DESIGN AND IN VITRO EVALUATION OF NOVEL NICORANDIL SUSTAINED RELEASE MATRIX TABLETS BASED ON COMBINATION OF HYDROPHILIC AND HYDROPHOBIC MATRIX SYSTEM

Bhupendra G.Prajapati*, Patel Krunal R.
S.K.Patel College of Pharmaceutical Education and Research,
Ganpat University, Kherva-382711, Mehsana, Gujarat State, INDIA.
*****E-mail: bhupen_27@yahoo.co.in

ABSTRACT

Conventional drug delivery system for treating the anginal are not much effective as the drug do not reach the site of action in appropriate concentration. Thus an effective and safe therapy of this anginal disorder using specific drug delivery system is a challenging task to the pharmaceutical technologists. Most commonly used method of modulating the drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance. Formulation of Nicorandil matrix tablet was prepared by the polymers blend with to get desirable release profile. Formulated tablets were also characterized by parameters like thickness, weight variation test, drug content uniformity, hardness, friability and the in-vitro release rate profile was compared with the marketed product's release profile with the help of similarity factor (f_2) value. Formulation prepared with HPMC K200M: Eudragit RSPO (1:1) indicates 94.46% of drug release at 22 hrs and it has similarity factor (f2) value 68.07. Hydrophilic and Hydrophobic polymer combination showed 22 hrs release using combination of hydrophilic or hydrophobic polymers.

KEYWORDS: Nicorandil, HPMC K200M, Eudragit RSPO, Ethyl cellulose, Sustained release, Matrix tablets.

INTRODUCTION

Most common cardiovascular diseases are hypertension and angina pectoris, which require constant monitoring. Potassium channel openers are presently most important class of drug for hypertension and angina pectoris. First therapeutic drug shown to possess an ability to hyperpolarize smooth muscle cell membranes is nicorandil, a potent coronary vasodilator.[1] Nicorandil has a short half-life, and the usual oral dosage regimen is 5 to 40 mg taken 2 to 4 times a day. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained-release formulation of nicorandil is desirable. Drug is freely soluble in water, and hence judicious selection of release-retarding excipients is necessary to achieve a constant in vivo input rate of the drug. Most commonly used method of modulating the drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.[2] hence, in the present work, an attempt has been made to develop once-daily sustained-release matrix tablets of nicorandil using hydrophilic matrix materials such as hydroxypropylmethylcellulose (HPMC). Drug release for extended duration, particularly for highly water-soluble drugs, using a hydrophilic matrix system is restricted because of rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs with high water solubility, hydrophobic polymers are suitable, along with a hydrophilic matrix for developing sustained-release dosage forms. Hydrophobic polymers provide several advantages, ranging from good stability at varying pH values and moisture levels to well-established safe applications. Therefore, in this study, the hydrophobic polymers like ethylcellulose (EC), Eudragit RSPO were used. Main objective of study is to formulate hydrophilic and hydrophobic matrix systems by polymer material to investigate the effect of both[3].

The objective of the present study was to develop hydrophilic polymer (HPMC K200M) and hydrophobic polymer (Ethyl cellulose, Eudragit RSPO) based Nicorandil matrix sustained release tablet which can release the drug up to time of 24 hrs.

MATERIALS AND METHODS:

Materials

Nicorandil, HPMC K 200M, Ethyl cellulose, Eudragit RSPO, DCP, Aerosil, Mg.stearate.

Methods

Preparation of Tablets

Nicorandil SR matrix tablets were prepared by direct compression technique. Drug was passed through 40# sieve. HPMC K 200M, Eudragit RSPO and Ethyl cellulose were passed through 30# sieve. All other ingredients were passed through 40# sieve. All ingredients were mixed for 15-20 min. After mixing, Mg. stearate (60# sieve), was added to mixer blend and mix again for 3-5 min. Prepared blend was compressed (10/30 diameter, flat punches) using Hydraulic Pellet Press Machine (Type: KP-587, PCI services, Mumbai). Each tablet contains 20 mg of Nicorandil and other pharmaceuticals ingredients as listed in Table 1.

Evaluation of powder

Angel of Repose

Angel of Repose of powder was determined by the funnel method. Accurately weight powder blend were taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angel of repose was calculated using the following equation. [4, 5]

$$\tan \alpha = h/r$$

Density

a) Bulk density (BD): Weigh accurately 25 g of drug, which was previously passed through 20# sieve and transffered in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsetteled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula. [4, 5]

Bulk density = Weigh of powder/ Bulk volume

b) Tapped density (TD): Weigh accurately 25 g of drug, which was previously passed through 20# sieve and transffered in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tap volume (V_2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V_2). Calculate the tapped bulk density in gm/ml by the following formula. [4, 5]

Tapped density = Weigh of powder / Tapped volume

Carr's Index

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down [4, 5]. The formula for Carr's index is as below:

Carr's index (%) = [(TD-BD)*100] / TD

Hausner's Ratio

Hausner's Ratio is a number that is correlated to the flowability of a powder. [4, 5]

Husner's Ratio = TD / BD

Table 1: Composition of Sustained release tablets of Nicorandil*

Ingredients	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
Drug(Nicorandil)	20	20	20	20	20	20	20	20	20	20	20	20
HPMC K 200M	20	30	40	-	-	-	-	-	-	-	-	-
EC	-	-	-	15	20	25	-	-	-	-	-	-
HPMC K 200M: EC	-	-	-	-	-	-	15:15	10:20	20:10	-	-	-
HPMC K 200M: Eudragit RSPO	-	-	-	-	-	-	-	-	-	15:15	10:20	20:10
Dibasic Calcium phospate anhydrous	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	**155 mg**											

*qs indicate quantity sufficient.

Table 2: Evaluation of powder Blend*

Powder Blend	Angel of Repose	Bulk density	Tapped density	Carr's index (%)	Hausner's ratio
A1	24.12	0.483	0.584	17.29	1.20
A2	23.33	0.487	0.564	13.65	1.16
A3	25.56	0.475	0.586	18.94	1.23
A4	24.89	0.484	0.579	16.41	1.19
A5	23.14	0.497	0.576	13.72	1.16
A6	24.15	0.482	0.566	14.84	1.17
A7	26.13	0.491	0.587	16.35	1.19
A8	25.64	0.483	0.578	16.43	1.19
A9	25.86	0.489	0.584	16.27	1.19
A10	26.54	0.493	0.575	14.26	1.17
A11	25.47	0.496	0.583	14.92	1.18
A12	25.56	0.499	0.594	15.99	1.19

***all results were average of n=3 observation

Evaluation of Tablets

Thickness

Thickness of the tablets was determined using a vernier caliper (For-bro engineers, Mumbai, India).[6]

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Sartorius electronic balance: Model CP-2245, Labtronic), and the test was performed according to the official method.[7]

Drug content (Assay)

Drug content was determined by taking an accurately weight amount of powdered Nicorandil with water and solution was filtered through 45µ membrane. The absorbance was measured at 262 nm, using double beam UV visible spectrophotometer.[8]

Hardness

Hardness of the tablets was determined using a hardness testing apparatus (Monseto Type). A tablet hardness of about 5-6 kg/cm^2 is considered adequate for mechanical stability.[9]

Friability

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai, India). Tablets of a known weight (W_0) or a sample of tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1% w/w.[10]

% Friability = $(W_0\text{-}W)/ W_0 \times 100$

Table 3: Evaluation of Tablets*

Batches	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Avg.wt (mg)	Assay (%)
A1	5.1±0.1	2.2±0.1	0.062±0.003	155.8±1.2	99.47±0.30
A2	5.4±0.1	2.2±0.1	0.056±0.002	155.2±0.6	98.98±0.51
A3	5.4±0.4	2.4±0.06	0.062±0.005	157.5±1.1	99.54±0.16
A4	5.6±0.2	2.2±0.1	0.062±0.004	156.4±1.7	98.32±0.58
A5	5.2±0.1	2.2±0.2	0.059±0.002	155.7±1.1	98.66±0.96
A6	5.4±0.3	2.5±0.2	0.058±0.004	156.2±1.9	99.70±0.15
A7	6.0±0.3	2.2±0.05	0.063±0.001	156.3±1.5	98.82±0.56
A8	5.5±0.3	2.2±0.1	0.062±0.005	152.3±0.8	99.11±0.64
A9	6.2±0.3	2.3±0.2	0.063±0.005	155.3±0.6	99.39±0.52
A10	5.8±0.4	2.3±0.1	0.058±0.005	157.7±0.4	99.76±0.10
A11	6.1±0.6	2.2±0.1	0.060±0.002	155.0±0.5	98.38±0.46
A12	6.5±0.2	2.2±0.2	0.064±0.002	154.8±1.4	99.49±0.16

*above values shows Mean ± S.D

Figure 1: Cumulative percentage Drug release from batch A1 to A6

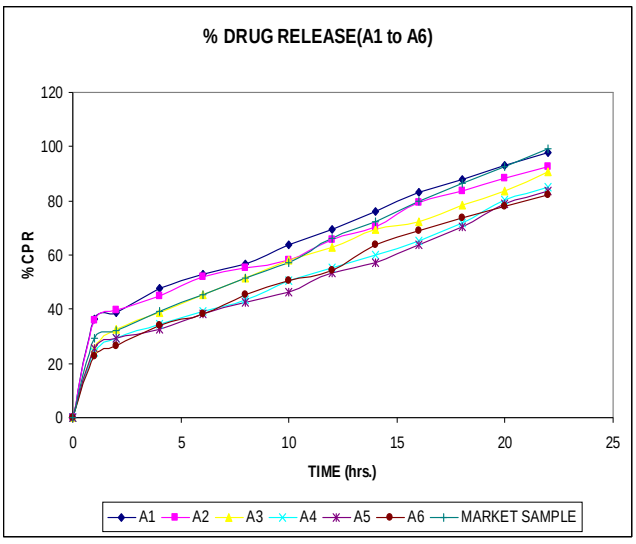
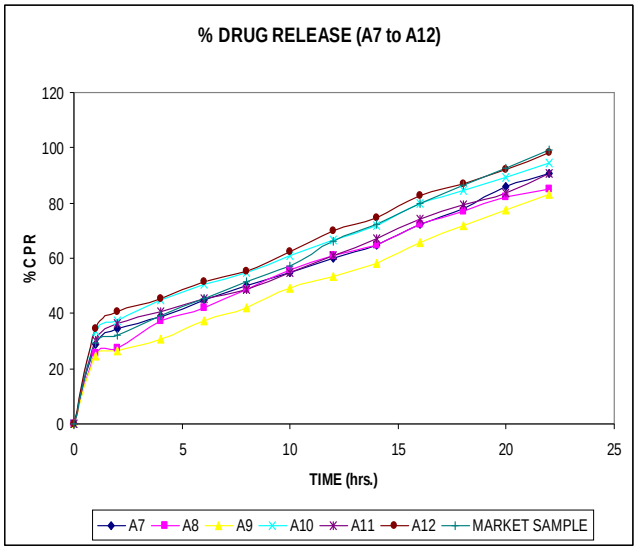


Figure 2: Cumulative percentage Drug release from batch A7 to A12



In Vitro Release Studies

In vitro dissolution studies were carried out using USP apparatus type II (at 75 rpm. Dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hours and phosphate buffer pH 6.8 from 3 to 24 hours, maintained at 37°C ± 0.5°C. Drug release at different time intervals was measured by UV-visible spectrophotometer at 262 nm. *In vitro* drug release profile of all batches was compared with market product drug release profile[11]shown in fig.1, 2.

RESULTS AND DISCUSSION

Nicorandil is a potent potassium channel opener and coronary vasodilator presently considered an important drug for the treatment of hypertension and angina pectoris. In case of cardiovascular diseases, successful treatment can be achieved only by maintaining blood pressure at a normal physiological level, and for this a constant and uniform supply of drug is desired. Multiple dose administration at intervals of 6 to 8 hours is difficult for a hypertensive patient or a patient with angina, which can lead to patient noncompliance. Nicorandil with all evident advantages proved to be a suitable candidate for development of a controlled-release dosage form. In the present study, HPMC K200M, which was used in hydrophilic matrix drug delivery systems, have been employed to formulate sustained-release tablets of nicorandil but alone it did not gives a good results. So it was used in combination with hydrophobic polymer like Eudragit RSPO and Ethyl cellulose.

Batches of Nicorandil were prepared with HPMC K200 M, Ethyl Cellulose, and HPMC K 200M-Ethyl cellulose combination, and HPMC K200M- Eudragit RSPO combination. Prepared powder blend of different batches were evaluated. Result showed that powder blend have, Angle of repose range from 23 to 27, Carr's index range from 13 to19 and Hausner's ratio range form 1.16 to 1.23, which indicate good flow property. Hardness, thickness and friability were found to be in range of 5.1 to 6.5, 2.2 to 2.5 and 0.056 to 0.064 respectively, which is in acceptable criteria in tablet formulation.

Results of angle of repose (<30) indicate good flow properties of the powder.[12,13] This was further supported by lower Carr's index values. Generally, compressibility index values up to 15-21% result in good to excellent flow properties.[12] Powder density and hardness are often interrelated properties. In addition, powder density may influence compressibility, tablet porosity, dissolution, and other properties. Drug content in the weighed amount of powder of all formulations was found to be uniform. All these results indicate that the powder possessed satisfactory flow properties, compressibility, and drug content. Tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, drug content, hardness, friability, and in vitro dissolution. All formulations showed uniform thickness. In a weight variation test, pharmacopoeias limit for the percentage deviation for tablets of more than 155 mg is ±5%. Average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements.[14] Good uniformity in drug content was found among different batches of tablets and percentage of drug content was more than 95%.Tablet hardness is not an absolute indicator of strength.[15] Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, percentage friability for all formulations was below 1%, indicating that friability was within the prescribed limits.[15]All tablet formulations showed acceptable Pharmacotechnical properties and complied with the in-house specifications for weight variation, drug content, hardness, and friability.

All Batches were evaluated for the cumulative drug release and similarity factor (f2) value. Nicorandil tablets were prepared using plain hydrophilic and plain hydrophobic as well as blend of Hydrophilic-hydrophobic combination. From *in vitro* dissolution profile, the batch (A1) and batch (A2) prepared with 15% and 20% concentration of hydrophilic polymer (HPMC K200M), indicates initially release was not superimposed to market sample. These two batches shows similarity value 60.73 and 62.81. Batch (A3) prepared with 25% concentration of HPMC K200M showed 90.88 % release at 22 hrs and similarity value is 61.59. Increase in concentration of HPMC may result in increase in the tortuosity or gel strength of the polymer.[12-15]

From *in–vitro* dissolution profile of batches (A4 to A6) prepared with three different concentration of ethyl cellulose, the drug release was nearer to 85% in all batches at the end of 22 hrs. All batches have f_2 values less than 50. Because of hydrophobicity of Ethyl-cellulose, it retards release for longer period.[16-18]

Batches A7, A8, A9 were prepared with the blend of HPMC K200M and Ethylcellulose respectively in the ratio of 1:1, 1:2 and 2:1. Batches 7 and 8 showed drug release of 85 to 90% at the end of 22 hrs and have similarity factor values more than 50. While in batch 9 releases was about 83 % and have similarity factor value less than 50 showed insignificant batch.

Batch A10, A11 and A12 was prepared with blend of HPMC K200M and Eudragit RSPO in the ratio of 1:1, 1:2 and 2:1 respectively, where drug release was about 94-98%. Batch A10 showed highest similarity factor values (f_2 = 68.07).

To know mechanism of drug release from these formulations, data were treated according to first-order (log cumulative percentage of drug remaining vs time), Higuchi's[23] (cumulative percentage of drug released vs square root of time), and Korsmeyer et al's[24] (log cumulative percentage of drug released vs log time) equations along with zero order (cumulative amount of drug released vs time) pattern. As clearly indicated in (Figure1, 2), the formulations did not follow a zero-order release pattern. The release rate kinetic data for all the other equations can be seen in Table 4.

Table 4: Kinetic Values Obtained From Different Plots of Formulations, A1 to A12

Tablets	First-Order Plots*	Higuchi's Plots†	Korsmeyer et al's Plots‡	
	Regression Coefficient (R^2)	Regression Coefficient (R^2)	Slope (n)	Regression Coefficient (R^2)
A1	0.9874	0.9835	0.3187	0.9710
A2	0.9879	0.9751	0.2987	0.9624
A3	0.9700	0.9902	0.3865	0.9894
A4	0.9880	0.9743	0.3833	0.9724
A5	0.9934	0.9632	0.3675	0.9564
A6	0.9783	0.9855	0.4129	0.9818
A7	0.9880	0.9733	0.3487	0.9683
A8	0.9728	0.9915	0.3988	0.9853
A9	0.9916	0.9747	0.3967	0.9654
A10	0.9860	0.9840	0.3278	0.9747
A11	0.9913	0.9730	0.3329	0.9624
A12	0.9890	0.9820	0.3237	0.9705

*First-order equation, Log C = log Co – Kt/2.303.
†Higuchi's equation, $Q = Kt_{1/2}$.
‡Koresmeyer et al's equation, $Mt/M\alpha = Kt^n$.

When the data were plotted according to the first-order equation, the formulations showed a fair linearity, with regression values between 0.9700 and 0.9934. Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into the in vitro study fluid depending on the concentration. As gradient varies, the drug is released, and the distance for diffusion increases. 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.[24] In our experiments, *in vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity (R^2: 0.9632 to 0.9915). To confirm diffusion mechanism, data were fit into Korsmeyer et al's equation. Formulations A1 to A12 showed good linearity (R^2: 0.9564 to 0.9894), with slope (n) values ranging from 0.2987 to 0.4129, indicating that diffusion is the dominant mechanism of drug release with these formulations.

CONCLUSION

Hydrophilic matrix of HPMC alone could not control the Nicorandil release effectively for 24 hours. It is evident from the results that a matrix tablet prepared with hydrophilic polymer and hydrophobic polymer is a better system for once-daily sustained release of a highly water-soluble drug like Nicorandil. All formulations exhibited diffusion-dominated drug release.

REFERENCE:

1. Frydman MA, Chapelle P, Diekmann H. Pharmacokinetics of nicoran-dil. Am J Cardiol. 1989; 20:25-33.
2. Lordi GN. Sustained release dosage forms. In: Lachman L, Liberman HA, Kanig JL, eds. The Theory and Practice of Industrial Pharmacy: Varghese Publishing House; Mumbai, India 1987:430-456.
3. Brabander CD, Vervacet C and Remon JP. Development and evaluation of sustained release matrix tablet. J. Controlled Release. 2002; 77(1): 245-258.
4. Rajeev Garg; Pre-formulation: A need for dosage form design; pharmainfo. Net; 2008, vol.6.
5. G.Banker and C.T. Rhodes, Modern Pharmaceutics, Marcel Dekker, Inc., 2000.
6. The British Pharmacopoeia, department of health/by stationary office on behalf of the medicine and health care product regulatory agency, crown copy right, 2005; 5th Ed. 1303-1304, 2588-2589, A133.
7. Krishanaiah YS, Lath K, Nageshwara L, Karthikeyan RS, Bhaskar Pand Satyanarayana V. Development of colon target oral guar gum matrix tablet of Albendazole for the treatment of Helminthiasis. Indian J. Pharm. Sci. 2003; 65 (4): 378-385
8. Roldy RK, Midovert S and Redlen S. Once dailymatrix tablet of azithromicine in-vitro and in-vivo evaluation. Pharm. Sci. Tech. 2003; 4(4):55-59

9. British Pharmacopoeia, vol. 2. Her Majesty's stationary office, London,England.2000: 266-268
10. Lachman.L, Liberman.A, Kinig.J.L. The theory and practice of industrial Pharmacy, 4th edition, Varghese publishing house, Bombay.1991:67-68
11. Paulo Costa , Jos manuel Sousa lobo, Modeling and comparison of dissolution profiles, European journal of pharmaceutical sciences;2001,12:123-133
12. Aulton ME, Wells TI. Pharmaceutics: The Science of Dosage Form Design. London, England: Churchill Livingstone; 1988.
13. Martin A. Micromeritics. In: Martin A, ed. Physical Pharmacy. Balti-more, MD: Lippincott Williams & Wilkins; 2001:423-454.
14. Pharmacopoeia of India. New Delhi: Ministry of Health and Family Welfare, Government of India, Controller of Publications; 1996.
15. Banker GS, Anderson LR. Tablets. In: Lachman L, Liberman HA, Kanig JL, eds. The Theory and Practice of Industrial Pharmacy. Mumbai, India: Varghese Publishing House; 1987:293-345.
16. J Heller, Use of Polymers in controlled release of active agents, controlled drug delivery. Fundamentals and applications, J R Robinson, V H L Lee, Marcel Dekker; New York, 1987:179-212.
17. M A Longer, J R Robinson, Sustained –release drug delivery System. Remington's Pharmaceutical Sciences, 18th edition; 1990:1676-1693.
18. P Colombo, Swelling-controlled release in hydrogel matrices for oral Route. Adv.Drug Del. Rev.; 1993, 11:37-57.
19. H Lapidus, N G Lordi, Drug Release From Compressed Hydrophilic Matrices.,J. Pharm. Sci.;1968,57(8):1292-1301.
20. Muschert S., Siepmann F., Leclercq B.; drug release mechanism from ethyl cellulose: PVA-PEG graft copolymer coated pellets; European journal of pharmaceutics and bio pharmaceutics; 2009, 72(1); 130-137.
21. Quinten T., Gonnisen Y., Adriaens E.; Development Of Injection Moulded Matrix Tablet Based On Mixture Of Ethyl Cellulose And Low Substituted Hydroxyl Propylcellulose; European journal of pharmaceutical science; 2009,Feb 21
22. Chandran S., A Asghar L., Mantha N.; design and evaluation of ethyl cellulose based matrix tablets of ibuprofen with pH modulated release kinetics; 2008; vol.70; 5; 596-602.
23. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963; 52:1145-1149.
24. Korsmeyer RW, Gurny R, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983; 15:25-35.

****