Review Article

REVIEW: IN-VITRO DRUG RELEASE CHARACTERIZATION MODELS

Gautam Singhvi, Mahaveer Singh

Address for Correspondence

Birla Institute of Technology and Science, Pilani Rajasthan 333 031

Email:singhvigautam@gmail.com

INTRODUCTION

Drug release is the process by which a drug leaves a drug product and is subjected to absorption, distribution, metabolism, and excretion (ADME), eventually becoming available for pharmacological action. Drug release is described in several ways. *Immediate release* drug products allow drugs to dissolve with no intention of delaying or prolonging dissolution or absorption of the drug. *Modified release* dosage forms include both delayed and extended release drug products. *Delayed release* is defined as the release of a drug at a time other than immediately following administration. *Extended release* products are formulated to make the drug available over an extended period after administration. Finally, *controlled release* includes extended and pulsatile release products. *Pulsatile release* involves the release of finite amounts of drug at distinct time intervals that are programmed into the drug product.

In vitro dissolution has been recognized as an important element in drug development. Under certain conditions it can be used as a surrogate for assessment of bioequivalence. Several theories/kinetics models describe drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where ft is a function of t (time) related to the amount of drug dissolved from the pharmaceutical dosage system. The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of a generic equation that mathematically translates the dissolution curve in the function of some other parameters related with the pharmaceutical dosage forms. In some cases, that equation can be deduced by a theoretical analysis of the process, as for example, in zero order kinetics. In most cases, with tablets, capsules, coated forms or prolonged release forms that theoretical fundament does not exist and some times a more adequate empirical equation is used. The kind of drug, its polymorphic form, crystallinity, particle size, solubility and amount in the pharmaceutical dosage form can influence the release kinetic. A water soluble drug incorporated in a matrix is mainly released by diffusion, while for a low water soluble drug the self – erosion of the matrix will be the principle release mechanism.

THEORIES OF DISSOLUTION

Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of liquid/solid interface, temperature and solvent composition. The basic step in drug dissolution is the reaction of the solid drug with the fluid and/or the components of the dissolution medium. This reaction takes

place at the solid—liquid interface and therefore dissolution kinetics are dependent on three factors, namely the flow rate of the dissolution medium toward the solid—liquid interface, the reaction rate at the interface, and the molecular diffusion of the dissolved drug molecules from the interface toward the bulk solution, Figure 1.

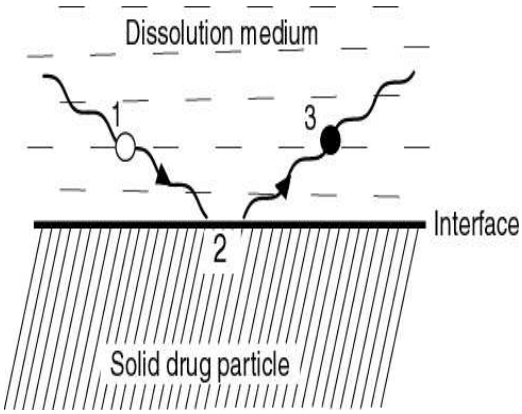

Figure 1: The basic steps in the drug dissolution mechanism. (1) The molecules (◦) of solvent and/or the components of the dissolution medium are moving toward the interface; (2) adsorption—reaction takes place at the liquid—solid interface; (3) the dissolved drug molecules (•) move toward the bulk solution

Scientists have reviewed the factors which can affect the dissolution of tablets and these include the stirring speed, temperature, viscosity, pH, composition of the dissolution medium and the presence or absence of wetting agents.

Physical models have been set up to account for the observed dissolution of tablets. According to Higuchi, there are three models which either alone or in combination, can be used to describe the dissolution mechanisms. These are:

(i) The Diffusion layer model

This model (Fig 2) assumes that a layer of liquid, H cm thick, adjacent to the solid surface remains stagnant as the bulk liquid passes over the surface with a certain velocity.

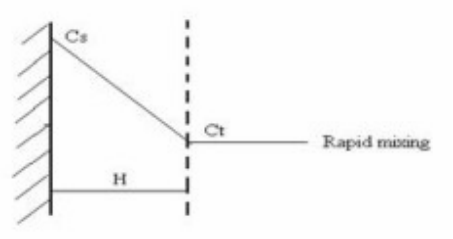

Fig.2. Diffusion Layer Model

The reaction at the solid/liquid interface is assumed to be instantaneous forming a saturated solution, C_s, of the solid in the static liquid film. The rate of dissolution is governed entirely by the diffusion of the solid molecules from the static liquid film to the bulk liquid according to Fick's first law:

$J = - D_f \, dc / dx$

where J is the amount of substance passing perpendicularly through a unit surface area per time, D_f, is the diffusion coefficient and dc / dx, is the concentration gradient. After a time t, the concentration between the limit of the static liquid layer and the bulk liquid becomes C_t. Once the solid molecules pass into the bulk liquid, it is assumed that there is rapid mixing and the concentration gradient disappears.

The theory predicts that if the concentration gradient is always constant i. e. $C_s - C_t$ is constant because $C_s >> C_t$ ("sink" conditions which usually mean $C_s > 10 C_t$) then a uniform rate of dissolution is obtained.

(ii) The Interfacial Barrier Model

In the interfacial barrier model (Fig 3), it is assumed that the reaction at the solid/liquid interface is not instantaneous due to a high activation free energy barrier which has to be surmounted before the solid can dissolve. Thereafter the dissolution mechanism is essentially the same as in (i) above, with the concentration at the limit of the static layer of liquid becoming C_t after time t.

The rate of diffusion in the static layer is relatively fast in comparison with the surmounting of the energy barrier, which therefore becomes rate limiting in the dissolution process.

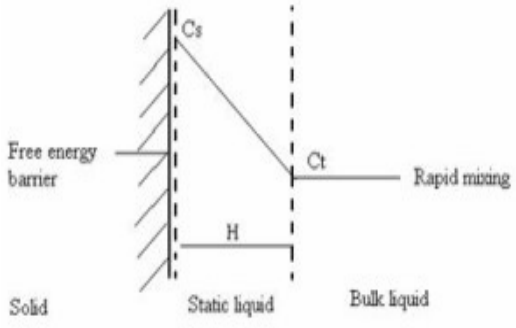

Fig.3. Diagrammatic representation of the free energy barrier to dissolution

(iii) The Danckwert's Model

The Danckwert's model (Fig 4) assumes that macroscopic packets of solvent reach the solid/liquid interface by eddy diffusion in some random fashion.

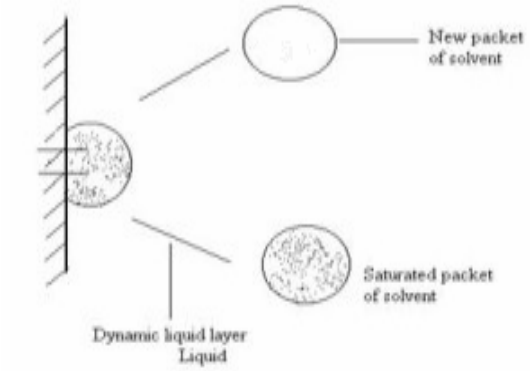

Fig.4. The Danckwert's Model.

At the interface, the packet is able to absorb solute according to the laws of diffusion and is then replaced by a new packet of solvent. This surface renewal process is related to the solute transport rate and hence to the dissolution rate. Though the diffusion layer model is the most commonly used, various alterations have been proposed. The current views of the diffusion layer model are based on the so-called *effective diffusion boundary layer*, the structure of which is heavily dependent on the hydrodynamic conditions. Aguiar et al proposed a scheme which holds that dissolution occurs only when the drug is in small particles. Wagner modified this idea and showed that dissolution occurs from both the intact tablet and the aggregates and/or granules produced after disintegration by using a plot of the percentage of drug dissolved versus time on logarithmic - probability graph papers.

MATHEMATICAL MODELS

Zero order release kinetics

Ideal delivery of drugs would follow "zero-order kinetics", wherein blood levels of drugs would remain constant throughout the delivery period. This ideal delivery is particularly important in certain classes of medicines intended, for example, for antibiotic delivery, heart and blood pressure maintenance, pain control and antidepressants. Consequently, there has been substantial activity by scientists searching for improved methods of achieving both controlled and sustained delivery of drugs.

Zero order release kinetics refers to the process of constant drug release from a drug delivery device such as oral osmotic tablets, transdermal systems, matrix tablets with low-soluble drugs and other delivery systems. In its simplest form, zero order release can be represented as

$$\mathbf{Q = Q_0 + K_0 t}$$

Where Q is the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), Q_0 is the initial amount of drug in solution (it is usually zero), and K_0 is the zero order release constant. The plot made: *cumulative % drug release vs. time* (zero order kinetic model).

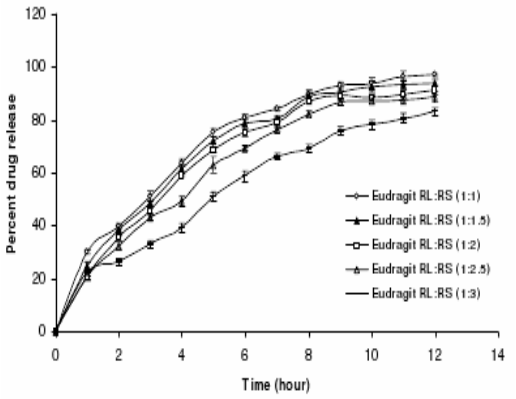

Fig. 5: Zero order release profile of Ambroxol HCl from coated pellets (mean ±S.D., n=3).

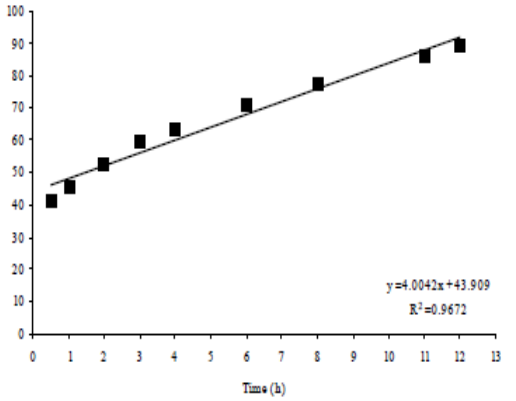

Fig. 6: Zero order release model of Ibuprofen sustained release formulation.

First order release kinetics

The rate laws predicted by the different mechanisms of dissolution both alone and in combination, have been discussed by Higuchi. However, the earliest equation expressing dissolution rate in a quantitative manner was proposed by Noyes and Whitney as:-

$dC / dt = k (C_s - C_t)$

where dC / dt is the rate of change in concentration with respect to time, and k is the rate constant. The integrated form of the equation is:

$In [C_s / (C_s - C_t)] = kt$

$Log C = Log C_0 - kt / 2.303$

Where, C_0 is the initial concentration of drug and K is first order constant.

The equation in resemblance to the other rate law equations, predicts a first order dependence on the concentration gradient (i.e. $C_s - C_t$) between the static liquid layer next to the solid surface and the bulk liquid. Noyes and Whitney explained their dissolution data using a concept similar to that used for the diffusion model. These considerations relate to conditions in which there is no change in the shape of the solid during the dissolution process (i. e. the surface area remains constant). However, for pharmaceutical tablets, disintegration occurs during the dissolution process and the surface area generated therefore varies with time. The plot made: *log cumulative of % drug remaining vs. time* (first order kinetic model).

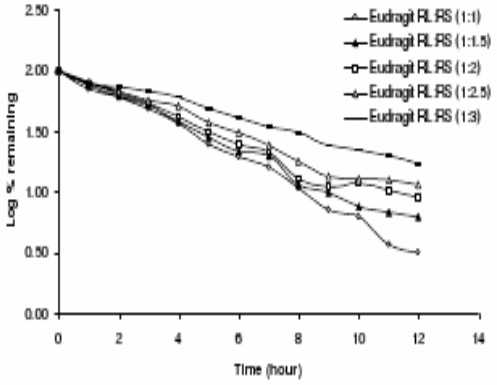

Fig. 7: First order release profile of Ambroxol HCl from coated pellets (n=3).

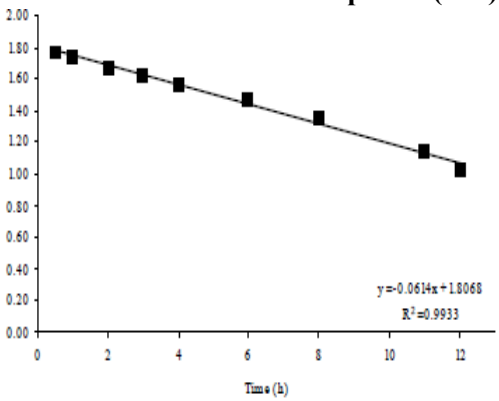

Fig. 8: First order release model of Ibuprofen sustained release formulation.

Hixson-Crowell cube-root Model

The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles or tablets. For a drug powder consisting of uniformly sized particles, it is possible to derive an equation that expresses the rate of dissolution based on the cube root of the particles.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t$$

Where, Qt is the amount of drug released in time t, Q0 is the initial amount of the drug in tablet and KHC is the rate constant for Hixson-Crowell rate equation.

The plot made: *cube root of drug % remaining in matrix vs. time* (Hixson-Crowell cube root law).

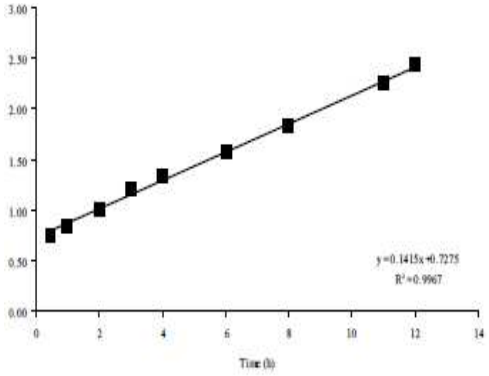

Fig. 9: Hixson-Crowell cube root plots of Ibuprofen sustained release formulation.

Higuchi Model

Ideally, controlled drug-delivery systems should deliver the drug at a controlled rate over a desired duration. The primary objectives of the controlled drug-delivery systems are to ensure safety and to improve efficacy of drugs, as well as to improve patient compliance. Of the approaches known for obtaining controlled drug release, hydrophilic matrix is recognized as the simplest and is the most widely used. Hydrophilic matrix tablets swell upon ingestion, and a gel layer forms on the tablet surface. This gel layer retards further ingress of fluid and subsequent drug release. It has been shown that in the case of hydrophilic matrices, swelling and erosion of the polymer occurs simultaneously, and both of them contribute to the overall drug-release rate. It is well documented that drug release from hydrophilic matrices shows a typical time-dependent profile (ie, decreased drug release with time because of increased diffusion path length). This inherent limitation leads to first-order release kinetics.

Many controlled-release products are designed on the principle of embedding the drug in a porous matrix. Liquid penetrates the matrix and dissolves the drug, which then diffuses into the exterior liquid. Higuchi tried to relate the drug release rate to the physical constants based on simple laws of diffusion. Release rate from both a planar surface and a sphere was considered. The analysis suggested that in the case of spherical pellets, the time required to release 50% of the drug was normally expected to be 10% of the time required to dissolve the last trace of solid drug in the center of the pellet. Higuchi was the first to derive an equation to describe the release of a drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion.

$$Q_t = [2DS\varepsilon\,(A - 0.5S\varepsilon)]^{0.5} * t^{0.5}$$

Simplifying,

$$Q_t = k_H\,(t)^{0.5}$$

Where, *Qt* is the amount of drug released in time *t, D* is the diffusion coefficient, *S* is the solubility of drug in the dissolution medium, $\varepsilon$is the porosity, *A* is the drug content per cubic centimeter of matrix tablet, and *kH* is the release rate constant for the Higuchi model.

The release of a solid drug from a granular matrix involves the simultaneous penetration of the surrounding liquid, dissolution of the drug, and leaching out of the drug through interstitial channels or pores. The volume and length of the opening in the matrix must be accounted for in the diffusional equation, leading to a second form of the Higuchi equation:

$$Q = [D\varepsilon/\tau\ (2A - \varepsilon C_s)\ C_s t]^{0.5}$$

Porosity, ε, is the fraction of matrix that exists as pores or channels into which the surrounding liquid can penetrate.

Tortuosity, τ, is introduced in equation to account for an increase in the path length of diffusion due to branching and bending of the pores, as compared to the shortest "straight- through" pores. Tortuosity tends to reduce the amount of drug release in a given interval of time. A straight channel has a tortuosity of unity, and a channel through spherical beads of uniform size has a tortuosity of 2 or 3.

The plot made: *cumulative % drug release vs. square root of time* (Higuchi model).

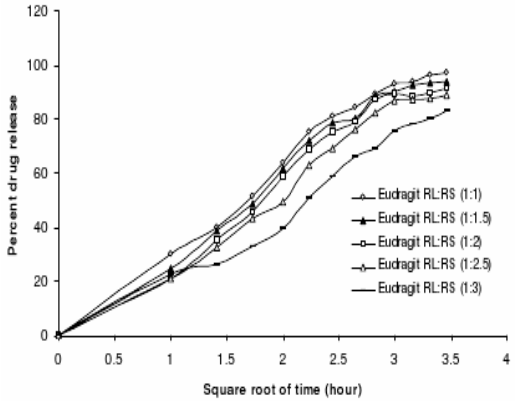

Fig. 10: Higuchi release profile of Ambroxol HCl from coated pellets. (n=3).

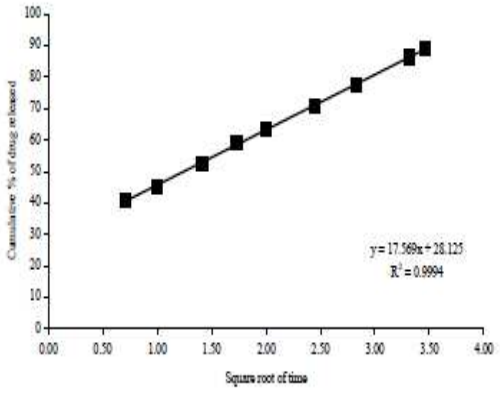

Fig. 11: Higuchi release model of Ibuprofen sustained release formulation.

Korsmeyer-Peppas Model

Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:

$$M_t/M_\infty = Kt^n$$

Where Mt / M∞ is fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in table 1 for cylindrical shaped matrices:

Table No 1

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

There are several simultaneous processes considered in this model:

- Diffusion of water into the tablet
- Swelling of the tablet as water enters
- Formation of gel
- Diffusion of drug and filler out of the tablet
- Dissolution of the polymer matrix

Key attributes of the model include:

- Tablet geometry is cylindrical
- Water and drug diffusion coefficients vary as functions of water concentration
- Polymer dissolution is incorporated
- Change in tablet volume is considered

By incorporating the first 60% of release data, mechanism of release can be indicated according to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case-II relaxational release are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and

state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion. Table 2 describes the limits of this analysis for cylindrical shape, e.g. a tablet. The value of the release exponent in ibuprofen sustained release obtained as 0.2465 which as per table 1 is beyond the limits of Korsmeyer model so-called power law. The power law can only give limited insight into the exact release mechanism of the drug. Even if values of the exponent n are found that would indicate a diffusion controlled drug release mechanism.

The plot made: *log cumulative % drug release vs. log time* (Korsmeyer-Peppas model).

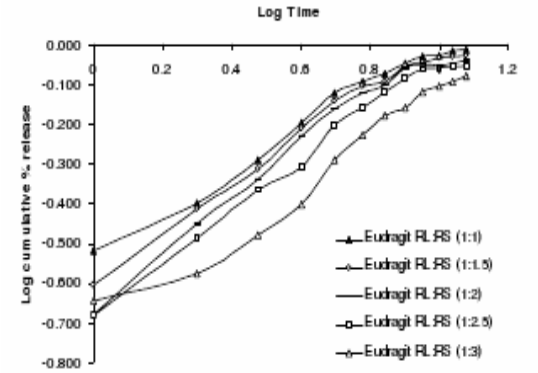

Fig 12: Korsmeyer release profile of Ambroxol HCl from coated pellets (n=3).

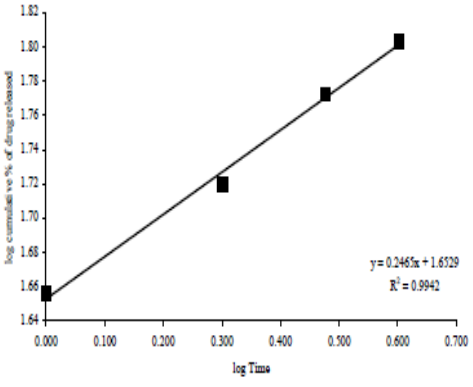

Fig. 13: Korsmeyer – Peppas Model for mechanism of drug release (first 60% drug release)

CONCLUSION

Drug transport inside pharmaceutical systems involves multiple steps provoked by different physical or chemical phenomenon, making it difficult, or even impossible, to get a mathematical model describing it in the correct way. The release models with major application and best describing drug release phenomena are, in general, the Higuchi model, zero order model, first order model and Korsemeyer-Peppas model. Further, it can be added that the physicochemical properties of the drug as well as polymer and the drug to polymer ratio govern the release of drug from the formulation and thus, modify the release kinetics accordingly.

REFERENCES

1. Higuchi, W. I., Diffusional models useful in biopharmaceutics drug release rate processes. *J. Pharm. Sci.,* 1967, 56: 315-324.
2. Noyes, A. A. and Whitney, W. R. The rate of solution of solid substances in their own solutions. *J. Am. Chem. Soc.,*1897, 19: 930-934.
3. Lakshmi, P.K. Dissolution testing is widely used in the pharmaceutical industry for optimization of formulation and quality control of different dosage forms, Pharma info.net 2010
4. Siepmann, J. and Peppas, N.A. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv. Drug Deliv. Rev.* 48, 2001,139-157.
5. Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A. Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm*. 15, 1983, 25-35.
6. Ahmed et.al, In vitro Release Kinetics Study of Ambroxol Hydrochloride Pellets Developed by Extrusion Spheronization Technique followed by Acrylic polymer coating, Dhaka Univ. J. Pharm. Sci. 7(1), 2008, pp 75-81.
7. Costa P.et.al, Modelling and comparison of dissolution profiles, European Journal of Pharmaceutical Sciences, 13, 2001, pp 123-133.

8. M Harris et al, Evaluation Of Drug Release Kinetics From Ibuprofen Matrix Tablets Using HPMC, Pak Journal of Pharmaceutical Sciences, 19(2), 2006, pp 119-124.
9. Mukesh C Gohel et al, Novel Mathematical Method for Quantitative Expression of Deviation from the Higuchi Model, AAPS PharmSciTech, 1(4) article 31, 2000.
10. Ragnarsson, G, et.al,. Development of a new controlled release metoprolol product. *Drug Dev. Ind. Pharm.* 13,1987, 1495-1509.
11. Kibria, G. and Jalil, R. *In vitro* release kinetics study of Diclofenac Sodium from acrylic polymer coated pellets. *Dhaka Univ. J. Pharm. Sci.* 2007, 6, 1-7.
12. Varelas, C.G., Dixon, D.G., Steiner, C., Zero-order release from biphasic polymer hydrogels. J. Control. Release 34, 1995, 185–192.
13. Ebube N.K., Hikal A., Wyandt C.M., Beer D.C., Miller L.G. and Jones A.B.: Susatained release of acetomenophen from heterogeneous matrix tablets, influence of polymer ratio, polymer loading and coactive on drug release, Phar DevTechnol. 1997;2: 161-170.
14. Martin's Physical Pharmacy and Pharmaceutical Sciences, 5th Edition.