Effects of drug solubility on the release kinetics of water soluble and insoluble drugs from HPMC based matrix formulations

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The purpose of the present research work was to observe the effects of drug solubility on their release kinetics of water soluble verpamil hydrochloride and insoluble aceclofenac from hydrophilic polymer based matrix formulations. Matrix formulations were prepared by the direct compression method. The formulations were evaluated for various physical parameters. Along with the dynamics of water uptake and erosion, SEM and *in vitro* drug release of the tablets were studied. Applying an exponential equation, it was found that the kinetics of soluble drug release followed anomalous non-Fickian diffusion transport whereas insoluble drug showed zero-order release. SEM study showed pore formation on the tablet surface that differed depending on drug solubility. *t*-Test pointed to a significant difference in amount of both drugs released due to the difference in solubility. Solubility of the drug effects kinetics and the mechanism of drug release.

Keywords: solubility, release kinetics, swelling, erosion, matrix tablets, statistical analysis

Hydrophilic matrices are widely used to develop oral sustained release formulations. They can be used for controled release of both water soluble and insoluble drugs. The release of drugs varies with the nature of the matrix and also with the complex interaction of swelling, diffusion and erosion process (1). Oral controlled release dosage forms have been developed to restrict this system to specific regions of the gastrointestinal tract, to improve the pharmacological activity and to reduce toxicity (2). The most important method of fabricating controlled release formulations is incorporation of the drug in a matrix containing a hydrophilic, rate controlling polymer like HPMC (3). Hydrophilic polymer matrix systems are widely used because of their flexibility to provide a desirable drug release profile, cost effectiveness and broad regulatory acceptance (4). Verapamil hydrochloride (VP), the first calcium channel blocker, with a short elimination half-life, is considered a good candidate for the gastro-retentive dosage form because this

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will allow gradual release of VP to the upper part of the small intestine, where it is mainly absorbed, which will maximize its absorption compared to other controlled release approaches. Aceclofenac (AC) [2-(2',6'-dichlorophenyl)amino]phenylacetoxyacetic acid is a phenylacetic acid derivative with potent analgesic and anti-inflammatory properties. The high concentration with rapid drug absorption causes adverse effects to GIT. To improve the therapeutic efficacy of aceclofenac and reduce the severity of upper GI tract side-effects a dosage form with modified release properties should be prepared.

Thus, the objective of the present study was to develop a controlled release formulation of VP and AC as matrix tablets, to find out the effects of HPMC on the release pattern of both drugs and the effects of drug solubility on the drug release kinetics of both the water soluble and insoluble drug. In the present study, verapamil hydrochloride and aceclofenac matrix formulations were prepared by using different concentrations of HPMC (K15M).

EXPERIMENTAL

Materials

Verapamil hydrochloride and aceclofenac were gift samples from Nichloas Piramal India Ltd, India. Hydroxypropylmethyl cellulose (HPMC) K15M was procured from Genuine Chemicals, India. Microcrystalline cellulose (MCC), magnesium stearate and talc were procured from Nice Chemicals, India. Other materials and solvents used were of analytical grade.

Preparation of tablets

All formulations were prepared by the direct compression method. The drugs VP and AC (80 mg per tablet and 100 mg per tablet, respectively), polymer and other excipients were mixed in a double cone blender for 15 min. The amounts of polymer and other ingredients are given in Table I. The quantities of ingredients required for preparing sustained release formulations were compressed using a single punch-tableting machine (Cadmach® Machinery Co. Pvt. Ltd., India) equipped with 6.5 mm circular, flat and plain punches. The batch size of each formulation for each drug was 100 tablets.

Evaluation of matrix tablets

Quality control tests for the matrix tablets, such as hardness, friability and mass variation were determined using the reported procedure. Mass variation was determined by weighing 20 tablets individually, hardness was determined by taking 6 tablets from each formulation using a digital tablet hardness tester (Electro lab Ltd, India), friability was determined using 10 tablets in a Roche® friabilator (Electrolab Pvt. Ltd., India), which was rotated for 4 min at 25 rpm and the thickness of tablets was determined using a digital screw gauge (Mitutoyo, Japan), using five tablets from each batch. Table II summarizes the data.

Table I. Composition of sustained release matrix tablets of verapamil hydrochloride (80 mg)[a] and aceclofenac (100 mg)[a]

Formulation	Verapamil HCl (mg)	Aceclofenac (mg)	HPMC K15M (mg)	MCC (mg)	Talc (mg)	Mg-stearate (mg)
		Ingredients (mg/tablet)				
F1	80	–	10	100	5	5
F2	80	–	20	90	5	5
F3	80	–	30	80	5	5
F4	80	–	40	70	5	5
F5	–	100	10	80	5	5
F6	–	100	20	70	5	5
F7	–	100	30	60	5	5
F8	–	100	40	50	5	5

[a] Tablet mass: 200 mg
MCC – microcrystalline cellulose.

Drug content uniformity

Ten tablets were finely powdered and an amount equivalent to 80 mg of verapamil hydrochloride and 100 mg of aceclofenac tablet powder was accurately weighed and transferred to a 100 mL volumetric flask and extracted with phosphate buffer (pH 7.2). The mixture was then filtered and 1 mL of the filtrate was suitably diluted and analyzed at 278 nm for verapamil hydrochloride content and at 273 nm for aceclofenac using a

Table II. Properties of compressed tablets[a]

Formulation	Thickness (mm)[b]	Hardness (kg cm^{-2})[c]	Friability (%)[d]	Mass variation (%)[e]	Drug content (%)[f]
F1	4.8 ± 0.4	5.1 ± 0.4	1.0 ± 0.1	3.4 ± 0.7	100.3 ± 1.3
F2	4.6 ± 0.3	5.6 ± 0.5	0.4 ± 0.1	2.7 ± 0.7	101.0 ± 0.8
F3	4.7 ± 0.2	5.4 ± 0.5	0.7 ± 0.1	2.9 ± 0.4	100.2 ± 1.0
F4	4.4 ± 0.5	6.2 ± 0.7	0.1 ± 0.1	1.2 ± 0.2	99.4 ± 1.4
F5	4.6 ± 0.1	5.7 ± 0.4	0.4 ± 0.1	2.7 ± 0.3	98.9 ± 3.8
F6	4.8 ± 0.2	5.2 ± 0.9	0.8 ± 0.1	3.1 ± 0.9	99.7 ± 2.5
F7	4.5 ± 0.1	6.0 ± 0.7	0.2 ± 0.1	2.1 ± 0.2	100.7 ± 1.3
F8	4.5 ± 0.4	5.8 ± 0.3	0.3 ± 0.1	2.1 ± 0.1	100.2 ± 1.1

[a] All values are expressed as mean ± SD.
[b] $n = 5$
[c] $n = 6$
[d] $n = 10$
[e] $n = 20$
[f] $n = 3$

UV/Visible double beam spectrophotometer (UV-2450, Shimadzu, Japan). The method was validated for linearity, precision and accuracy. Table II summarizes the data.

In vitro *drug release*

Release of VP and AC was determined using a six stage dissolution rate test apparatus (5) (Erweka, Germany) at 50 rpm. The dissolution rate was studied using 900 mL of 0.1 mol L^{-1} HCl (pH 1.2) for the first 2 h, followed by phosphate buffer (pH 7.2) for the remaining time. The temperature was maintained at 37 ± 0.2 °C. Samples of 5 mL each were withdrawn at different time intervals, *i.e.*, 30, 60, 90, 120, 150, 180 up to 720 min, filtered through Whatman filter paper No. 1 (Auroco Pvt Ltd, Thailand) and replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and analyzed for VP and AC content spectrophotometrically. Release studies were conducted in triplicate.

The rate and mechanism of release of both drugs from the prepared matrix tablets were analyzed by fitting the dissolution data into the zero-order equation:

$$Q = k_0 t$$

where Q is the amount of drug released at time t and k_0 is the release rate constant, first order equation:

$$ln\,(100 - Q) = ln\,100 - k_1 t$$

where k_1 is the release rate constant and Higuchi's equation:

$$Q = k_2 t^{1/2}$$

where k_2 is the diffusion rate constant.

Drug release data was further analyzed by the Peppas equation (7, 8):

$$\frac{M_t}{M_\infty} = k t^n$$

where n is the release exponent indicative of the mechanism of release, M_t/M_∞ is the fractional release of the drug, t is the release time, k is the kinetic constant.

Swelling and erosion

Swelling and erosion studies were performed on twelve tablets using the method described by Reynold *et al.* (9) in phosphate buffer (pH 7.2) at 37 °C. The experiment was repeated three times for each individual time interval. Swelling and erosion studies were carried out at a stirring speed of 100 rpm (paddle type) (Figs. 3a and b).

Scanning electron microscopy

Optimized formulations of both drugs were removed from the dissolution apparatus at predetermined time intervals and sectioned through an undisturbed portion of the gel formed at the flat face of the tablet. The samples were then placed on the sample holder so as to present a cross-section of the tablet to the microscope. Samples were coated with gold and visualized under a scanning electron microscope (SEM) (LEO 430, UK). The diagram is given in Fig. 4.

Statistical analysis

In vitro drug release data of different formulations of verapamil hydrochloride and aceclofenac were subjected to the one way analysis of variance (one way ANOVA) to find out whether there was any significant difference between the formulations. Statistical analysis of the data was performed using the PRISM software (Graphpad, San Diego, CA, USA). A *t*-test was performed to find out if there was any significant difference in the release pattern of the two drugs, verapamil hydrochloride and aceclofenac (F1 and F5, respectively), at the same polymer concentration (10 % HPMC).

RESULTS AND DISCUSSION

Physical characterization of tablets

All formulations were prepared according to the formula given in Table I. The prepared matrix tablets were evaluated for various physical properties, as indicated in Table II. All the batches were produced under similar conditions to avoid processing variables. The mean hardness of the tablets was 5.7 ± 0.6 kg cm^{-2}, avarage mass variation was 2.7 ± 0.5 %, mean thickness was 4.63 ± 0.46 mm. The percentage friability of all formulations was between 0.1 and 1.0 %. The results of the hardness and friability tests indicate good handling properties of prepared tablets. The mean drug content in the tablets was 99.9 ± 2.3 %.

In vitro *drug release*

Formulations containing verapamil HCl (80 mg) and aceclofenac (100 mg) were developed by the simple direct compression method using HPMC K15M. The effect of polymer level on the release of water soluble VP and water insoluble AC was studied for tablets containing 5, 10, 15 and 20 % HPMC K15M (formulations F1-F8, respectively). Figs. 1a and b show how the amount of HPMC affects the release of both drugs. The release rate was found to be decreasing as the concentration of polymer increased from 5 to 20 %. Formulations F1, F2 and F3 containing 5, 10 and 15 % HPMC respectively, were able to sustain the drug release for 4, 7 and 9 hours respectively. For F1 94.1 % of the drug was released after 4 hours, for F2 93.5 % after 7 hours and for F3 94.1 % after 9 hours.

Formulations F1 and F2 underwent erosion before complete swelling could take place, resulting in faster drug release. Formulation F3 showed faster drug release in the first hour and then sustained the drug release for 9 hours. In this case, VP is a water-soluble hydrophilic material, which allows quicker penetration of water in the system, resulting in faster release of the drug and therefore a larger amount of polymer was required to sustain the release for 12 hours. On increasing the quantity of HPMC to 20 % (formulation F4), prolonged release was achieved up to 12 hours. The reason for this could be that the gel layer formed around the tablet becomes stronger, with few interstitial spaces between the microgels (10). Formulations containing water soluble drug showed a rapid release in the first hour. This phenomenon may be attributed to surface erosion and initial disaggregation of the matrix tablet, which occurs due to the formation of the gel layer around the tablet core (11).

Water insoluble aceclofenac formulations F5, F6 and F7 containing 5, 10 and 15 % HPMC, respectively, were able to sustain the drug release for 8, 10 and 12 hours, respectively. For F5 96.1 % of the drug was released after 8 hours, for F6 94.4 % after 10 hours and for F7 94.2 % after 12 hours. Formulations F5 and F6 underwent swelling; then gradually erosion could take place, resulting in slower release due to the hydrophobic nature of the drug. In the case of formulation F7, 15 % of HPMC was sufficient to sustain the drug release for 12 hours. On increasing the quantity of HPMC up to 20 %, the release of the drug was too slow and only 78.2 % of the drug was released after 12 hours. It was observed that when the polymer concentration was increased, the drug release rate decreased. This is due to the lower degree of the swelling because of higher concentration of polymers. However, further increase in polymer concentration did not significantly affect the drug release rate. Water insoluble drug required a smaller amount of polymer to sustain the release compared to the water soluble drug because the hydrophobic nature of the drug restricts the penetration of the solvent inside the matrix, which retarded drug release from the matrix.
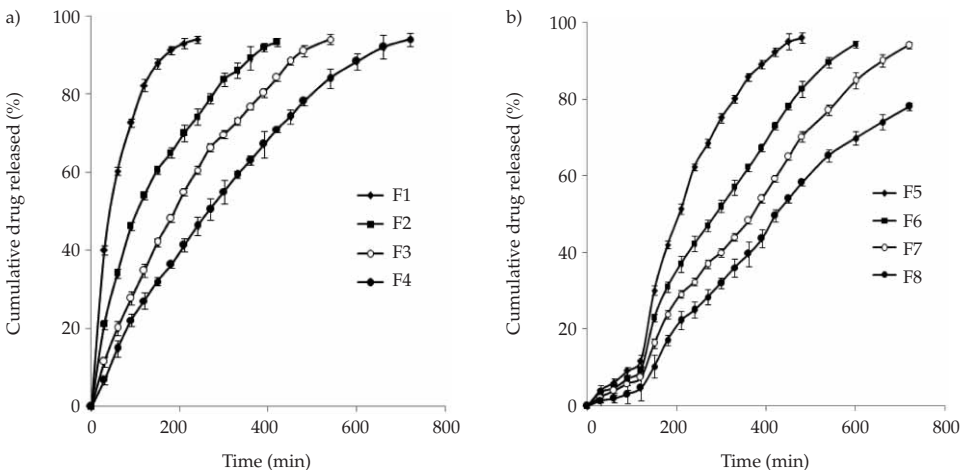

Fig. 1. Cumulative drug released (%) *vs.* time (mean ± SD, *n* = 3) from formulations: a) F1, F2, F3, F4 (containing verapamil hydrochloride) and b) F5, F6, F7, F8 (containing aceclofenac).
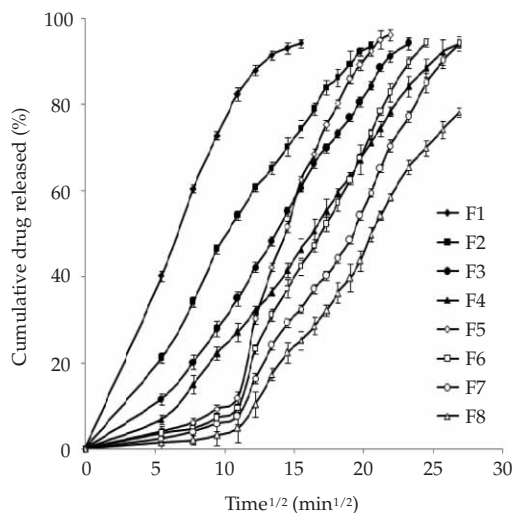
Fig. 2. Higuchi plot for cumulative percent drug released *vs.* square root of time (mean ± SD, *n* = 3) from different formulations.

From formulations F1, F2, F3 and F4, 14 to 60 % of verapamil hydrochloride was released within the first hour of the dissolution study whereas from formulations F5, F6, F7 and F8, where hydrophobic drug was combined with hydrophilic polymer, no burst release was observed (only 2 to 6 % drug release in 1 hour). It has been reported that if more than 30 % of the drug is released in the first hour of dissolution, this may indicate a chance of dose dumping (12). So, there is a probability of dose dumping for formulations containing hydrophilic drug with hydrophilic polymer HPMC. It can be also observed from Fig. 5 that by using the same polymer concentration, drug release of both drugs varied due to the solubility differences that allowed rapid disintegration of the polymeric layer and faster release of the drug. The soluble drug showed rapid release compared to the insoluble drug.

Table III. Kinetics of drug release from verapamil hydrochloride and aceclofenac matrix tablets[a]

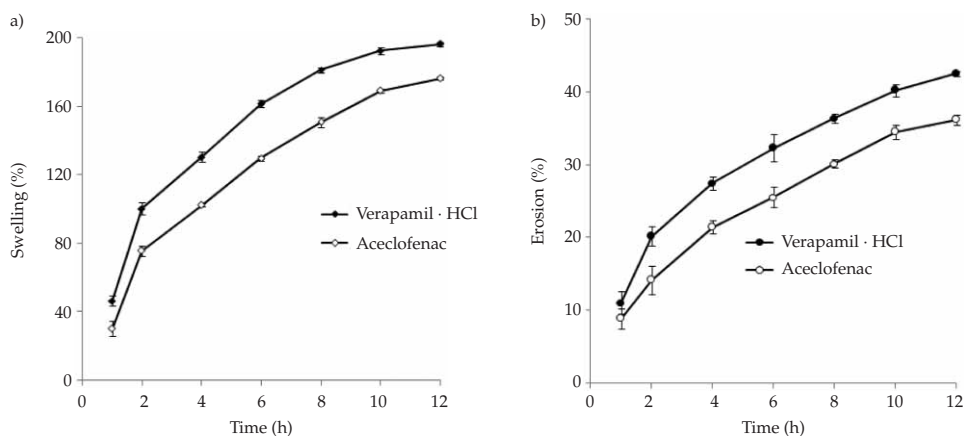| Formulation	Drug release kinetics (R^2)				Release exponent (*n*)
	Zero-order	First-order	Higuchi	Korsmeyer	
F1	0.788	0.983	0.989	0.999	0.510
F2	0.901	0.991	0.993	0.996	0.665
F3	0.958	0.971	0.994	0.994	0.799
F4	0.964	0.966	0.990	0.991	0.866
F5	0.959	0.945	0.904	0.890	0.910
F6	0.985	0.916	0.919	0.936	0.929
F7	0.990	0.908	0.917	0.961	0.967
F8	0.987	0.968	0.905	0.965	1.000

Fig. 3. a) Swelling and b) erosion behavior of verapamil · HCl and aceclofenac matrix tablets, respectively (mean ± SD, *n* = 3).

The linear regression analysis is given in Table III. The kinetic data of formulations F1 to F4 showed good fit in the Korsmeyer-Peppas model (13) (R^2 = 0.9909–0.999), whereas formulations F5 to F8 showed high linearity with the zero-order equation (R^2 = 0.959–0.990). The value of release exponent *n* ranged from 0.590 to 0.866 in case of formulations F1 to F4 with verapamil hydrochloride and 0.910 to 1.000 in case of formulations F5 to F8 containing aceclofenac.

From the release exponent in the Korsmeyer-Peppas model, it can be suggested that the mechanism that led to the release of verapamil was an anomalous non-Fickian diffusion transport (14), which indicates that the drug release occured through diffusion in the hydrated matrix and polymer relaxation. In case of aceclofenac, the mechanism of drug release shifted from anomalous non-Fickian diffusion to swelling controlled drug delivery systems with zero-order kinetics.

Swelling and erosion

Swelling and erosion studies indicate that swelling and erosion mechanisms might be operative during the drug release from matrix formulations F4 and F7 (Figs. 3a,b). It was observed that all the formulations were initially intact and when they were placed in dissolution media they gradually formed pores. It was also observed that swelling and erosion increased with time. It was observed for all formulations that swelling and erosion occurred simultaneously in the matrix helping to constant release of the drug from the matrices (15). Constant release in such situations occurs because the increase in the diffusion path length due to swelling is compensated by continuous erosion of the matrix (16). It was also observed that the formulations containing the water soluble drug showed higher water uptake and erosion capacity than the water in soluble drug, because, the former allows the solvent to penetrate the matrix and form a viscous gel around it, whereas the insoluble drug restricts solvent penetration inside the matrix and retards matrix swelling and erosion.
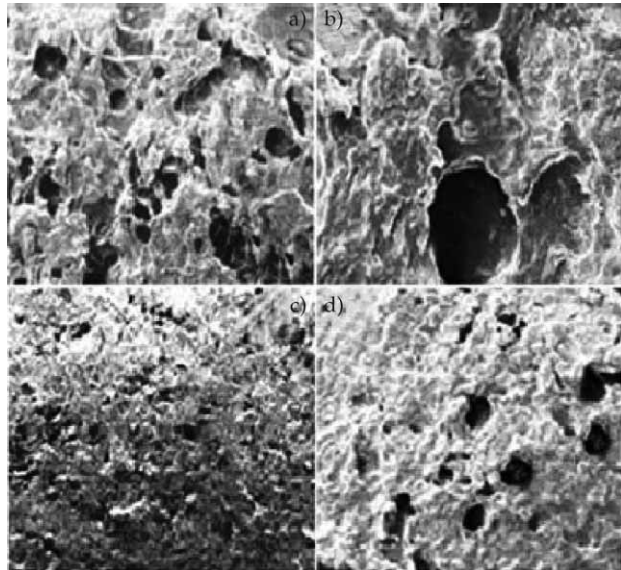
Fig. 4. SEM photographs (5000 X) of matrix tablets with verapamil hydrochloride after 2 and 8 hours (a, b) and aceclofenac after 2 and 8 hours (c, d).

SEM study also confirmed that in the case of optimized formulations F4 for VP and F7 for AC, both diffusion and erosion mechanisms might be operative for sustaining the drug release. SEM photographs showed that the matrix was initially intact and that pores formed throughout the matrix with time. Figs. 4a and b show that in the case of verapamil, the swelling and simultaneous formation of pores was more pronounced compared to aceclofenac (Figs. 4c and d). It was also observed that matrix erosion increased with time, and that pores were gradually formed and their diameter increased with time. This study also revealed that formation of gelling structure indicated the chances of matrix swelling.
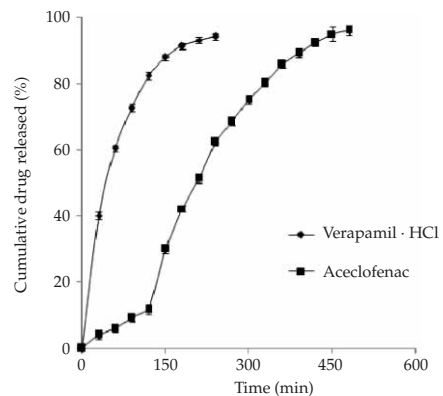

Fig. 5. Effect of drug solubility on the drug release at the same polymer concentration (mean ± SD, n = 3).

CONCLUSIONS

Verapamil hydrochloride and aceclofenac sustained release matrix tablets were prepared successfully using HPMC as polymer to retard the release and achieve the required dissolution profiles. Results of the present study demonstrate that drug solubility has a significant effect on the release kinetics and mechanism of drug release. Water soluble drug required a larger amount of polymer to sustain the drug release compared to the insoluble drug the mechanism of drug release followed anomalous non-Fickian diffusion transport and zero-order for water soluble and insoluble drugs, respectively.

In vito drug release data showed a significant difference among all the formulations containing different concentrations of HPMC and *t*-test further suggested that at same polymer concentration there was a significant difference between the release patterns of both drugs. This might be attributed to different solubility profiles of both drugs affecting the drug release kinetics.

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S A Ž E T A K

Učinak topljivosti na kinetiku oslobađanja vodotopljivih i vodonetopljivih lijekova iz matriksnog sustava na bazi HPMC

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Cilj rada bio je praćenje učinka topljivosti na kinetiku oslobađanja vodotopljivog verapamil hidroklorida i netopljivog lijeka aceklofenaka iz matriksnih sustava na bazi hidrofilnog polimera. Matriksni sustavi pripravljeni su izravnom metodom kompresije. Uz ispitivanje uobičajenih fizikalnih svojstava, ispitivana je i dinamika primanja vode, te erozija, SEM i i*n vitro* oslobađanje ljekovite tvari iz tableta. Primjenom eksponencijalne jednadžbe utvrđeno je da mehanizam oslobađanja topljivih lijekova slijedi anomalni ne-Fickov difuzijski transport, dok netopljivi lijekovi slijede kinetiku nultog reda. SEM ispitivanja pokazala su pore na površini matriksa ovisne o topljivosti ljekovite tvari. *t*-test ukazuje da količina oslobođenog lijeka značajno ovisi o njegovoj topljivosti. Topljivost lijeka ima značajan učinak na kinetiku i mehanizam oslobađanja.

Ključne riječi: topljivost, kinetika oslobađanja, bubrenje, erozija, matriksne tablete, statistička analiza

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