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EFFECT OF POLYMERIC EXCIPIENT MOLECULAR WEIGHT ON DRUG RELEASE PROFILES INVESTIGATED BY ONLINE MONITORED CONTROLLED RELEASE STUDIES

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ABSTRACT

Ascorbic acid loaded polyvinylpyrrolidone tablets are prepared and ascorbic acid release profiles are monitored by the automatic continuous online monitoring of polymerization (ACOMP) system. Three different molecular weights of polymers are used in tablets. Parallel experiments are performed using powder samples. Drug release from tablets is investigated as zeroth and halfth order processes for the dissolution step and a first order process for the diffusion step. Powder samples are investigated on the basis of a first order diffusion model. Kinetic rate constants for the dissolution and diffusion processes are calculated. Release profiles are found to depend strongly on the molecular weights of the polymers. Higher molecular weights are found to slow down both the dissolution and the diffusion processes. Diffusion constants are compared with independent viscosity measurements.
Keywords: Online monitoring, drug delivery systems, biomedical applications, dissolution, diffusion.

KONTROLLÜ SALIM ÇALIŞMALARINDA KATILAN POLİMER MOLEKÜL AĞIRLIĞININ İLAÇ SALIM PROFİLİNE ETKİSİ SÜREKLİ İZLEME YÖNTEMİ İLE İNCELENDİ

ÖZ

Askorbik asit yüklü polivinilpirolidon tabletleri hazırlandı ve askorbik asit salım profilleri sürekli izleme sistemi ile izlendi.Tabletlerde üç farklı molekül ağırlığında polimer kullanıldı. Toz örnekler kullanılarak paralel deneyler yürütüldü. Tabletlerden ilacın salımı çözünme basamağında sıfırıncı ve yarımıncı diffüzyon basamağında ise birinci mertebeden olarak incelendi. Toz örneler ise diffüzyon modeline dayanarak birinci mertebeden olarak incelendi. Çözünme ve diffüzyon süreçleri için kinetik hız sabitleri hesaplandı. Salım profillerinin polimerlerin molekül ağırlığına kuvvetle bağlı olduğu bulundu. Yüksek molekül ağırlığının hem çözünme hem de difüzyon süreçlerini yavaşlattığı görüldü. Difüzyon sabitleri bağımsız viskozite deneyleri ile kontrol edildi.
Anahtar Sözcükler: Sürekli izleme, ilaç salım sistemleri, biyomedikal uygulamalar, çözünme, diffüzyon.

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1. INTRODUCTION

Controlled release drug systems are very important for drug development. They help to reduce the frequency of drug administration, improving patient comfort. In vitro release experiments and appropriate mathematical modeling are important tools for the investigation of these systems. Depending on the type of drug system, dissolution profiles and models differ considerably. Polymer based drug release systems are designed in numerous structures. Release from these structures include many concomitant processes like dissolution, diffusion, adsorption and desorption. These processes depend on polymer properties and production method in addition to the drug system.

Cast or molded, and subsequently annealed dissolution-controlled release systems, made of semi-crystalline polyvinyl acetate, were investigated by Peppas [1,2]. Kurnik developed an analytical model for transdermal patches including dispersed crystals [3]. The effect of the polymer molecular weight of pH sensitive and thermo sensitive beads on the insulin release profile was investigated by Ramkissoon-Ganorkar [4]. Synthetic polydisperse binders [4-10], and / or biopolymeric binder materials [11-15] are used in in-vitro controlled release studies. Crosslinked gel or bead systems have also been examined in release system productions [6,11-14]. In the case of synthetic linear polymers, molecular weight and polymer's heterogeneity are important factors. Crosslinking density is another factor which has to be considered in crosslinked and gel systems, polymeric films, biodegradable implants and tissue engineering scaffolds. Mathematical studies include models proposed for various designed products and experimental conditions [16-24]. Recently release from water insoluble ethyl cellulose coated pellets were investigated by Marucci et al. [25].

Due to its water solubility, bio-compatibility, and edible nature, polyvinylpyrrolidone (PVP) is preferred in a large number of applications, either alone or in compounded form. It is frequently used as a binder in controlled release tablet formulations [7,8,15] however the effect of the molecular weights of these polymers on the release profiles of the loaded drugs has not been investigated in detail. The main aim of this work is to investigate the effect of PVP molecular weight on the tablet dissolution kinetics for combined dissolution and diffusion processes, both of which must be included in a realistic description of drug absorption from a confined volume. In most of the in vitro controlled release studies, drug included sample is loaded into a solution or water of constant volume. Concentration measurements are then performed either by sequential sampling or in situ from the same volume. Administration of a drug by tablet includes both the dissolution of tablet and the diffusion of the drug through the stomach fluid to its surface and a realistic model should include both processes.

In this work, release of ascorbic acid from PVP tablets are monitored with automatic continuous online monitoring of polymerization system (ACOMP). ACOMP is a modified HPLC system allowing simultaneous use of light scattering, viscosity and refractive index detectors and an UV spectrophotometer, during time dependent processes. Polymerization [26,27] copolymerization [28-30]and physical processes, like ultrasonic degradation [31-33] were monitored with ACOMP.

Different molecular weight polymeric tablets are expected to create different entanglement environments and result in different dissolution and diffusion profiles for the loaded drug. In this work the effect of molecular weight on the release properties are investigated. Ascorbic acid loaded PVP tablets are placed in a dialysis bag and dissolution and diffusion of the ascorbic acid is monitored outside of the dialysis bag. The diffusion experiments are repeated with powder samples (not pressed in tablet form). Viscosities of the PVP samples are measured separately.

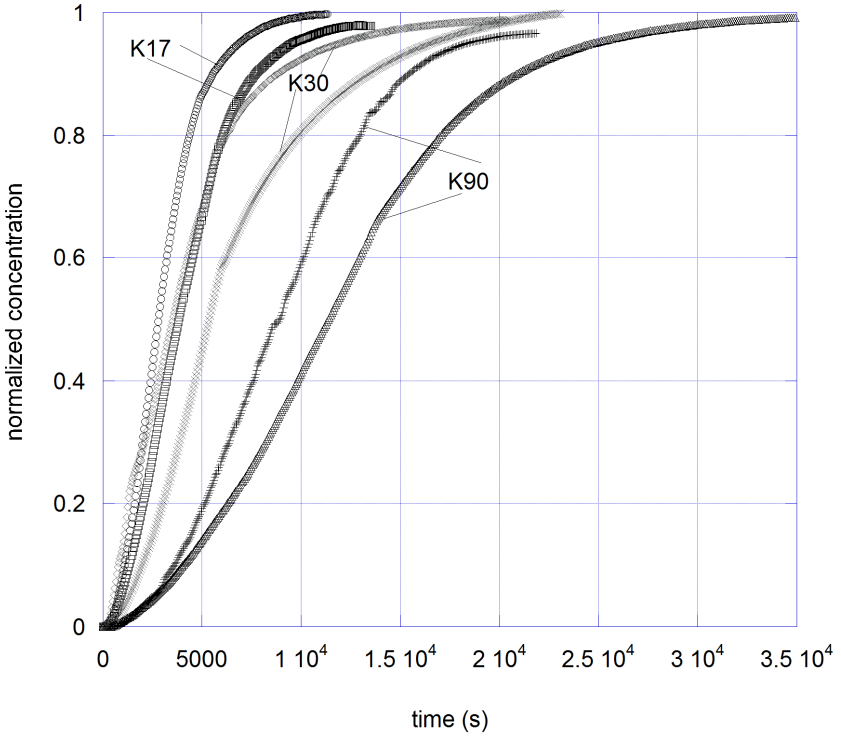

Figure 1. Ascorbic acid release profiles from tablets (Two tablet samples for each PVP molecular weight are shown in the figure)

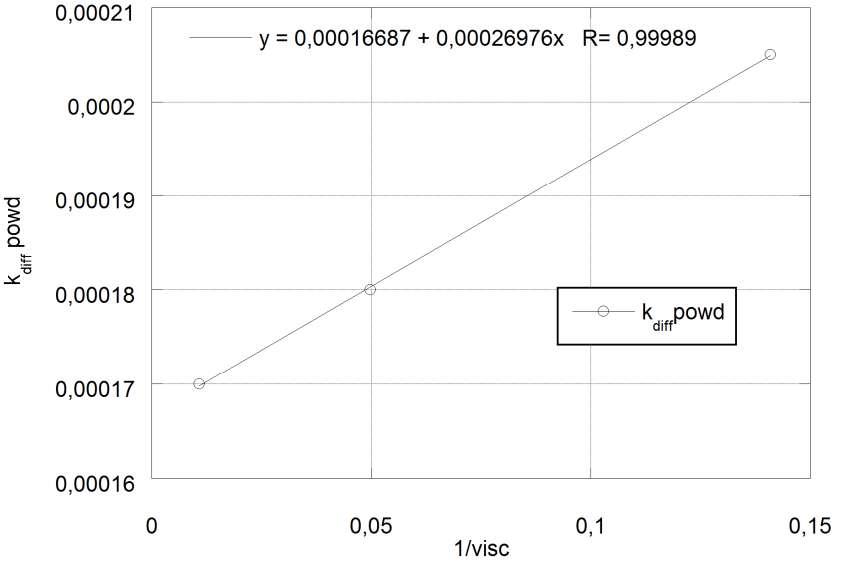

Figure 2. The diffusion rate constants are plotted versus the inverse viscosity for powder samples

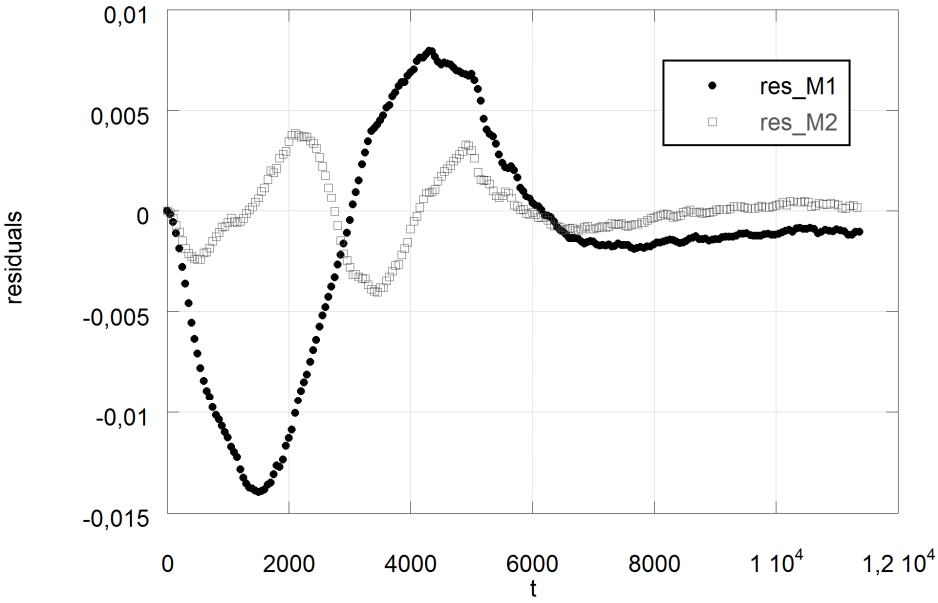

Figure 3. Residuals for M1and M2 models for tablet 2810K17

2. THEORY

2.1. Drug Dissolution and Diffusion Processes

The drug delivery process mainly consists of dissolution and diffusion steps. The order of the dissolution process of a surface eroding tablet depends on its geometry. For surface eroding systems dissolution rate is proportional to the surface area of the tablet. Surface areas of flat tablets change little during dissolution. Dissolution of these systems can be modeled as a zero'th order process. Volume of a thin and long cylinder is proportional to the square of its radius and its surface area is proportional to its radius, thus, its surface area is roughly proportional to the square root of its volume. Surface area of a sphere is proportional to 2/3rd power of its volume. It is appropriate to model their dissolutions as halfth and 2/3rd order processes respectively. Bulk erosion is a first order process. The diffusion step is also first order, if it is assumed to be Fickian. As the PVP dissolves, ascorbic acid diffuses through the PVP chains and diffuses out of the dialysis bag according to the Equation 1;

$$X \overset{k_0}{\rightarrow} Y \overset{k_1}{\rightarrow} Z \tag{1}$$

Here k_0 and k_1 are rate constants for dissolution and diffusion steps and X, Y and Z denote the ascorbic acid in the tablet, in the dialysis bag and outside the dialysis bag respectively. The tablets used in these experiments were cylindrical with diameters approximately three times their heights. During erosion their aspect ratios naturally increased, geometry becoming more like a flat disk. Dissolution begins as a halfth to two third order process and evolves toward zeroth order as the tablet flattens.

Two models are considered for tablets. M1 (model1) with halfth order dissolution and first order diffusion steps, and M2 (model 2) with zeroth order dissolution and first order diffusion steps.

In model M1 ascorbic acid concentration out of the dialysis bag, [Z], before complete dissolution of tablet ($t \leq \tau_0$) is given by Equation 2.

$$[Z]= [Z]_e \{1-(1-t/\tau_0)^2- 2\tau_1/\tau_0 [(1+\tau_1/\tau_0) (1-\exp (-t/\tau_1) -t/\tau_0]\} \qquad t \leq \tau_0 \tag{2}$$

Here $[Z]_e$ is the equilibrium value of [Z], $\tau_0=1/k_0$, $\tau_1=1/k_1$

After the complete dissolution of tablet, ascorbic acid concentration is given by Equation 3.

$$[Z]= [Z]_e (1 - 2\tau_1/\tau_0 [(1+\tau_1/\tau_0) (1- \exp (-\tau_0/\tau_1))-1] \exp (-(t-\tau_0)/\tau_0)\} \quad t \geq \tau_0 \tag{3}$$

Assuming the zeroth order dissolution and first order diffusion steps, (M2) with the same definitions above, time dependence of ascorbic acid concentration, before complete dissolution of tablet is given by Equation 4.

$$[Z]= ([Z]_e/\tau_0) [t-(1-\exp (-t/\tau_1))\tau_1] \qquad t \leq \tau_0 \tag{4}$$

After the complete dissolution of the tablet ($t \geq \tau_0$) ascorbic acid concentration is given by Equation 5.

$$[Z]= [Z]_e (1 - \tau_1/\tau_0 (\exp (\tau_0/\tau_1) – 1) \exp (-t/\tau_1)) \quad t \geq \tau_0 \tag{5}$$

For powder samples only first order diffusion kinetics is applied to the results because the dissolution step is so rapid that it is considered to be instantaneous.

3. EXPERIMENTAL

3.1. Materials and Methods

PVP samples (K17, K30, K90) were used for tablet preparation, molecular weight ranges are given in Table 1. PVP samples and ascorbic acid were used as received. Deionized water was used in experiments. Ascorbic acid concentration was measured by the UV detector (Shimadzu SPD10AV) at 250 nm. Each PVP (0.25g) and ascorbic acid (0.04g) sample were mixed thoroughly and pressed into cylindrical tablets of 1 cm diameter and 0.3 cm thickness at 200 kPa in a controlled hydraulic press. Tablet was then placed in a dialysis bag containing 30 ml water and placed in the reactor containing 70 ml of water. A sample stream of solution was withdrawn by a peristaltic pump from outside of the dialysis bag and send through the UV detector and returned to the main solution to keep the volume constant. Data were recorded every five seconds. During the process the system temperature was kept constant at 25^0C. UV measurements were continued until a steady-state profile was obtained. Each experiment was repeated three times. Parallel sets of experiments with polymer and ascorbic acid in powder form were also performed. PVP never got out of the dialysis bag used, at any molecular weight. Viscosity and light scattering detectors showed no polymer detection.

Viscosities of polymer samples, K17, K30 and K90 were measured with the viscosity detector (Validyne) of the ACOMP system and are given Table 1.

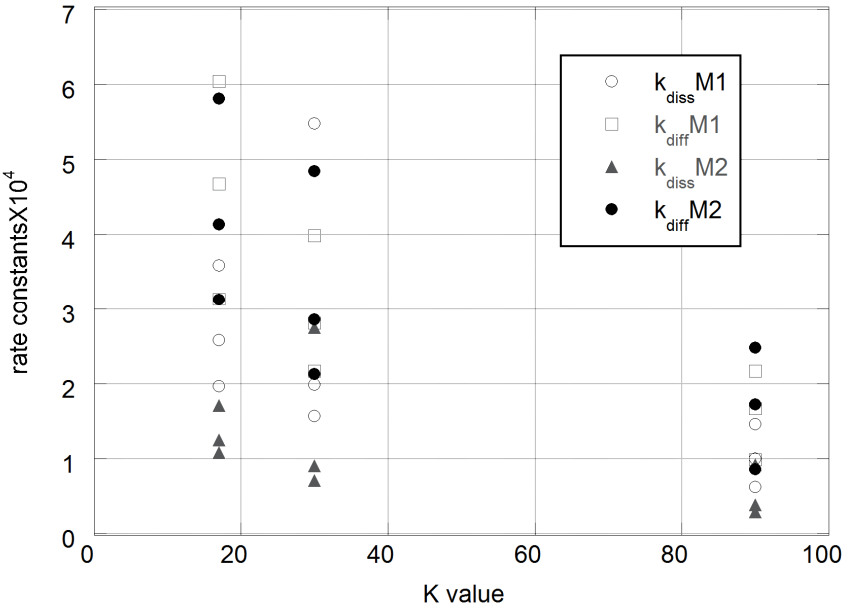

Figure 4a. All dissolution and diffusion rate constants for tablets versus K values of the PVP, for both models

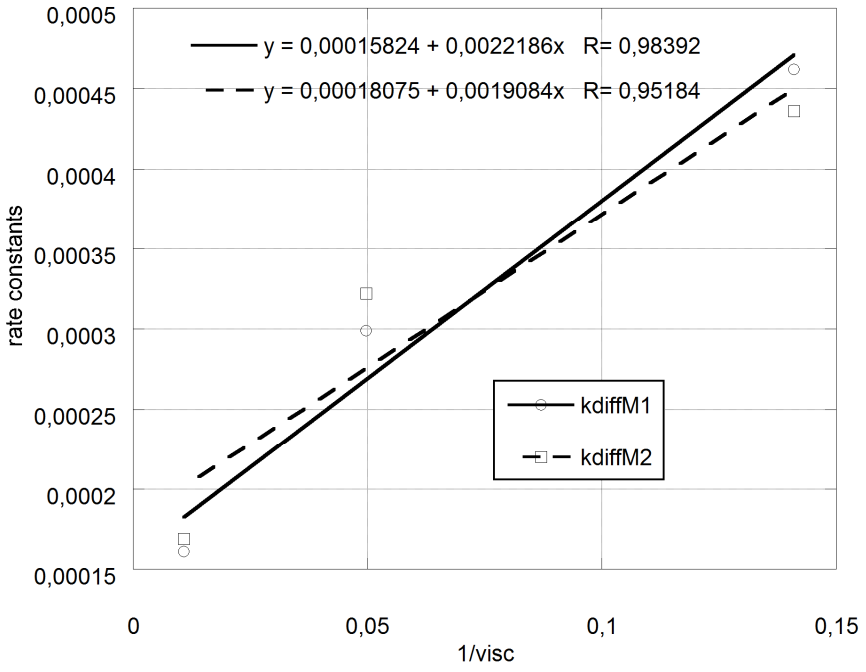

Figure 4b. Diffusion rate constants versus one over viscosity. In this figure the diffusion rate constants are the averages of three experiments

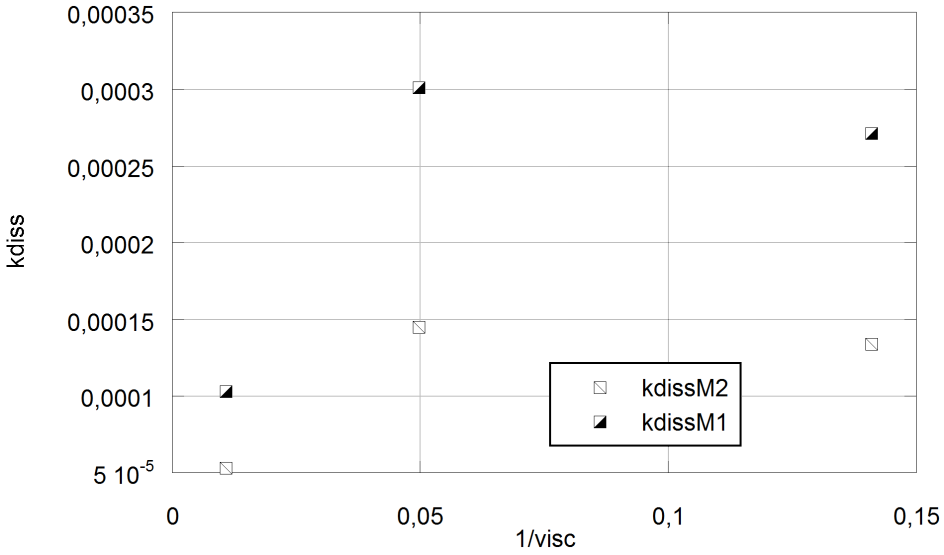

Figure 4c. Dissolution rate constants versus one over viscosity. In this figure the dissolution rate constants are the averages of three experiments

Table 1. Limit intrinsic viscosities and molecular weight ranges of PVP used in the tablets and powder samples

K value	Molecular Weight range	Limit viscosity [visc] (ml/g)	1/[visc]	R
1110K17	7000-11000	7.09	0.141	.9984
2210K30	40000-65000	19.3	0.0518	.9905
1810K30	40000-65000	20.9	0.0478	.9819
1210K90	900000-1500000	81.32	0.0123	.9965
0510K90	900000-1500000	107.57	0.0093	.9937

4. RESULTS AND DISCUSSION

Ascorbic acid release includes the steps of tablet dissolution, ascorbic acid diffusion out of the PVP tablet, ascorbic acid diffusion through the dialysis membrane, ascorbic acid release from the dialysis bag, and detection of the ascorbic acid by the UV detector.

Experimental results for tablets are given in Figure 1 (Two tablet samples for each molecular weight are shown in the figure). As can be seen from the figure, higher PVP molecular weights correspond to slower release and longer time scales. The extremely large number of data points obtained by online monitoring enabled analyzing the data in terms of dissolution and diffusion processes. Figure 1 shows that the times to reach the equilibrium concentrations are approximately 10000-13000s, 20000s and 30000s for K17, K30 and K90 tablets respectively.

In powder samples, dissolution is immediate and the first order diffusion rate constants are given in Table 2. Diffusion rate decreases with increasing polymer molecular weight.

The diffusion rate constants are plotted versus the inverse of viscosities (1/visc) in Figure 2. It is seen that all data fit on a straight line, showing the diffusion is directly proportional to 1/visc.

Table 2. Ascorbic acid diffusion rate constants from powder PVP samples

Sample No	t_{diss}	Diffusion k_{diff} powd x10^4
1110K17	0.21	2.0
2810K17	0.30	2.1
2210K30	0.33	1.8
1210K90	0.36	1.7

Table 3. Dissolution and diffusion rate constants, and tablet dissolution times for models and experimental tablet dissolution times

	M1 (Half-Fist order model)			M2 (Zero-First order model)			Exp
Sample No	k_{diss}M1 x10^4	k_{diff}M1 x10^4	t_{diss}	k_{diss}M2x10^4	k_{diff}M2 x10^4	t_{diss}	t_{diss}
1110K17	1.97	4.68	6690	1.08	4.14	4040	5360
2810K17	2.58	6.04	4730	1.25	5.81	2980	3790
1710K17	3.59	3.14	3680	1.71	3.13	2550	-----
2210K30	5.48	2.81	2270	2.75	2.68	1420	-----
1810K30	1.57	3.99	8620	0.71	4.85	6580	7390
1210K90	0.623	1.67	19300	0.29	1.72	13500	15000
0510K90	1.00	2.17	13000	0.39	2.48	10900	-----

Dissolution and diffusion rate constants and tablet dissolution times according to the two models and experimental tablet dissolution times are given in Table 3. Best fit parameters of M1 model are given in second and third columns and the best fit parameters of M2 are given in fifth and sixth columns. Residuals of both models for 2810K17 are shown in Figure 3. Both models fit the data well. M2 the zero-first order model gave a slightly better fit. However the residuals showed some structure because the exact time dependent geometry is not taken into account. Data for the other experiments gave similar results. As the purpose of this work is to find the effect of the molecular weight of the binder polymer on the release profile and not obtaining the exact (and geometry dependent) shape of the profile, the fits are sufficiently good.

The dissolution and diffusion rate constants for tablets versus K values of the PVP, for both models, are summarized in Figure 4a. All rate constants decreased monotonically with increasing K value i.e. the molecular weight.

Figure 4b shows the diffusion rate constants of both models versus (1/visc). The plots are almost linear, R values are close to one and we can see that the diffusion rate is determined by the polymer solution viscosity which is a direct measure of polymer molecular weight.

Figure 4c shows the dissolution rate constants of the models versus (1/visc). The averages of three experiments are shown in Figures 4b and 4c. Here the behavior is clearly not linear. The dissolution rate constant increases from K90 (1/visc)= 0.01 to K30 (1/visc)=0.05 but does not change significantly from K30 to K17 (1/visc)= 0.14. This nonlinear behavior shows that viscosity is not the sole determining factor for the dissolution process.

5. CONCLUSION

As K values increase and 1/visc decrease, all rate constants decreased remarkably and time to reach the equilibrium concentration increased. The dissolution and diffusion rate constants of both models decreased by almost a factor of 3 as one goes from K17 to K90. The plot of the tablet diffusion rate constants versus inverse viscosity shows that the diffusion constant is almost linear with inverse viscosity. The dissolution constant by contrast reaches a saturation value as 1/visc reaches about 0.1. This indicates that polymer molecular weight and viscosity are not the sole factor in determining the dissolution constant.

The results clearly show that the polymer molecular weight is an extremely important factor in determining the drug release profile and should be considered in planning drug systems.

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