ORIGINAL RESEARCH article

Mechanism of Ibuprofen release from chitosan granules

Fadia Mussa, Fathia Almani and **Mahmud S. Treki** *

Department of Pharmaceutics, Faculty of Pharmacy, University of Tripoli, Tripoli, Libya
*Author to whom correspondence should be addressed

Keywords: Chitosan, drug release, granules, hydroxylpropyl cellulose, Ibuprofen, FTIR spectroscopy

Abstract: Attempts have been made to formulate controlled release drug dosage forms using chitosan as a release controlling polymer. Granules of a combination of chitosan, hydroxylpropyl cellulose, lactose, starch and Ibuprofen were prepared by wet granulation method using 1.0% lactic acid solution. The granules were physico-chemically characterized in terms of density, porosity, angle of repose, carr's index and housner ratio and were found to be free flowing with good compressibility. FTIR spectroscopy was used and confirmed that there was no interaction between the drug and the added polymers. *In vitro* release of Ibuprofen, in phosphate buffer at pH 7.4, showed a steady and slow increase in the percentage of drug released over 24 hours as the percentage of chitosan was increased in the formulations compared to that from commercial tablets which released over 80.0% of their content in only two hours. The kinetic analysis using different mathematical models of the data revealed that the release kinetics of the drug from these formulations is somewhere between diffusion controlled, Fickian (anomalous) and non-Fickian which refers to a combination of diffusion and erosion-controlled release. Thus, the high correlation coefficient of the data of drug release from most granules when zero order kinetics was applied revealed that there is a constant drug release with time for 24 hours.

Introduction

Various approaches are used to formulate sustained release drug delivery systems as diffusion sustained systems, dissolution sustained systems, swelling, expansion systems, floating systems and bio-adhesive or muco-adhesive systems. Matrix tablets using wet and dry granulation are used approaches to sustain the drug action. Matrix tablets are oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout hydrophilic or hydrophobic matrices that serve as a release rate of retardants. A combination of chitosan and hydroxyl propyl cellulose (HPC) was reported to be successful in preparing formulations that are able of sustaining Ibuprofen release for a few hours [1]. Matrix drug delivery systems release the drug in a continuous manner where they release the drug by dissolution controlled and diffusion-controlled mechanisms [2]. Although a high interest in the effect of chitosan on drug release, taking into consideration its chemical properties, less attention was given to the effects of its physical properties. However, the effect of the gel formation of chitosan

in granules is investigated in terms of drug release. It is well-documented that drug release is affected by gel formation of chitosan in acidic media [3]. The results indicated chitosan granules acted as slow-release formulations and the kinetic constant of Ibuprofen release ranged from 22.0% per hour to 31.0% per hour [4].

When a new solid dosage form is developed drug dissolution is an important test used to evaluate drug release from solid and semisolid dosage forms. The values obtained from the dissolution study can be quantitatively analyzed by different mathematical formulae. Because qualitative and quantitative changes in the formulation may alter the release of any drug and *in vivo* performance, developing tools that facilitate product development by reducing the necessity of bio-studies is always desirable leading to the development of mathematical models. The mathematical modeling helps to optimize the design of therapeutic devices to yield information on the efficacy of various release models [5]. Different mathematical models are used to determine the kinetics of drug release from drug delivery systems as zero order, first order, Hixson-Crowell, Higuchi and other models. The mechanism of drug release from matrix systems, and the release data were fitted to selected models as first order kinetics, Higuchi equation and Korsmeyer exponential equation. The pharmaceutical dosage forms following this profile release the same amount of drug by a unit of time and it is the ideal method of drug release to achieve constant pharmacological action. Dissolution of drug from pharmaceutical dosage forms that do not disaggregate and release the drug slowly can be represented as Qt= $Q_0 + K_{0t}$ where Qt is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution and K_0 is the zero-order release constant. This relationship is used to describe drug dissolution from several types of modified release pharmaceutical dosage forms [6, 7]. Linear kinetics is a process that is directly proportional to drug concentration. This model is used to describe the absorption and - or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis, however, the release of the drug which follows first-order kinetics can be expressed by Ln (100-Q)=ln (Q_0) - K_1t where (Q) is percentage of drug released at time (t), (Q_0) is the initial amount of drug in the solution and (K_1) is the first order release constant obtained by plotting the natural logarithm of percentage or amount of drug remaining to be released against time. This is used to describe drug dissolution in pharmaceutical dosage forms as those containing water soluble drugs in porous matrices [8]. This is the first mathematical model that describes drug release from a matrix system proposed by Higuchi [9]. Initial drug concentration in the matrix is much higher than drug solubility, drug diffusion takes place only in one dimension, drug particles are much smaller than the thickness of the system, swelling of matrix and dissolution is less or negligible, drug diffusivity is constant and perfect sink condition are always attained in the release environment. Dissolution from a planar system having a homogeneous matrix can be obtained by ft =Q= $K_H\sqrt{t}$ where K_H is the Higuchi dissolution constant, Q=percentage or amount of drug released at the time (t). Higuchi describes drug release as a diffusion process based on Fick's law, the square root of time-dependent. The drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs [10]. Korsemeyer and others [11] derived a simple relationship to describe drug release from polymeric system to describe the mechanism of drug release, first 60.0% of drug release data were fitted in Korsemeyer-Peppas module: Log [F]=n log [t]+log [K_P] where: K_P is release rate constant, n is diffusion exponent which is indicative of the mechanism of drug release, was obtained by plotting the log value of the percent of drug released (F) against log time (t) for each formulation. An (n) value of n=0.45 indicates Fickian (case I) release, (0.45 < n <0.89) is a non-Fickian (anomalous) release and n>0.89 indicates a super case II type of release. Case II refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of diffusion and erosion-controlled release. This equation is used to linearization of release data from formulations of microcapsules or microspheres and modified release dosage forms. The main objective of this work is to study

the release characteristics and mechanism of Ibuprofen release from already prepared a granule of combination of chitosan and HPC which are successful in sustaining Ibuprofen release for a few hours. Granules of this combination were prepared by wet granulation method using 1.0% lactic acid solution [1]. Different mathematical models will be adopted in an attempt to explain the mechanism of drug release from this system.

Materials and methods

Chitosan from shrimp shells 75.0% deacetylation (Sigma Aldrich, Iceland). HPC average mw 100,000 (Hass, ctradinghouse, Belgium). Iboprofen, mw 206.28 (Sigma-Aldrich, China). Lactic acid (BDH chemicals ltd Poole England). Lactose (E. Merck, Darmstadt, Germany). USP Dissolution apparatus-Pharmatest DT70. Germany. UV/VIS Spectroph-ptometer-JENWAY 6305, Germany. Granulator-Erweka AR 400, Germany. Drying oven-memert um 300, Germany. Magnetic Stirrer-IKA Labortechnik pH basic, USA. Scanning electron microscope (SEM)-LEO, Germany. Fourier transform infrared spectroscopy (FTIR)-IR prestige, Shimadzu, Germany.

Preparation of the granules: formulations prepared by wet granulation, A1-A4: Accurately weighed quantity (pre-sieved through 250 µ sieve) of chitosan, HPC, lactose, starch and Ibuprofen (**Table 1**) were mixed by mortar and pestle for 15 min. A sufficient quantity of 1.0% lactic acid was added gradually to form a wet mass and mixed for five min. The mixture was then granulated using an oscillating granulator. The granules were collected and air dried for one hour at 55°C, then left for drying at room temperature for 24°C and finally were sieved through 1,000-500 µ sieve. The granules were stored in desiccators using anhydrous calcium chloride for further use. The required dose was filled in hard gelatin capsules for the release studies [12].

Table 1: Composition of formulations (A1-A4)

Ingredients	Formulations			
	A1	**A2**	**A3**	**A4**
	% (w/w)	% (w/w)	% (w/w)	% (w/w)
Ibuprofen	50.0%	50.0%	50.0%	50.0%
Chitosan	40.0%	30.0%	20.0%	10.0%
HPC	-	10.0%	20.0%	30.0%
Lactose	10.0%	10.0%	10.0%	10.0%
01.0% lactic acid	Qs	Qs	Qs	Qs

Statistical analysis: A SPSS statistic software package (version 20) was used for logical batched and non-batched statistical analysis. The test of significance and lack of significance among treatments at a 95% confidence interval and α equal to 0.05 was carried out by using an overall ANOVA test. A test of Tukeýs allowable difference was calculated to find out the difference between the individual treatments.

Results

In-vitro release studies of Ibuprofen from granules of formulations A1 - A4: **Table 2** and **Figure 1** depict the drug release profile of the percentage of Ibuprofen released from a matrix system composed mainly from chitosan (40.0%), formulation A1. It is noticeable that 82.0% of the drug content was released from these granules after 24 hours with near perfect linearity of the drug release profile.
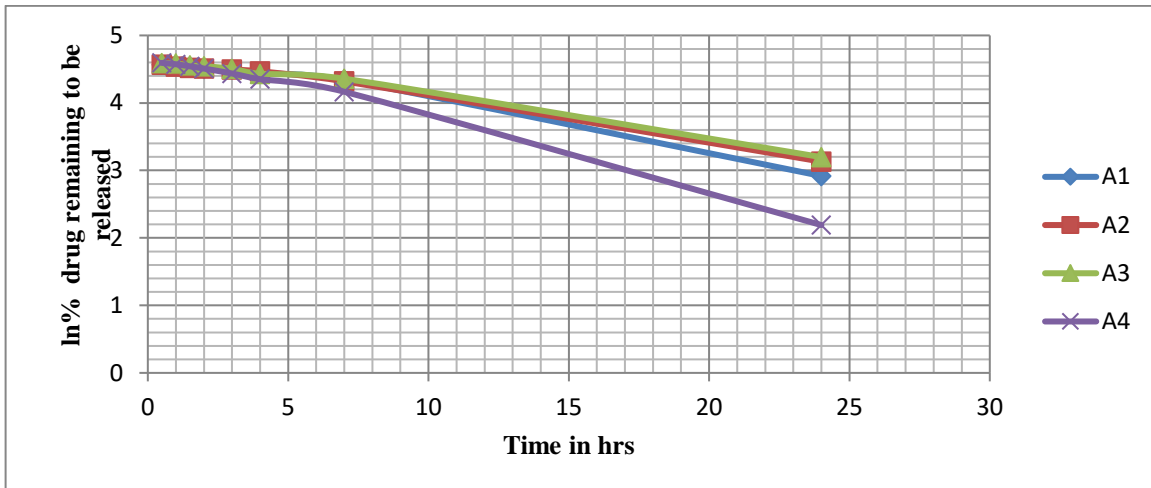
Kinetic data analysis for formulations A1 - A4: **Tables 3** and **4** show that the R^2 values for all mechanisms studied. The high R^2 values show that the release characteristics can be described by near zero-order kinetics for formulations A1, A2 and A3 and first-order kinetics for formulation A4. However, the release kinetics from formulation A1 - A4 can also be described by Higuchi as well as Korrsmeyer-Peppas models (**Figures 2, 3** and **4**). The data shown in **Table 5** reveals similar results in terms of release studies of chitosan / HPC granules in which a significant change is observed only by increasing the concentration of HPC up to 60.0% (p<0.05).

**Table 2:** Release of Ibuprofen from granules of formulations A1-A4

| Time (hrs)	Percentage of drug released and the amount released (mg)							
	Amount mg ± SD A1	% released A1	Amount mg ± SD A2	% released A2	Amount mg ± SD A3	% released A3	Amount mg ± SD A4	% released A4
00	00	00	00	00	00	00	00	00
0.5	15.60 ± 0.383	03.90	14.53 ± 0.254	03.63	5.503 ± 0.197	01.27	4.815 ± 0.021	01.14
1.0	21.76 ± 1.682	05.44	25.22 ± 0.028	06.30	8.210 ± 0.763	02.05	11.66 ± 0.339	03.13
1.5	27.23 ± 0.601	06.80	33.42 ± 0.268	08.35	21.60 ± 1.598	04.71	25.71 ± 1.032	06.10
2.0	37.32 ± 0.961	09.30	37.02 ± 0.844	09.25	23.00 ± 0.593	05.75	39.39 ± 1.711	09.12
3.0	40.58 ± 1.300	10.15	41.41 ± 1.290	10.35	37.73 ± 1.180	09.43	62.13 ± 0.926	15.53
4.0	61.80 ± 0.989	15.45	51.61 ± 0.135	12.90	64.01 ± 0.123	15.99	89.72 ± 1.138	22.41
5.0	73.07 ± 0.044	18.26	74.90 ± 0.106	18.72	60.23 ± 1.260	15.05	85.11 ± 1.011	21.27
7.0	92.54 ± 2.623	23.13	98.99 ± 0.742	24.74	95.75 ± 1.760	21.75	142.0 ± 3.181	35.50
24	326.0 ± 2.687	81.50	307.3 ± 0.346	77.00	302.1 ± 1.970	75.53	365.67 ± 0.49	91.06
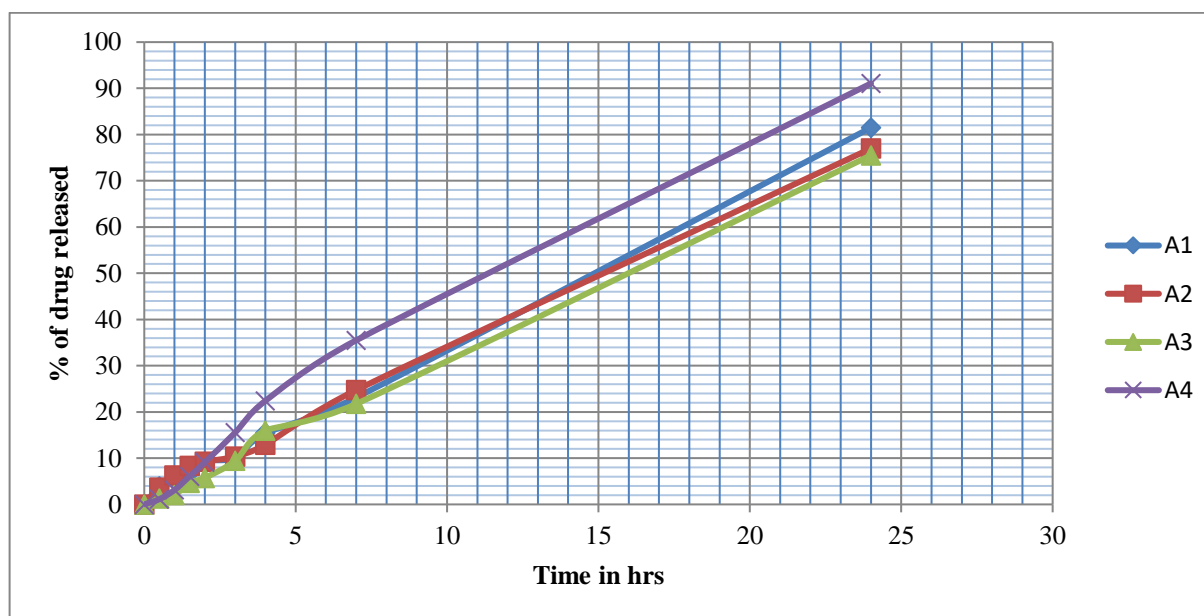
Figure 1: Cumulative percentage of Ibuprofen released from formulations A1-A4 against time

Figure 2: First-order plot of formulations (A1-A4)
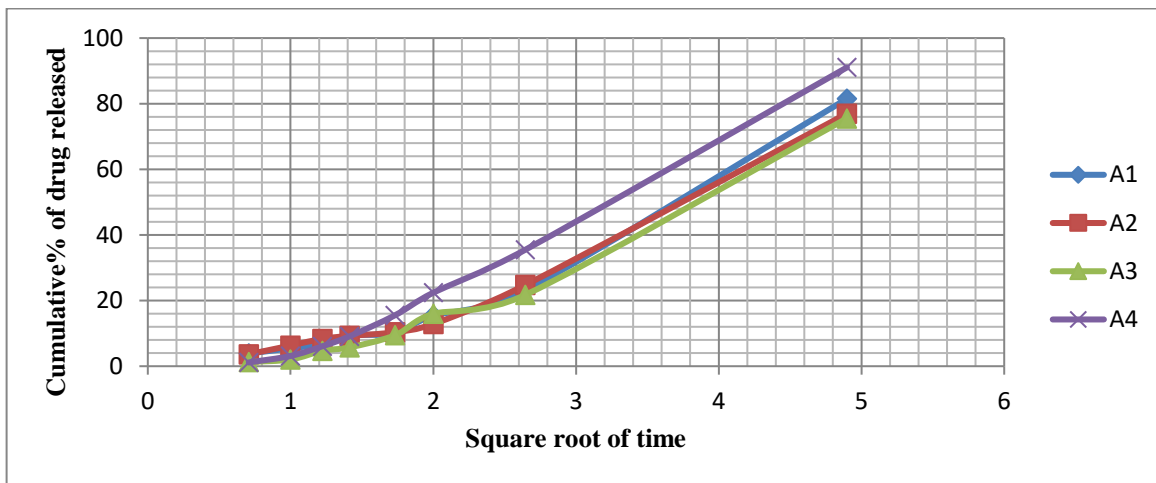
Figure 3: Higuchi equation plot for formulations (A1-A4)
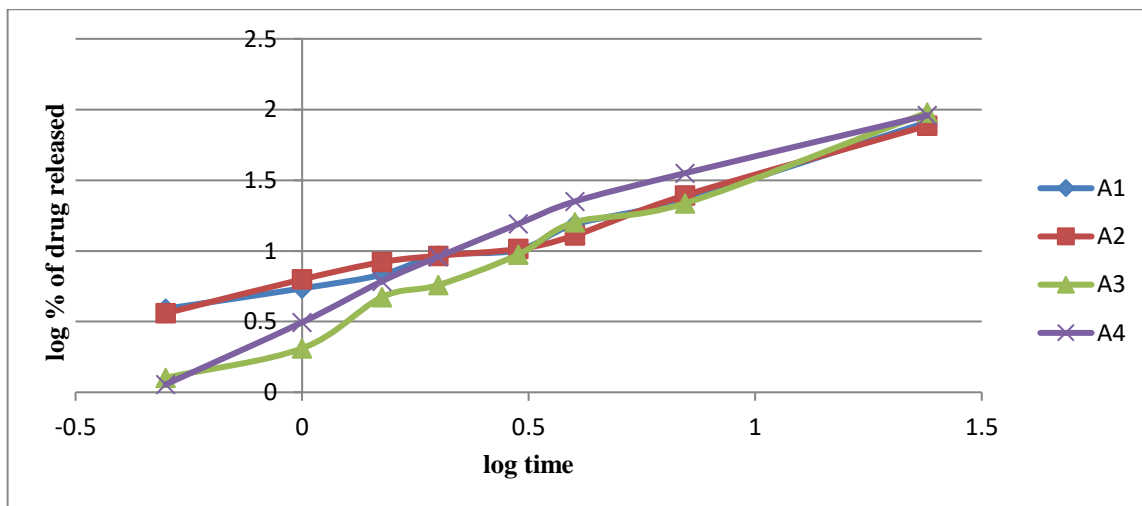
Figure 4: Korsmeyer-Peppas plot for formulations (A1-A4)

Table 3: Kinetic data analysis for formulation A1-A4

Zero order equation			First order equation		Higuchi equation	
Formula code	K°	R^2	K^1	R^2	K^H	R^2
A1	3.323	0.998	-0.071	0.980	18.78	0.944
A2	3.128	0.997	-0.061	0.985	17.67	0.947
A3	3.155	0.997	-0.060	0.989	18.11	0.962
A4	3.809	0.984	-0.103	0.991	22.16	0.989

Table 4: Drug release kinetics from formulations A1-A4 using peppas exponential model equation

Formulation	n	K^P	R^2	Drug release mechanism
A1 (40.0% chitosan)	0.789	5.370	0.974	Non-Fickian (anomalous)
A2 (20.0% chitosan: 20 HPC)	0.762	5.617	0.971	Non-Fickian (anomalous)
A3 (10.0% chitosan: 30 HPC)	1.139	2.636	0.989	Super case II type
A4 (30.0% chitosan:10 HPC)	1.140	3.527	0.968	Super case II type

Table 5: Statistical analysis of selected data of the release studies of granules

Test	A2	A3	A4	ANOVA	Tukey's test
% Ibuprofen released after 7 hrs	24.74	21.75	35.5	P<0.05 P=0.234	No significant difference
% Ibuprofen released after 24 hrs	77.00	75.53	91.06	P<0.05 P=0.018	A2 & A3, P=0.391< 0.05 A2 & A4, P=0.016 < 0.05 A3& A4, P=0.009 < 0.05

Discussion

When HPC was introduced into formulations A2 - A4 in addition to chitosan, it can be noticed that the percentage of drug released decreased after 24 hours from 82.0% to 75.0% as the percentage of chitosan decreased from 40.0% to 10.0% (**Table 2** and **Figure 1**). However, this percentage of drug released was significantly increased to reach 91.0% from granules of formulation A4 despite the increase of chitosan concentration to 30.0% which is most likely attributed to the presence of a low percentage of HPC (10.0%) in this formulation. Thus, chitosan as a cationic polymer in combination with nonionic water-soluble polymers such as HPC can enhance the ability of this system to sustain the drug release for at least 24 hours. In most cases, extended-release effect of the combination system is because HPC is a hydrophilic polymer that swells and becomes a state of hydro-gel in water and releases drugs in a controlled matter [13]. Ibuprofen conventional commercial tablets with a 400 mg dose have released the whole dose within the first six hours, in clear contrast to the chitosan granules. The n value indicates that the drug release follows an anomalous diffusion process, where the drug release from formulations A3 and A4 follows a non-Fickian diffusion process by super case II (swelling and relaxation of the polymer) which is attributed to the high content of HPC and chitosan, respectively. Since the n value for formulation A3 is approximately equal to 1.139 which is >0.9, in clear agreement with the fact that the drug release from systems with HPC is by dissolution and diffusion mechanisms which is mainly attributed to its hydrophilic properties [13].

Conclusion: In vitro, release of Ibuprofen in phosphate buffer from granules of chitosan revealed that chitosan release is increased in the formulations and corresponding steady increase in the percentage of drug released over 24 hours compared to commercial tablets which released over 80.0% of their content in two hours. Mathematical modeling of data revealed high correlation coefficients of drug release from most granules when zero order kinetics is constant drug release with time for 24 hours indicating release of drug can follow near-zero order kinetics. Treatment of data using other mathematical models revealed drug release might be described somewhere between diffusion-controlled, Fickian (anomalous) and non-Fickian which refers to a combination of diffusion and erosion-controlled release.

Author contributions: FM & FA contributed to the collection, analysis and interpretation of the data. MST conceived and designed the study and drafted the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for its contents.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Ethical issues: Including plagiarism, informed consent, data fabrication or falsification and double publication or submission were completely observed by the authors.
Author declarations: The authors confirm that all relevant ethical guidelines have been followed and any necessary IRB and/or ethics committee approvals have been obtained.

References

1. Mussa F, Almani F, Treki M (2020) The use of Chitosan to formulate Ibuprofen granules I: Physico-Chemical characterization. European Journal of Biomedical and Pharmaceutical Sciences. 7 (12): 68 -75. doi: Nil.
2. NGR R, Raj KRP, Nayak BS (2013) Review on matrix tablet as sustained release. International Journal of Pharmaceutical Research & Allied Sciences. 2 (3): 1-17. doi: Nil.
3. Säkkinen M, Seppälä U, Heinänen P, Marvola M (2002) In vitro evaluation of microcrystalline chitosan (MCCh) as gel-forming excipient in matrix granules. European Journal of Pharmaceutics and Biopharmaceutics. 54: 33-40. doi: 10.1016/s0939-6411(02)00019-x
4. Säkkinen M, Linna A, Ojala S, Jürjenson H, Veski P, Marvola M (2003) In vivo evaluation of matrix granules containing microcrystalline chitosan as a gel-forming excipient. International Journal of Pharmaceutics. 250: 227-237. doi: 10.1016/s0378-5173(02)00547-1
5. Ramteke KH, Dighe PA, Kharat AR, Patil SV (2014) Mathematical models of drug dissolution: A review. Scholars Academic Journal of Pharmacy. 3 (5): 388-396. Corpus ID: 29696977.
6. Dash S, Murthy PN, Nath L, Chowdhury P (2010) Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica. 67 (3): 217-223. PMID: 20524422.
7. Freitas MN, Marchetti JM, (2005) Nimesulide PLA microspheres as a potential sustained release system for the treatment of inflammatory diseases. International Journal of Pharmaceutics. 295 (1-2): 201-211. doi: 10.1016/j.ij pharm.2005.03.003
8. Gibaldi M, Perrier D (1982) Statistical methods for pharmacokinetic modeling. Drugs and the Pharmaceutical Sciences, 2nd ed., Marcel Dekker, Inc, New York and Basel. doi: 10.1002/bdd.2510040213
9. Higuchi T (1963) Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. Journal of Pharmaceutical Sciences. 52: 1145-1149. doi: 10.1002/jps.2600521210
10. Shoaib HM, Tazeen J, Merchant HA, Yousuf RI (2006) Evaluation of drug release kinetics from Ibuprofen matrix tablets using HPMC. Pakistan Journal of Pharmaceutical Sciences. 19 (2): 119-124. PMID: 16751122.
11. Siepmann J, Peppas NA (2001) Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Advanced Drug Delivery Reviews. 48 (2-3): 139-157. doi: 10.1016/s0169-409x(01) 00112-0

12. Ramesh KVRNS, Bhemakirnamayi BH, Sailaja M (2012) Design and evaluation of controlled release matrix tablets of Flurbirofen. International Journal of Chemical Science. 10 (4): 2199-2208. doi: Nil.

13. Picker-Freyer KM, Durig T (2007) Physical mechanical and tablet formation properties of hydroxypropylcellulose: In pure form and in mixtures. American Association of Pharmaceutical Scientists. Pharmaceutical Sciences and Technology. 8 (4) E92. doi: 10.1208/pt0804092