is used in the polymeric dosage form when the release mechanism is unknown or more than one release phenomena is present in the preparation.

RESULTS AND DISCUSSION:

Table-4: Physical Properties of Ranolazine containing matrix tablets

Physical properties of Ranolazine matrix tablets			
Formulation Code	Average Hardness (± SD) (kp) (n=10)	Average Thickness (mm) (n=5)	Average Length x Width (mm) (n=5)
RHPMC50F1	21.8 ± 0.01	7.69	19.02x8.80
RHPMC50F2	23.2 ± 0.02	7.70	19.01x8.80
RHPMC50F3	24.7 ± 0.02	7.68	19.02x8.81
RHPMC50F4	25.3 ± 0.01	7.69	19.00x8.80
RHPMC50F5	26.5 ± 0.01	7.70	19.01x8.82
RHPMC50F6	27.2 ± 0.02	7.72	19.01x8.81

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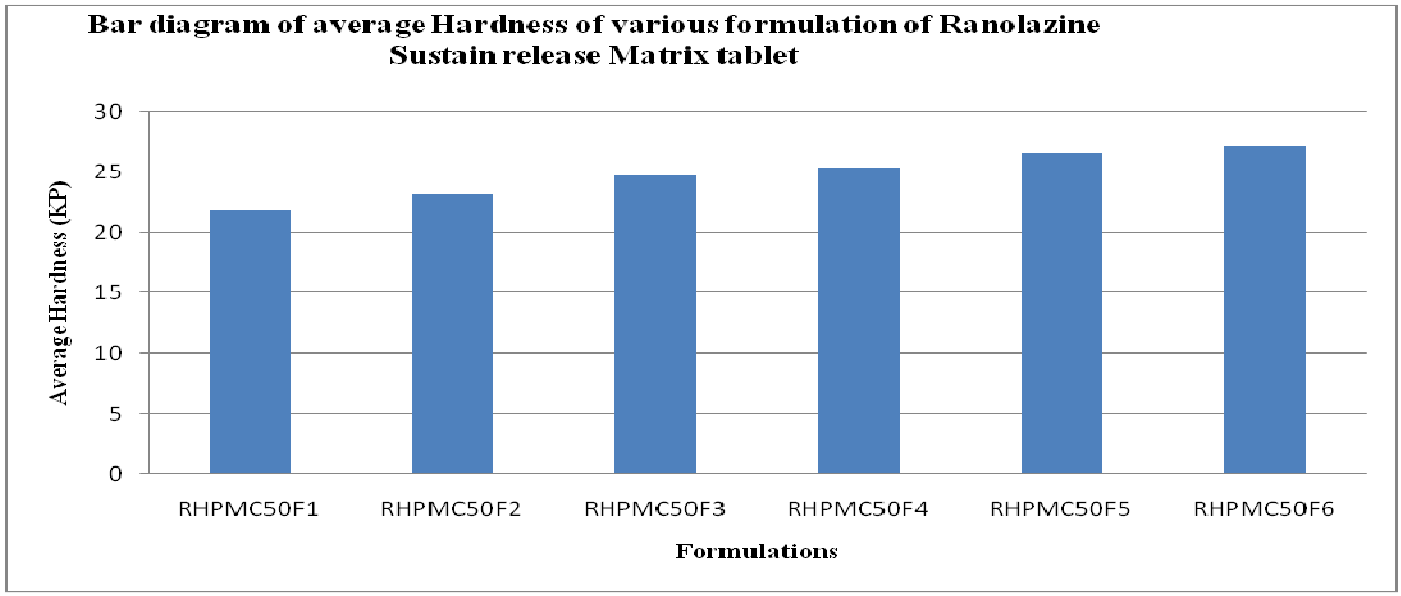

Figure 1: Bar diagram of average hardness of various formulations of Ranolazine sustain release matrix tablets.

Effect of HYPROMELLOSE 50 (HPMC 50 cps) on release pattern of Ranolazine

HYPROMELLOSE 50 (HPMC 50 cps) matrix tablet containing Ranolazine as active ingredient was prepared according to table-2 with formulation code RHPMC50F1, RHPMC50F2, RHPMC50F3, RHPMC50F4, RHPMC50F5, RHPMC50F6. The release profile of Ranolazine was monitored up to 12 hours in same way. The zero order release pattern is shown in figure 2. Figure 3 represents the Higuchi impact. First order release kinetics is shown in figure 4 and Korsmeyer in figure 5.

From the graphs, release kinetics of Ranolazine containing HYPROMELLOSE 50 matrix tablet of six formulations was obtained. The 100 % release of Ranolazine from the formulation RHPMC50F1, RHPMC50F2, RHPMC50F3, RHPMC50F4, RHPMC50F5 and RHPMC50F6 was found within 6, 9, 10, 11, 11 and 12 hour respectively. It has been observed that the release rate and extend of drug release was found to be inversely related to the amount of HPMC 50 cps present in the matrix structure, i.e. the drug release increased with decrease in the polymer content of the matrix tablet.

It is observed that the formulation containing 5%, 10% and 15% polymer releases more than 50% drug within first hour. So, these formulations do not sustain the release of drug significantly. Only the formulation containing 30% polymer sustains the release of drug up to 12 hrs. No formulations of this class shows reproducible release pattern which may be due to low viscosity of polymer. The formulation RHPMC50F2 follows first order release whereas the remaining follow Higuchi model. All the formulation indicates Fickian diffusion mechanism.

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Table-5: Zero order release profile of Ranolazine from HYPROMELLOSE 50 matrices.

Time (hrs)	RHPMC50F1	RHPMC50F2	RHPMC50F3	RHPMC50F4	RHPMC50F5	RHPMC50F6
0	0	0	0	0	0	0
1	72.85	60.93	53.15	44.86	40.38	36.85
2	78.60	71.96	65.07	58.81	56.07	47.29
3	84.54	79.14	74.02	69.56	62.13	58.64
4	89.46	85.40	78.88	79.74	72.95	67.73
5	95.12	87.46	83.46	81.74	77.93	73.17
6	99.98	93.47	84.54	83.32	81.31	79.11
7	98.84	94.78	90.61	89.43	87.49	85.46
8	97.87	99.13	93.47	92.86	91.27	88.52
9	97.64	99.93	97.98	96.04	93.22	92.89
10	97.13	98.84	99.84	97.73	94.82	94.21
11	96.95	97.64	98.87	99.47	99.00	97.87
12	96.84	97.53	97.75	97.81	97.65	99.76

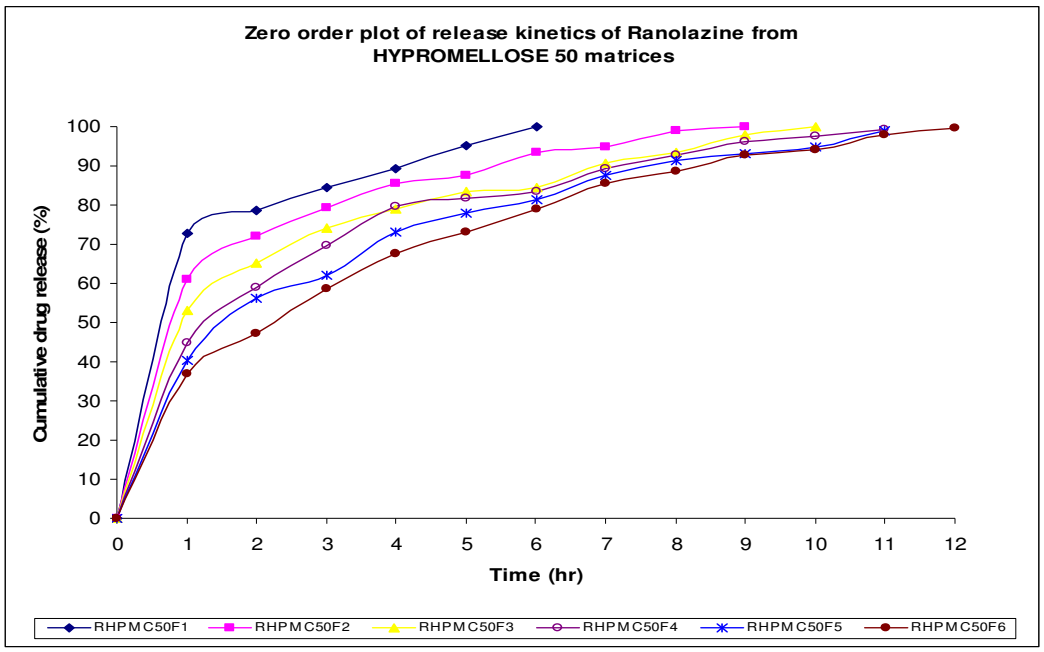

Figure-2: Zero order plot of release kinetics of Ranolazine from HYPROMELLOSE 50 matrices.

Table-6: Higuchi release profile of Ranolazine from HYPROMELLOSE 50 matrices.

SQRT	RHPMC50F1	RHPMC50F2	RHPMC50F3	RHPMC50F4	RHPMC50F5	RHPMC50F6
0	0	0	0	0	0	0
1.0000	72.85	60.93	53.15	44.86	40.38	36.85
1.4142	78.60	71.96	65.07	58.81	56.07	47.29
1.7321	84.54	79.14	74.02	69.56	62.13	58.64
2.0000	89.46	85.40	78.88	79.74	72.95	67.73
2.2361	95.12	87.46	83.46	81.74	77.93	73.17
2.4495	99.98	93.47	84.54	83.32	81.31	79.11
2.6458	98.84	94.78	90.61	89.43	87.49	85.46
2.8284	97.87	99.13	93.47	92.86	91.27	88.52
3.0000	97.64	99.93	97.98	96.04	93.22	92.89
3.1623	97.13	98.84	99.84	97.73	94.82	94.21
3.3166	96.95	97.64	98.87	99.47	99.00	97.87
3.4641	96.84	97.53	97.75	97.81	97.65	99.76

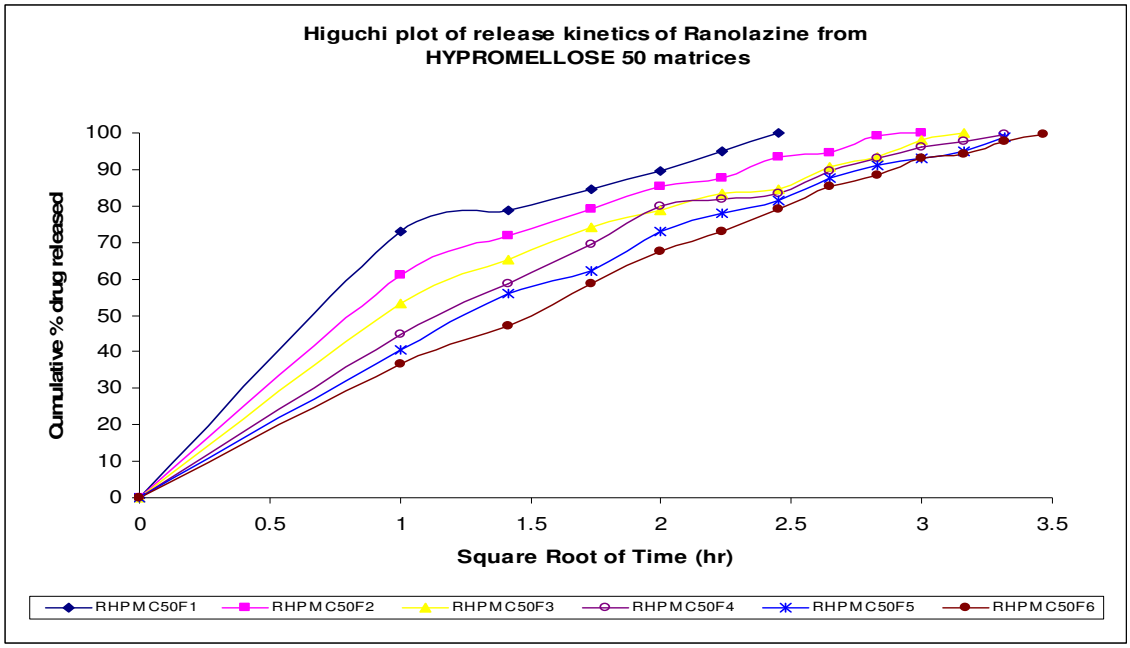

Figure-3: Higuchi plot of release kinetics of Ranolazine from HYPROMELLOSE 50 matrices.

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Table-7: First order release kinetics of Ranolazine from HYPROMELLOSE 50 matrices

Time (hrs)	RHPMC50F1	RHPMC50F2	RHPMC50F3	RHPMC50F4	RHPMC50F5	RHPMC50F6
0	2.0000	2.0000	2.0000	2.0000	2.0000	2.0000
1	1.4338	1.5919	1.6707	1.7415	1.7754	1.8003
2	1.3305	1.4477	1.5431	1.6148	1.6428	1.7219
3	1.1891	1.3193	1.4146	1.4834	1.5782	1.6166
4	1.0227	1.1643	1.3246	1.3066	1.4321	1.5088
5	0.6881	1.0983	1.2186	1.2614	1.3438	1.4287
6	-1.8001	0.8152	1.1891	1.2223	1.2716	1.3199
7	0.0643	0.7176	0.9728	1.0239	1.0972	1.1626
8	0.3287	-0.0587	0.8152	0.8534	0.9411	1.0599
9	0.3730	-1.1365	0.3048	0.5979	0.8315	0.8517
10	0.4586	0.0643	-0.7991	0.3569	0.7145	0.7628
11	0.4838	0.3730	0.0534	-0.2753	0.0014	0.3287
12	0.4998	0.3935	0.3514	0.3402	0.3708	-0.6116

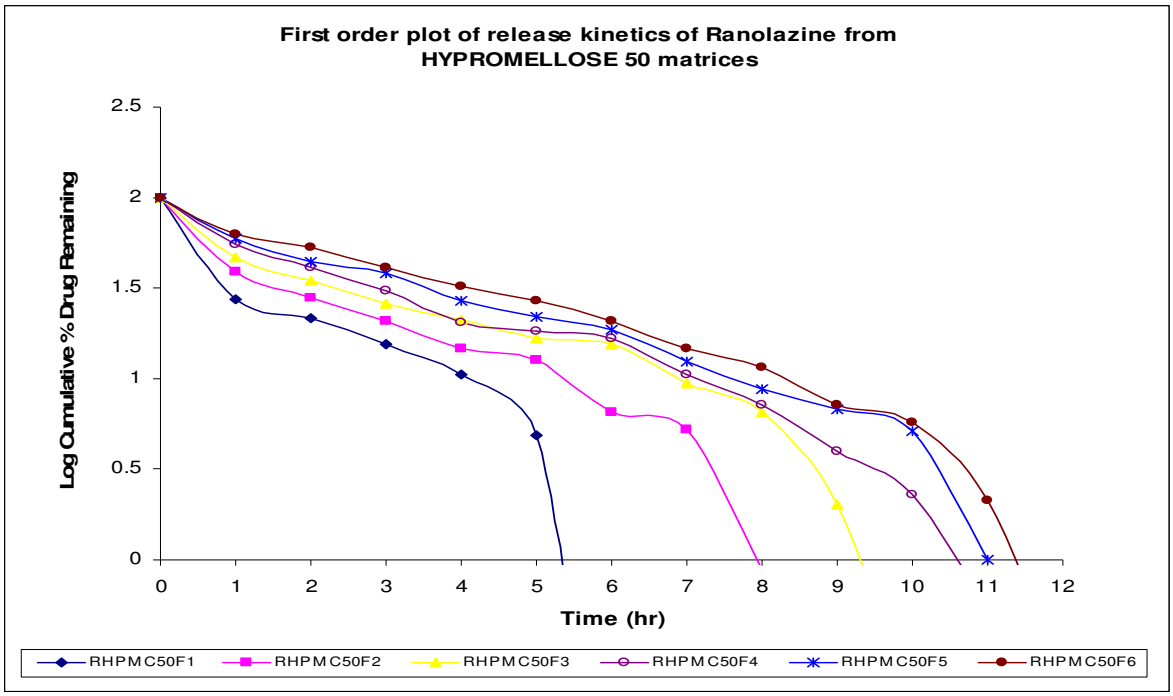

Figure-4: First order plot of release kinetics of Ranolazine from HYPROMELLOSE 50 matrices.

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Table-8: Korsmeyer release kinetics of Ranolazine from HYPROMELLOSE 50 matrices.

Log Time	RHPMC50F1	RHPMC50F2	RHPMC50F3	RHPMC50F4	RHPMC50F5	RHPMC50F6
0	1.8624	1.7848	1.7255	1.6519	1.6062	1.5665
0.3010	1.8954	1.8571	1.8134	1.7695	1.7487	1.6748
0.4771	1.9271	1.8984	1.8694	1.8424	1.7933	1.7682
0.6021	1.9516	1.9315	1.8970	1.9017	1.8630	1.8308
0.6990	1.9783	1.9418	1.9215	1.9124	1.8917	1.8643
0.7782	1.9999	1.9707	1.9271	1.9207	1.9101	1.8982
0.8451	1.9949	1.9767	1.9572	1.9515	1.9420	1.9318
0.9031	1.9906	1.9962	1.9707	1.9679	1.9603	1.9470
0.9542	1.9896	1.9997	1.9911	1.9824	1.9695	1.9680
1.0000	1.9873	1.9949	1.9993	1.9900	1.9769	1.9741
1.0414	1.9866	1.9896	1.9951	1.9977	1.9956	1.9906
1.0792	1.9861	1.9891	1.9901	1.9904	1.9897	1.9989

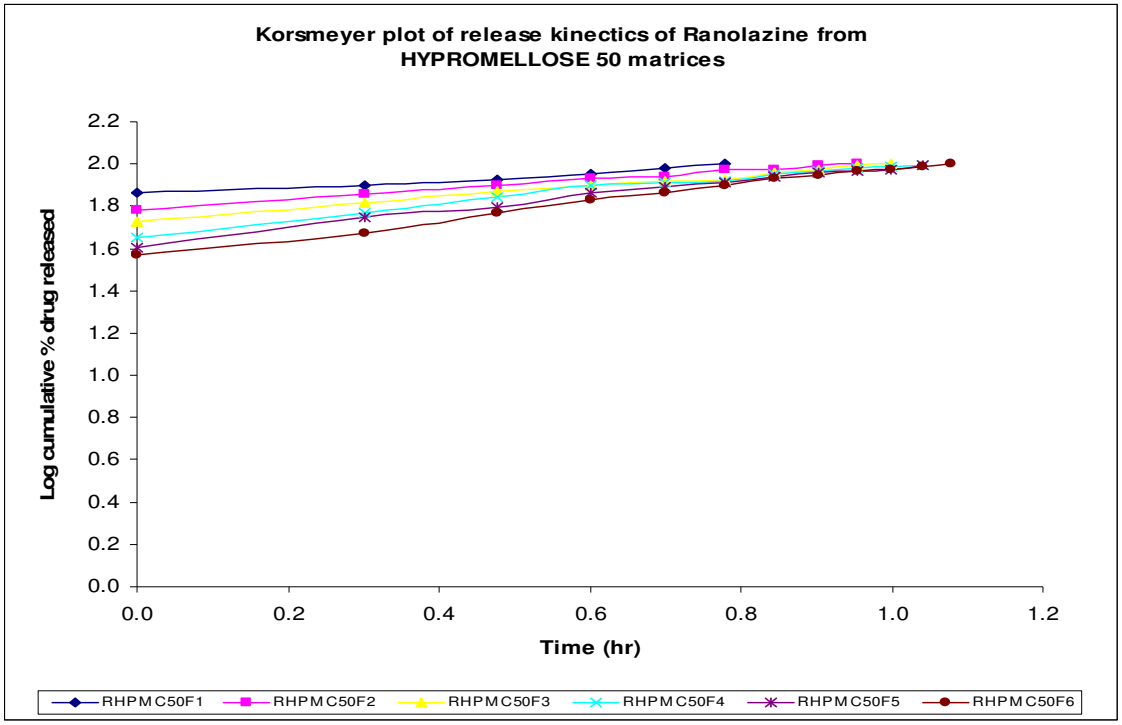

Figure-5: Korsmeyer plot of release kinetics of Ranolazine from HYPROMELLOSE 50 matrices.

Table-9: Release kinetics of Ranolazine from HYPROMELLOSE 50 matrices.

Formulation code	Zero order		First order		Higuchi		Korsmeyer	
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
RHPMC50F1	0.6471	12.6920	0.6847	0.4714	0.8824	38.0900	0.9660	0.1759
RHPMC50F2	0.6659	8.0354	0.9099	0.2057	0.8950	30.4370	0.9960	0.2270
RHPMC50F3	0.7221	7.2957	0.8020	0.2060	0.9269	28.7260	0.9946	0.2683
RHPMC50F4	0.7561	6.9150	0.9235	0.1701	0.9465	28.4250	0.9810	0.3271
RHPMC50F5	0.8050	7.1035	0.9193	0.1450	0.9701	28.6490	0.9900	0.3665
RHPMC50F6	0.8484	6.8566	0.8490	0.1666	0.9853	28.5500	0.9939	0.4139

CONCLUSION

The purpose of this study was to develop sustain release solid dosage form of Ranolazine. For this reason, polymer has been used during the course of experiment to find out the release pattern. Ranolazine matrix tablets were prepared utilizing polymer as a carrier. Physical properties of all formulations were found to be satisfactory for the manufacturing. The cumulative percent of release of Ranolazine from all these formulations were plotted against time to get zero order plot (Figure 2). The cumulative percent of release of Ranolazine were plotted against Squre Root of Time (SQRT) to obtain Higuchi kinetics (Figure 3). The log % remaining was plotted against time to get first order kinetics (Figure 4). Again Log cumulative percent drug released were plotted against log time to get Korsmeyer plot (Figure 5).

The release data were treated in different fashion and their kinetic values were calculated to evaluate the release pattern (Table 9). The slope of Higuchi plots were calculated to get their release rate. The effect of polymer loading was also calculated. The best fit release kinetics with highest correlation coefficients was achieved with Higuchi model followed by zero order, first order and Korsmeyer equation. The release pattern of Ranolazine from low viscosity HYPROMELLOSE was mostly followed fickian transport mechanism. Compared to conventional tablets, release of Ranolazine from matrices prepared with the polymer was prolonged.

From the experimental point of view, it is clear that there is a chance of modulate the rate and extend of drug release with the polymer and formulations prepared in this experiment could be useful for the preparation by judicious combination between drug and release modifier. A further advance study in the *in-vitro* condition can justify the release pattern observed from this current work and a standard drug release profile of Ranolazine sustain release tablet could be commercially justified.

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