

RESEARCH ARTICLE

Mathematical Kinetic Modeling on Isoniazid Release from Dex-HEMA-PNIPAAm Nanogels

Maryam Jafari, Babak Kaffashi*

Department of Chemical engineering, Faculty of engineering, University of Tehran, Tehran, Iran

ARTICLE INFO

Article History:

Received 31 May 2016;

Accepted 5 August 2016 ;

Published 12 August 2016

Keywords:

First order

Higuchi

Modeling, zero order

Release kinetic

ABSTRACT

Objective(s): The quantitative calculation of release data is more facil when mathematics come to help. mathematically modeling could aid optimizing and amending the delivery systems design. Aim of this study is to find out the isoniazid release kinetic.

Methods: In this work degradable temperature sensitive dextran-hydroxy ethyl methacrylate- poly-N-isopropyl acryl amide (Dex-HEMA-PNIPAAm) nanogels which were synthesized by UV polymerization were loaded by Isoniazid. The Isoniazid release amounts taken from in vitro studies at two different temperatures, below and upper lower critical solution temperature (LCST) were mathematically modeled to investigate the kinetic of drug release. Mathematically inquiry of release phenomenon of Isoniazid makes it easy to predict and recognize the influence of delivery device laying out parameters on release kinetic formulation. The modeling was performed using model dependent methods, such as zero order, first order, Higuchi, Korsmeyer- Pepas, Hixon and Crowel.

Results: The best fitted model showing the highest determination coefficient (R²) was Korsmeyer-Pepas which means predominant release mechanism is controlled by diffusion.

Conclusions: The Isoniazid release pattern of most samples was combination of swelling, diffusion and degradation.

How to cite this article

Jafari M, Kaffashi B. Mathematical kinetic modeling on Isoniazid release from Dex-HEMA-PNIPAAm nanogels. *Nanomed Res J*, 2016; 1(2):90-96. DOI: 10.7508/nmrj.2016.02.005

INTRODUCTION

Intelligent drug delivery systems, showing brilliant features as pre-determined time delivery, pre-planned rate and self controlling, are widely used in various areas of pharmaceuticals world. Such delivery systems, mostly employing polymers to design new systems by help of nanotechnology, attracted large amount of attention in different medical applications. Size controlling, surface specification and release are among the most important requirements of nano-sized delivery systems[1-5]. Drug release includes steps of therapeutic agent freedom from drug which is then exposed to variety of mechanisms like absorption, distribution, metabolisms and exertion. Drug

may be released through diffusion, dissolution, erosion, leaching and mixed of them[6-9]. Drug release occurs in varied way. Sometimes release is immediate in which drug releases immediately. Delayed and extended are two types of modified release that drug will release after a while by delay and in an extended period, respectively. Ultimately, pulsatile release a type of controlled release makes drug free at specific time intervals.

In drug release studies kinetic is a key factor because it can be related to the drug concentration in plasma which is the available facile parameter to determine. Applying kinetic model is valuable in clarifying release mechanism which is helpful in the drug release control and design[8-15].

There are vast numbers of kinetic models

* Corresponding Author Email: kaffashi@ut.ac.ir

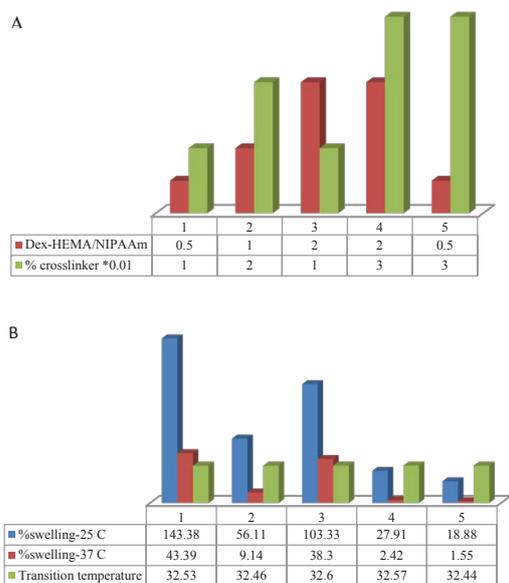


Fig. 1. (A) Structural parameters value (Dex-HEMA/NIPAAm: 1: (0.5,1), 2: (1,1), 3: (2,1), 4: (2,3), 5: (0.5, 2)) (B) Swelling% and LCST

illustrating drug release which can be categorised in three distinct groups:

- Statistical approaches
- Exploratory data analysis method
- Repeated measurement design
- Multivariate approach (ANOVA based model, analysis of variance)
- Model dependent approaches
- Diffusion model (Fick's law)
- Zero order model
- First order model
- Higuchi model
- Korsmeyer – Peppas model
- Hixon – Crowell model
- Weibull model
- Baker – Lonsdale model
- Hopfenberg model
- Gompertz model
- Sequential layer model
- Model independent approaches
- Ratio factors
- Fit factors (similarity factor, difference factor, resign index)

The other way of categorisation is empirical and semi-empirical methods like Peppas and Sahlin; and mechanistic and empirical methods [8,10,12,13,15–26].

In this present study we will mathematically model the release kinetic of Isoniazid release which is an antibiotic using in curing diseases like tuberculosis from five series of Dex-HEMA-PNIPAAm nano/micro gels. The comprehensive synthesis method, characterization, drug loading and other worth full relative data were narrated

in our previous publication [27,28]. The model dependent category is chosen to evaluate and predict the effect of cross linking agent amount and polymers kinds on the type of release. At the moment obtained release data will fit by the most important models which have been introduced above and the results will relate to the structure of the samples.

METHODS

Investigation of Isoniazid release kinetic from Dex-HEMA-PNIPAAm nanogels has been performed by applying nine kinetic models on release data obtained from five series of sample which were synthesized, characterized and loaded by Isoniazid previously in two different temperature, 25 °C and 37 °C. The determination is accomplished by comparison of determination coefficient; the higher the determination coefficient the most suitable model is achieved. Unexpurgated information of initial materials quantities and ratios, also Isoniazid release amounts were narrated before, here just a brief glance to the necessary data for comparison and interpretation of the samples behaviour and their structure is presented in (Figs. 1 and 2). As it is obvious a portion of release occurred as burst release at the beginning. Burst release may happen due to the high specific surface of Isoniazid carrier gels which is exposed to the media, instability of nanogels, exec amount of Isoniazid or just under the surface freedom.

Release kinetic data were fitted to the following models which are explained completely and in accordance with regression coefficient of determination (R²) models were compared and studied.

Zero order kinetic model

Zero order release reveals an ideal delivery of drugs due to constant remaining of drug in blood plasma during delivery process. This release model points out the constant release regime which will be applicable in the case of heart or blood pressure maintenance, pain control and etc. This model can be represented by the following equation:

$$Q_t = Q_0 + K_0 t$$

Where Q_t is the amount of drug release at time t , Q_0 IS initial amount of drug in solution which is often equal to zero, K_0 is the zero order constant and finally t is time. To investigate the release kinetic, experimental in vitro cumulative amounts were plotted versus time.

First order kinetic model

First order kinetic model was first employed by Gibaldi and Feldman (1967) and Wagner (1969). Mentioned model also has been used for

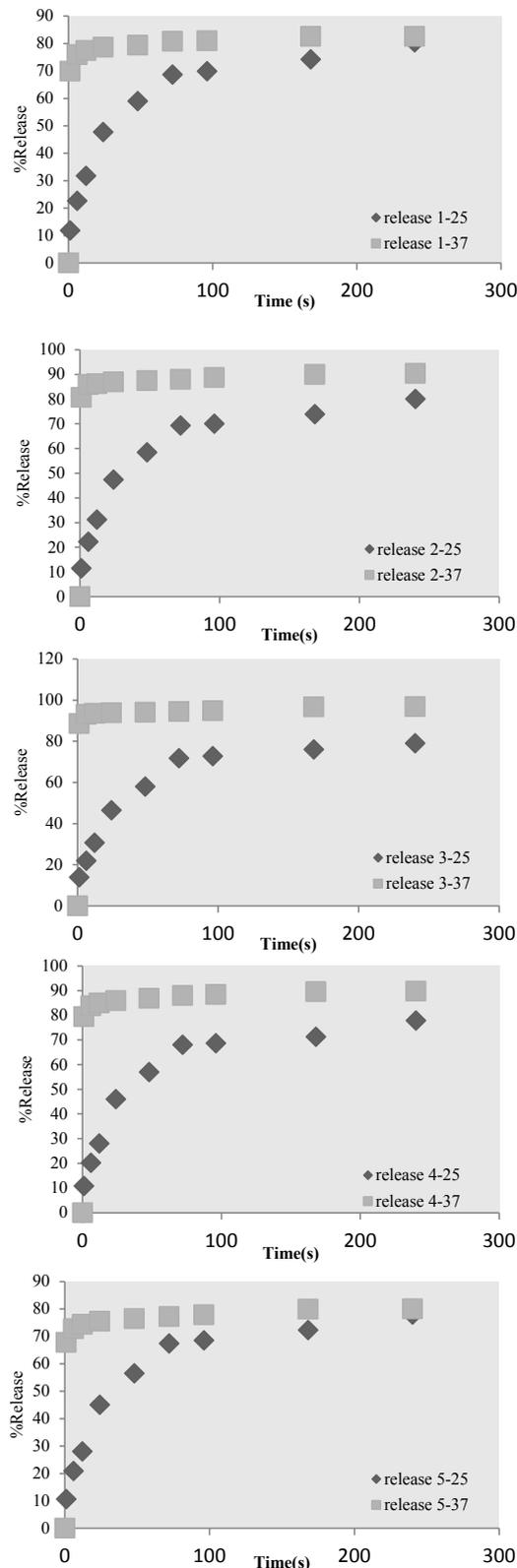


Fig. 2. % release from 5 series sample at temperatures 25 °C and 37 °C

absorption and elimination of some drugs (1982). However first order kinetic model cannot clarify the mechanisms due to theories.

In this case drug release will express by the following equation:

$$\log Q_t = \log Q_0 - (K/2.303)t$$

Where Q_t is the amount of drug release at time t , Q_0 IS initial amount of drug in solution, K is the first order constant and t is time.

To investigate the release kinetic, experimental in vitro log cumulative percentage of drug remaining were plotted versus time. The result will be a straight line having the slope of $-K/2.303$.

Higuchi model

Among all delivery systems hydrophilic ones are mostly used. Such systems can swell and make a layer on the drug surface and as a consequence will prevent more water entrance and drug release. In this case swelling and erosion/degradation both are responsible of drug release rate control. Hence, often time dependent behaviour especially drug release reduction as the time pass, are observed in hydrophilic delivery systems.

In 1961 and 1963 Higuchi proposed his models for water soluble and low soluble drugs in solid and semi-solid matrix. Simplified Higuchi model can be expressed by the following equation:

$$Q_t = K_H t^{(1/2)}$$

Where Q_t is the amount of drug release at time t , K_H is the Higuchi release rate constant and t is time. To investigate the release kinetic, experimental in vitro log cumulative percentage of drug remaining were plotted versus square root of time.

Korsmeyer - Peppas model

Korsmeyer and Peppas (1984) and Ritger and Peppas (1987) presented their equation analysing both Fickian and non-Fickian drug release from swelling and non-swelling polymeric matrix. Fickian release used in steady cases in which concentration does not change by time and it is just dependent to place. In the Fickian release in unsteady situations the concentration gradient in a special place is changing due to the time, in the other cases release follows non-Fickian regime. By fitting the first 60% of drug release to the model release mechanism can be fined out. The equation is represented as:

$$Q_t/Q_\infty = K t^n$$

Where Q_t/Q_∞ is the fraction of drug released at time t , K is the release rate constant, n is the release exponent that is shown in (Tables 1 and 2) and t is time.

In this model some factors are considered such as water diffusion in to the delivery system, swelling, gel formation, drug diffusion out, dissolution/

Table 1. Diffusion exponent and release mechanism of swellable systems

n:Thin film	n:Cylindrical sample	n:Spherical sample	Release mechanism
0.5	0.45	0.43	Fickian diffusion
0.5<n<1	0.45<n<0.89	0.43<n<0.85	Non-Fickian diffusion
1	0.89	0.85	Case II

Table 2. Diffusion exponent and release mechanism of non-swellable systems

n:Thin film	n:Cylindrical sample	n:Spherical sample	Release mechanism
0.5	0.45	0.43	Fickian diffusion
0.5<n<1	0.45<n<1	0.43<n<1	Non-Fickian diffusion
1	1	1	Zero order release

erosion of polymeric matrix. Plot may be catches by log cumulative percentage drug release vs. Log time to investigate the in vitro release kinetic.

When burst release is possible b parameter is added to the equation.

$$Q_t/Q_\infty = (K_t^n)^b + b$$

Weibull model

This model can be adapted to dissolution release and can be shown by the following equation:

$$Q/Q_0 = 1 - e^{-K(t-T)}$$

Where Q is the amount of drug released at time t, Q₀ is the total amount of drug released, T is the lag time and t is time.

Gompertz model

Proportional equation showing this model is as follow:

$$Q_t/Q_{max} = \exp[-\alpha e^{\beta \log t}]$$

Where Q_t is the amount of drug released at time t, Q_{max} is the maximum amount of drug released, t is time, α is unreleased amount of drug at t=1 and β is release rate per unit of time.

Baker- Lonsdale model

Baker and Lonsdale model was derived from Higuchi model in 1974 for spherical matrix and is represented as follow:

$$3/2[1 - (1 - Q_t/Q_\infty)^{2/3}] - Q_t/Q_\infty = Kt$$

Where Qt is the amount of drug released at time t, Q_∞ is the amount of drug released at infinite time, K is the release rate and t is time. Plot [d(Q_t/Q_∞)/d_t] respected to root of time inverse to study release kinetic of Isoniazid from nanogels.

Hopfenberg model

Hopfenberg model is used for the cases of release from eroding polymer surface in which surface area keep constant during the process. For spherical geometry following equation express the

mentioned model:

$$Q_t/Q_\infty = 1 - [1 - K_t/(Q_0 a)]^3$$

Where Qt is the amount of drug released at time t, Q_∞ is the total amount of drug released, Q₀ is the initial amount of drug in matrix, K is rate constant, t is time and a is system half thickness (radius).

Hixson-Crowell model

Hixson-Crowell model explain the release from systems in which surface area and diameter change. He suggested (1931) that the changes in diameter and area are relative to cube root of the volume and is described by the following equation:

$$Q_0^{1/3} - Q_t^{1/3} = Kt$$

Where Q_t is the remaining amount of drug in delivery particles at time t, Q₀ IS initial amount of drug in delivery particle, K is the rate constant and finally t is time. This model hypothesis is that the release rate is not controlled by the drug diffusion, but is controlled by particles erosion, dissolution and degradation.

To compare the release kinetic of Isoniazid by this model cube root of drug percentage remaining in matrix plotted vs. Time(8-17,19-24,29).

RESULTS AND DISCUSSION

Peer group comparisons of samples in each condition, temperature 25 °C and 37°C (considering and eliminating burst release), were performed and outcomes are revealed in (Tables 3 to 5).

Table 3 shows the release data fitted to the chosen models at 25°C. This temperature is below LCST temperature of the nanogels in which gels are in their swollen forms. The three most proper models fitted to data based on having closest R2 to 1 were Korsmeyer-Pepas, Baker-Lonsdale, and Hopfenberg respectively. This order represent that the most release controlling mechanism in the temperatures below phase transition temperature is diffusion; as the water penetrate in gels structure make them swell and in this situation the drug

Table 3. Correlation coefficient & Determination coefficient of models at 25 ° C

Model Sample	Zero order R&R2	First order R&R2	Higuchi R&R2	Korsmeyer-Pepas R&R2	n	Weibull R&R2	Gompertz R&R2	Baker-Lonsdale R&R2	Hopfenberg R&R2	Hixon R&R2
1	0.815	0.719	0.945	0.984	0.37	0.950	0.958	0.979	0.964	0.617
	0.664	0.517	0.893	0.969		0.902	0.918	0.958	0.929	0.381
2	0.814	0.717	0.944	0.984	0.37	0.925	0.956	0.975	0.962	0.619
	0.662	0.514	0.891	0.968		0.855	0.913	0.951	0.926	0.383
3	0.807	0.735	0.940	0.982	0.35	0.944	0.923	0.963	0.963	0.616
	0.652	0.54	0.884	0.964		0.892	0.852	0.928	0.928	0.379
4	0.812	0.718	0.942	0.981	0.38	0.801	0.952	0.969	0.958	0.625
	0.659	0.515	0.887	0.963		0.641	0.906	0.939	0.917	0.391
5	0.819	0.722	0.947	0.984	0.39	0.722	0.950	0.977	0.965	0.628
	0.671	0.521	0.896	0.969		0.521	0.903	0.955	0.931	0.395

Table 4. Correlation coefficient & Determination coefficient of models considering burst release at 37 ° C

Model Sample	Zero order R&R2	First order R&R2	Higuchi R&R2	Korsmeyer-Pepas R&R2	n	Weibull R&R2	Gompertz R&R2	Baker-Lonsdale R&R2	Hopfenberg R&R2	Hixon R&R2
1	0.394	0.729	0.559	0.981	0.029	0.829	0.742	0.741	0.780	0.326
	0.155	0.532	0.312	0.963		0.688	0.551	0.549	0.609	0.106
2	0.361	0.758	0.522	0.696	0.019	0.931	0.869	0.666	0.711	0.315
	0.130	0.574	0.272	0.938		0.866	0.755	0.443	0.505	0.099
3	0.346	0.767	0.505	0.950	0.014	0.867	0.729	0.632	0.694	0.310
	0.120	0.588	0.255	0.903		0.751	0.531	0.399	0.481	0.096
4	0.373	0.774	0.535	0.993	0.021	0.952	0.867	0.699	0.740	0.318
	0.139	0.599	0.286	0.986		0.906	0.751	0.488	0.547	0.101
5	0.400	0.784	0.562	0.990	0.029	0.784	0.723	0.764	0.792	0.327
	0.160	0.614	0.316	0.980		0.614	0.523	0.583	0.627	0.107

Table 5. Correlation coefficient & Determination coefficient of models no considering burst release at 37 ° C

Model Sample	Zero order R&R2	First order R&R2	Higuchi R&R2	Korsmeyer-Pepas R&R2	n	Weibull R&R2	Gompertz R&R2	Baker-Lonsdale R&R2	Hopfenberg R&R2	Hixon R&R2
1	0.887	0.881	0.961	0.994	0.023	0.918	0.754	0.961	0.969	0.883
	0.786	0.777	0.924	0.988		0.842	0.569	0.923	0.938	0.78
2	0.964	0.962	0.994	0.971	0.014	0.928	0.825	0.996	0.969	0.962
	0.929	0.925	0.989	0.942		0.861	0.68	0.993	0.939	0.926
3	0.973	0.973	0.973	0.969	0.0105	0.986	0.685	0.977	0.965	0.973
	0.947	0.947	0.947	0.938		0.973	0.469	0.954	0.931	0.947
4	0.898	0.894	0.970	0.997	0.019	0.952	0.873	0.974	0.980	0.896
	0.806	0.799	0.941	0.994		0.906	0.762	0.948	0.961	0.802
5	0.918	0.913	0.976	0.990	0.025	0.913	0.736	0.973	0.977	0.914
	0.842	0.833	0.952	0.981		0.833	0.542	0.946	0.955	0.836

particles diffuse out of swollen nanogels. Then after the degradation is the other mechanism of Isoniazid release from nanogels. The values of n ($n < 0.5$) reveal that diffusion pattern is of kind of Fickian diffusion.

At 37°C nanogels are in the temperature upper LCST, hence there are in their deswelling form. The burst release is much sharper here than 25 °C. As the gels were located in 37°C they transitioned from swelling form to deswelling form and as a sequence large amount of Isoniazid came out suddenly. Noting the determination coefficient of models, only Korsmeyer-Pepas model fitting results gave

$R^2 > 0.9$, which confirm that considering burst results the only release mechanism in nanogels are diffusion and hither also Fickian diffusion is dominant. (Table 4) shows the Determination coefficient of models considering burst release at 37 ° C.

Just as mentioned above a reason for sharp burst was the phase transition. Here neglecting the first hour release that mean omitting burst release, again data were fitted to the selected models. This time more models exist having $R^2 > 0.9$. From the comparison of average amount of R^2 it is find out that the total first four best models are Baker-Lonsdale, Higuchi, Korsmeyer-

Pepas and Hopfenberg, respectively. Now the first controlling mechanism is combination of swelling and degradation of spherical particles. Then after diffusion take parts in Isoniazid release. This means that here drug release does not obey one rule and both degradation and diffusion are responsible of release. For each sample individually the order is a bit unlike. Korsmeyer-Pepas, Baker-Lonsdale, Weibull, Korsmeyer-Pepas, Korsmeyer-Pepas proportionally belongs to sample 1 to 5 in an orderly manner. Diffusion is the main mechanism of Isoniazid from sample 1, in which Dex-HEMA/PNIPAAm ratio is 0.5, so because of small amount of hydrolysable ester group degradation is not dominant. More after cross linking agent value of sample 1 is equal to 1 that let the sample swell easily and drug molecules could travel out of nanogels. In sample 2 Dex-HEMA/PNIPAAm ratio and cross linking agent value are 1 and 2 respectively. In this case quantities of degradable parts are more in the structure and swelling characteristic of gel is fewer due to high cross links and as results proved Baker-Lonsdale best fitted for this sample that emphasis on swelling and degradation mechanism of Isoniazid release. (Table 5) shows the determination coefficient of models not considering burst release at 37 °C

In samples 3 and 4 Dex-HEMA/PNIPAAm ratio is 2 but cross linking agent value in sample 3 is 1 and in sample 4 in 3. Both samples contain equal and the maximum of hydrolysable ester groups' amounts but they release kinetic follow different regimes. In sample 3 Isoniazid release agree with Weibull model and sample 4 confirm the Korsmeyer-Pepas. As it is obvious the amount of cross links and as a consequence swelling ratio of nanogels can influence the release pattern. The more swelling happen the more degradation and the less diffusion observe. Finally sample 5 has less hydrolysable group in its structure and simultaneously the most cross links and so the less swelling which could lead to the diffusion. The data given in table

convince the Fickian diffusion as a best linear fitted release kinetic model.

CONCLUSIONS

Reviewing the various kinetic pattern open ups the correlation among drug release and structure of delivery systems mathematically. In this attempt, focuses were on Isoniazid release kinetic from Dex-HEMA-PNIPAAm nanogels. In vitro drug release investigation revealed controlled Isoniazid release containing a burst release at the beginning for all samples and all conditions. Considering that, these bursts were sharper upper phase transition temperature than ambient temperature. The Isoniazid release pattern of most samples was

combination of swelling, diffusion and degradation. Results best fitted with Korsmeyer-Pepas model with Fickian diffusion.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the financial support of University of Tehran Science and Technology Park for this research. This study was part of a PhD thesis under Tehran University.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. Langer R, Chasin M. Biodegradable polymers as drug delivery system. New York:Marcel Dekker; 1990. p.71–120.
2. Papazoglou ES, Parthasarathy A. BioNanotechnology. Synthesis Lectures on Biomedical Engineering. 2007;2(1):1-139.
3. Shargel L, Yu ABC. Biopharmaceutics. Encyclopedia of Clinical Pharmacy: Informa Healthcare; 2002. p. 82-102.
4. Park K. Controlled drug delivery systems: Past forward and future back. J Control Release. 2014;190:3-8.
5. Bennet D, Kim S. Polymer nanoparticles for smart drug delivery. In: Sezer AD(Ed.). Application of Nanotechnology in Drug Delivery. 2014.
6. Das SK. Drug Delivery: Principles and Applications. AM J PHARM Educ. 2006;70(4):94.
7. Tiwari G, Tiwari R, Bannerjee S, Bhati L, Pandey S, Pandey P, et al. Drug delivery systems: An updated review. Int J Pharma Investig. 2012;2(1):2.
8. D'Souza S. A Review of In Vitro Drug Release Test Methods for Nano-Sized Dosage Forms. Advances in Pharmaceutics. 2014;2014:1-12.
9. Xu W. Drug release and its relationship with kinetic and thermodynamic parameters of drug sorption onto polylactide, starch acetate, wheat gluten and soy protein fibers: THE UNIVERSITY OF NEBRASKA-LINCOLN; 2009.10.Archna Panday RJ. A Review of Kinetics of Nanoparticulated Delayed Release Formulations. J Nanomed Nanotechnol. 2015;06(04).
10. Archna Panday RJ. A Review of Kinetics of Nanoparticulated Delayed Release Formulations. J Nanomed Nanotechnol. 2015;06(04).
11. Pawar P, Sharma P, Chawla A, Mehta R. Formulation and in vitro evaluation of Eudragit S-100 coated naproxen matrix tablets for colon-targeted drug delivery system. J Adv Pharm Technol Res. 2013;4(1):31.
12. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm. 2010;67(3):217-23.
13. Chime S, Onunkwo G, Onyishi I. Kinetics and mechanisms of drug release from swellable and non swellable matrices: a review. Res J Pharm Biol Chem Sci. 2013;4(2):97-103.
14. Ford Versypt AN, Pack DW, Braatz RD. Mathematical modeling of drug delivery from autocatalytically degradable PLGA microspheres — A review. J Control Release. 2013;165(1):29-37.
15. Raval A, Parikh J, Engineer C. Mechanism of controlled release kinetics from medical devices. Braz J Chem Eng. 2010;27(2):211-25.
16. Sahoo C, Rao S, Sudhakar M, Satyanarayana K. The kinetic

- modeling of drug dissolution for drug delivery systems: An overview. *Pharm Lett.* 2015;7(9):186-94.
17. Mohammadi G, Barzegar-Jalali M, Shadbad MS, Azarmi S, Barzegar-Jalali A, Rasekhan M, et al. The effect of inorganic cations Ca^{2+} and Al^{3+} on the release rate of propranolol hydrochloride from sodium carboxymethylcellulose matrices. *DARU.* 2015;17(2):131-8.
18. Khan MA, T S. Role of Mathematical Modeling in Controlled Drug Delivery. *J Sci Res.* 2009;1(3).
19. Dash V. Release Kinetic Studies of Aspirin Microcapsules from Ethyl Cellulose, Cellulose Acetate Phthalate and their Mixtures by Emulsion Solvent Evaporation Method. *Sci Pharm.* 2010;78(1):93-101.
20. Fugit KD. Quantification of Factors Governing Drug Release Kinetics from Nanoparticles: A Combined Experimental and Mechanistic Modeling Approach [Theses and Dissertations-Pharmacy]: university of Kentucky; 2014.
21. Chavda HV, Patel CN. Preparation and In vitro evaluation of a stomach specific drug delivery system based on superporous hydrogel composite. *Indian J Pharm Sci.* 2011;73(1):30.
22. Frenning G. Modelling drug release from inert matrix systems: From moving-boundary to continuous-field descriptions. *Int J Pharm.* 2011;418(1):88-99.
23. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. *Eur J Pharm Sci.* 2001;13(2):123-33.
24. Mendyk A, Jachowicz R, Fijorek K, Dorożyński P, Kulinowski P, Polak S. KinetDS: An Open Source Software for Dissolution Test Data Analysis. *Dissolut Technol.* 2012;19(1):6-11.
25. Fattal E., Vauthier C. Nanoparticles as drug delivery systems. In *Encyclopedia of Pharmaceutical Technology*, Swarbrick J. & Boylan J. C. eds, Marcel Dekker Inc., Basel, Switzerland, 2002;1874-1892.
26. Hoffman AS. The origins and evolution of "controlled" drug delivery systems. *J Control Release.* 2008;132(3):153-63.
27. Jafari M, B K. Preparation and In vitro Evaluation of Isoniazid-Containing Dex-HEMA-Co-PNIPAAm Nanogels. *CeN.* 2015;37(1):55-62.
28. Jafari M, Kaffashi B. Synthesis and characterization of a novel solvent-free dextran-HEMA-PNIPAM thermosensitive nanogel. *J Macromol Sci A.* 2016;53(2):68-74.
29. Siepmann J. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv Drug Deliv Rev.* 2001;48(2-3):139-57.