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Modelling of drug release from polymer matrices: Effect of drug loading

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Abstract

The release kinetics of caffeine and potassium chloride (KCl) representing poorly soluble and water-soluble drugs from polyvinylpyrrolidone (PVP) matrices were studied using different mathematical models. Dissolution parameters obtained from the release data were employed to characterize the effect of drug loading on the release kinetics. The deviations observed from the predicted values for these parameters were explained using percolation theory as well as the release kinetics of the matrix material itself.

Keywords: Drug release; Polymer matrix; Mathematical modeling; Drug loading; Percolation theory; Critical percolation threshold

1. Introduction

Polymeric materials are extensively used in controlling the release of drugs. Biodegradable polymers based on polylactic acid or polyanhydrides have been used to control long time release from implants and other drug delivery systems. Hydrophilic water-soluble polymers, on the other hand, may be used for controlled release by the oral route. Ford et al. (1987) investigated the retarding effect of hydroxypropylmethylcellulose (HPMC) when used as a matrix for both water-soluble and poorly soluble drugs. Alderman (1984) related this effect of HPMC to the gelatinous layer formed when the polymer is hydrated by water. A water-soluble drug is released predominantly by diffusion out of this layer, whereas for a poorly soluble drug the erosion of the layer will be the predominant mechanism of release (Ford et al., 1991).

Polyvinylpyrrolidone (PVP) and polyethylene glycols (PEGs) are water-soluble polymers often used as tablet matrices. The mechanisms and the extent by which these polymers might affect drug release have been subjects of some recent studies. For example, it has been shown that PVP increased the dissolution rates of frusemide in both mixed and dispersion systems of this drug with PVP (Doherty and York, 1987).

A similar effect was attributed to PEGs when used in combination with different drugs (Corrigan and Timoney, 1976). Actually, the authors of

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the latter study determined these interactions by assaying the release rates of the polymer itself (Corrigan and Timoney, 1976; Corrigan et al., 1979).

The aim of the present study was to model (mathematically) changes in the release kinetics of drugs from PVP matrices in relation to the varying degree of drug loading.

It was also the purpose of this study to investigate the dissolution behaviour of the polymer matrix parallel to that of the drug itself.

2. Materials and methods

The materials used were: caffeine anhydrous pulvis (Sandoz lot 88828), true density 1.44 g/ml; potassium chloride (KCl) (Sandoz lot 78.60473), true density 1.983 g/ml; polyvinylpyrrolidone (PVP) (K-30, Sandoz lot 8781901), true density 1.175 g/ml. Binary mixtures were prepared by mixing drug (caffeine or KCl) and PVP in different ratios to cover the range of (10–100)% w/w of drug. The mixtures were homogenized by mixing them for 10 min in a Tubula mixer (Willy A. Bachofen AG, Basel, Switzerland). Tablets (round, flat, diameter 11 mm) were compressed to a constant relative porosity of $(10 \pm 0.3)\%$ using a computerized Zwick 1478 Universal Testing Instrument (Zwick GmbH, Ulm, Germany).

Dissolution studies were conducted in a rotating disk type of intrinsic dissolution apparatus described in detail by Bonny (1992). The tablets were embedded in paraffin (melting temperature $< 56°$ C, E. Merck, Darmstadt, Germany) in order to keep one tablet surface exposed to the dissolution medium. Dissolution tests were run in 1500 ml water at $(37 \pm 0.5)°$ C at 50 rpm. All studies were performed in triplicate.

The amount of released caffeine was followed spectrophotometrically at 273 nm at time intervals of 2 min for up to 4 h using an automated Beckman DU-65 Spectrophotometer equipped with soft-pac dissolution module (Beckman Instruments Inc., Fullerton, USA).

The amount of released KCl was assayed conductometrically using a Model 660 conductometer with an immersible measuring cell (cell constant $c = 0.8$ cm^{-1}), (Metrohm AG, Herisau, Switzerland) and calibration curves covering the concentration range of (0–800) μg/ml.

The amount of released PVP was followed spectrophotometrically at 206 nm using calibration curves. Because caffeine interferes at this wavelength, only binary mixtures of KCl and PVP were analyzed for PVP.

3. Results and discussion

3.1. Effect of drug type

The dissolution profiles of PVP-matrix tablets containing between 10 and 100% w/w of caffeine and KCl, respectively, were examined. For all drug loadings of caffeine investigated, the root time profiles show a gradual increase in release rates until up to approx. 6 min$^{1/2}$ followed by a more linear $\sqrt{}$time release. These findings are similar to the dissolution behaviour of other poorly soluble drugs, e.g., diazepam and indomethacin in HPMC matrices reported by Ford et al. (1985, 1987). The explanation for the sigmoidal shape of the profiles is indicative of the 'lag time' needed to elapse before the drug release starts to follow the root of time kinetics. The lag time was reported to increase with increase in hydrophobicity of the drug (Ford et al., 1991). Depending upon the loading, lag times of between 25 and 30 min were found in the caffeine PVP systems under study.

The dissolution profiles of KCl showed a more linear release especially at higher drug loadings ($> 50\%$ w/w). At low loadings of KCl the $\sqrt{}$time law does not accurately describe the release kinetics of this water-soluble drug.

3.2. Release models

Higuchi (1963) described the release of both poorly soluble and water-soluble drugs from a single face of a tablet as a $\sqrt{}$time-dependent process based on Fickian diffusion. Soluble drugs such as promethazine HCl, aminophylline and propranolol HCl have been reported to follow $\sqrt{}$time release from HPMC matrices (Ford et al.,

Table 1
Dissolution parameters for caffeine/PVP tablets obtained by linear regression based on: $Q(t) = a + b\sqrt{t}$

Caffeine loading		$a \pm$ SE [a]	$b \pm$ SE [a] (mg cm^{-2} min$^{-1/2}$)	n (data points)	r^2
% w/w	% v/v				
10	8.31	−10.8 ± 0.52	3.50 ± 0.07	29	0.988
20	16.94	−23.69 ± 1.43	8.05 ± 0.22	27	0.982
30	25.91	−34.5 ± 2.12	12.10 ± 0.33	28	0.981
40	35.23	−48.63 ± 3.6	17.26 ± 0.6	25	0.972
50	44.93	−82.12 ± 5.05	24.80 ± 0.84	22	0.977
60	55.03	−73.05 ± 6.1	26.17 ± 1.05	24	0.964
70	65.56	−90.99 ± 8.73	33.88 ± 1.6	22	0.955
80	76.55	−82.57 ± 7.41	32.32 ± 1.22	27	0.964
90	88.01	−83.73 ± 6.74	33.11 ± 1.06	29	0.972
100	100	−106.92 ± 11.84	42.74 ± 2.14	24	0.945

[a] SE, standard error.

1987). Within the range 5–70% of total drug dissolved, their release kinetics could be approximated with square root of time diffusion (Ford et al., 1985, 1987). In order to determine the deviation from root time release of caffeine and KCl from PVP matrices containing different ratios of drug and polymer, the amount released from one face of the tablet was plotted against $\sqrt{}$time. Only data which did not exceed 70% of total drug dissolved were included, since Fickian diffusional release is valid for the first 60% of dissolution (Ritger and Peppas, 1987). The data were then subjected to linear regression analysis using the model:

$$Q(t) = a + b\sqrt{t} \quad (1)$$

where $Q(t)$ is the amount of drug released per surface area (mg/cm^2) and t denotes the time (min$^{1/2}$). The regression parameters 'a' and 'b' and their standard errors are listed in Tables 1 and 2 for caffeine and KCl, respectively, together with the corresponding squared correlation coefficients. It can be seen from Table 1 that for all caffeine loadings there is a deviation from the root time law leading to poor correlation, as indicated by the r^2 values. In the case of KCl, as seen in Table 2, increasing the drug concentration above 30% w/w resulted in good agreement between the experimental data and the root time model. It follows from Tables 1 and 2 that not only the type of drug but also the amount of drug present in the systems affect the release kinetics from PVP matrices.

3.3. Other models

In order to compare the goodness of fit when other models are applied, plots of the amount of drug released vs time were generated for caffeine and KCl, respectively. Fig. 1 shows a typical plot

Table 2
Dissolution parameters for KCl/PVP tablets obtained by linear regression based on: $Q(t) = a + b\sqrt{t}$

KCl loading		$a \pm$ SE	$b \pm$ SE (mg cm^{-2} min$^{-1/2}$)	n (data points)	r^2
% w/w	% v/v				
10	6.18	−26.25 ± 2.68	4.67 ± 0.34	8	0.966
30	20.26	−71.17 ± 3.92	25.97 ± 0.9	11	0.989
50	37.22	−104.08 ± 5.66	54.64 ± 1.72	7	0.995
70	58.21	−123.12 ± 14.81	83.79 ± 5.24	7	0.981
90	84.24	−61.26 ± 20.54	129.71 ± 10.27	3	0.994
100	100	−247.11	281.66	2	> 0.999

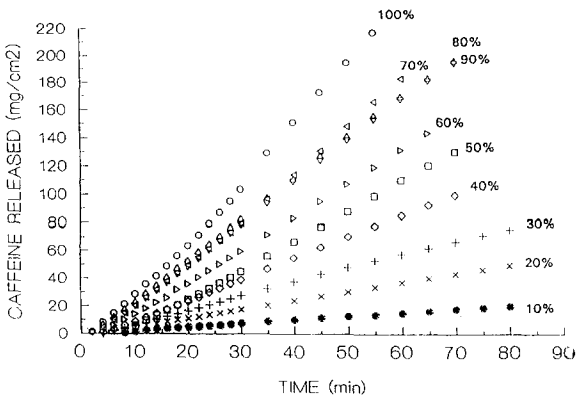

Fig. 1. Intrinsic dissolution rates of caffeine from caffeine/PVP tablets containing 10–100% w/w of drug.

for caffeine. These were then analyzed by linear regression based on the equation:

$$Q(t) = a' + b't \quad (2)$$

where $Q(t)$ is in mg/cm^2 and t in min. Tables 3 and 4 show the regression parameters with their standard errors along with the squared correlation coefficients for caffeine and KCl, respectively. By comparing the results from Tables 3 and 4 to those of Tables 1 and 2 it can be concluded that, whereas the correlation coefficients for KCl remained unchanged irrespective of the model used, those for caffeine improved visibly when plotting $Q(t)$ against time rather than $\sqrt{}$time.

3.4. Curve fitting

In order to define a model which will represent a better fit for caffeine, the modified equation for drug release proposed by Korsemeyer et al. (1983) was employed:

$$Q(t) = a't^k \quad (3)$$

where a' represents a kinetic constant and k is termed the diffusional exponent for drug release. Peppas (1985) used the k value in order to characterize the different release mechanisms. For

Table 3
Calculation of dissolution parameters for caffeine/PVP tablets by linear regression based on: $Q(t) = a' + b't$

Caffeine loading		$a' \pm$ SE	$b' \pm$ SE (mg cm^{-2} min)	$b'_{theor.}$	r^2
% w/w	% v/v				
10	8.31	-0.03 ± 0.1	0.25 ± 0.003	0.42	0.997
20	16.94	-1.49 ± 0.21	0.63 ± 0.004	0.83	0.999
30	25.91	-2.63 ± 0.44	0.98 ± 0.009	1.25	0.998
40	35.23	-5.90 ± 0.33	1.51 ± 0.007	1.66	0.999
50	44.93	-15.84 ± 0.42	2.09 ± 0.01	2.08	> 0.999
60	55.03	-9.94 ± 0.40	2.35 ± 0.01	2.49	> 0.999
70	65.56	-13.35 ± 1.04	3.24 ± 0.03	2.91	0.998
80	76.55	-6.46 ± 0.85	2.86 ± 0.02	3.32	0.999
90	88.01	-2.03 ± 1.31	2.77 ± 0.03	3.74	0.998
100	100	-14.21 ± 1.56	4.15 ± 0.04	4.15	0.998

Table 4
Calculation of dissolution parameters for KCL/PVP tablets by linear regression based on: $Q(t) = a' + b't$

KCl loading		$a' \pm$ SE	$b' \pm$ SE (mg cm^{-2} min)	$b'_{theor.}$	r^2
% w/w	% v/v				
10	6.18	-3.29 ± 1.17	0.22 ± 0.01	8.25	0.956
30	20.26	-17.05 ± 0.86	2.98 ± 0.04	24.76	0.998
50	37.22	-19.74 ± 5.68	8.32 ± 0.47	41.27	0.984
70	58.21	-24.36 ± 3.24	16.17 ± 0.36	57.78	0.998
90	84.24	58.80 ± 12.57	33.36 ± 5.22	74.28	0.976
100	100	-13.90	82.53	82.53	> 0.999

Table 5
An estimate of the diffusional exponent 'k' for drug release based on model: $Q(t) = a't^k$

Caffeine loading (% w/w)	$a' \pm$SE	$k \pm$SE	r^2
10	0.28 ± 0.02	0.98 ± 0.01	0.997
20	0.51 ± 0.03	1.05 ± 0.01	0.998
30	0.78 ± 0.06	1.04 ± 0.02	0.996
40	0.87 ± 0.06	1.12 ± 0.02	0.997
50	0.61 ± 0.06	1.27 ± 0.02	0.996
60	1.18 ± 0.06	1.15 ± 0.01	0.999
70	1.45 ± 0.04	1.18 ± 0.01	> 0.999
80	2.18 ± 0.13	1.06 ± 0.01	0.998
90	2.82 ± 0.17	0.99 ± 0.01	0.997
100	2.17 ± 0.12	1.15 ± 0.01	0.998

Fickian diffusion $k = 0.5$ and for non-Fickian transport k is between 0.5 and 1.0. He further postulated that drug release from slabs becomes independent of time and reaches zero-order release known as Case II transport. When other shapes such as cylinders or spheres are analyzed, Case II transport occurs as k approaches 1.0 ($k \Rightarrow 1.0$) due to the geometry of the system. In such cases, a diffusional exponent $k = 1.0$ is indicative of non-Fickian transport. Furthermore, the author described the transport mechanism occurring at $k > 1.0$ as super Case II transport.

Based on Eq. 3 estimates were made of the diffusional exponents of the different caffeine-PVP mixtures using a non-linear least-square method with a version 5. SYSTAT software. The results are shown in Table 5, from which it can be seen that for the range 30–70% of total drug dissolved, the kinetics of caffeine release from PVP matrices follows non-Fickian transport with diffusional exponent $k > 0.5$.

3.5. Normalization of the dissolution parameter

In order to characterize the effect of drug loading on the release kinetics, the dissolution parameter obtained from Eq. 2 was employed (Tables 3 and 4). The experimentally obtained dissolution parameters were compared to their normalized values. The latter were calculated from the b values at 100% drug multiplied by the fraction of drug present in the mixtures. For example, a normalized b value for 10% mixture is:

$$b'_{10\%} = 0.1(b'_{100\%}) \quad (4)$$

The normalized parameters calculated using Eq. 4 and designated '$b'_{\text{theor.}}$' are included in Tables 3 and 4 for caffeine and KCl, respectively. In Fig. 2 and 3 they are plotted respectively for caffeine and KCl together with the corresponding experimental values for the entire range of drug/polymer ratios investigated.

It can be seen from Fig. 2 that up to about 70% of caffeine loading there is a fairly good

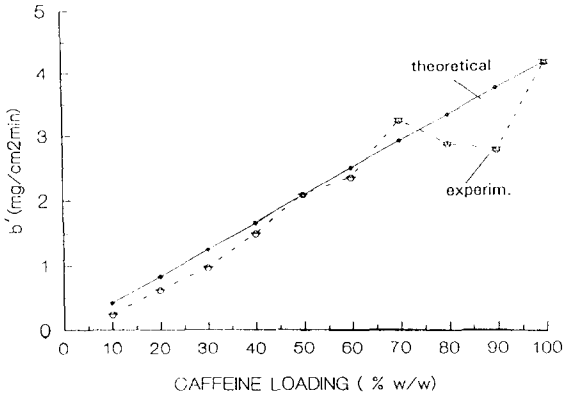

Fig. 2. Normalization of dissolution parameter b' in mg/cm^2 per min for caffeine based on model: $Q(t) = a' + b't$. Broken line represents experimentally obtained values; full line corresponds to predicted values obtained using Eq. 4.

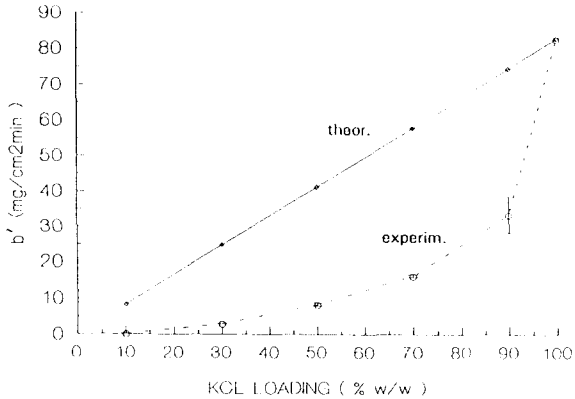

Fig. 3. Normalization of dissolution parameter b' in mg/cm^2 min for KCl based on model: $Q(t) = a' + b't$. Comparison of experimental values (broken line) and expected values (full line). Bars represent standard error.

agreement between the predicted and experimental values of the dissolution parameter. Upon exceeding 70% w/w drug loading a significant drop in the experimental b' values below the predicted values can be observed (Fig. 2).

The dissolution parameters for KCl and their normalized values are shown in Table 4 and in Fig. 3 from which it can be seen that the experimental b' values deviate significantly from the expected values for all drug/PVP ratios investigated. It can also be seen that the b' values decreased much faster within the first 30% w/w of added PVP after which the decrease continued at a slower rate (Fig. 3). Lapidus and Lordi (1968) showed that, based on the Higuchi diffusional law, there is a linear dependence between release rate and drug dose, W_0 (soluble drugs) or $W_0^{1/2}$ (poorly soluble drugs). The deviations from linearity observed in the systems under study may be due to a non-Fickian controlled drug release and to a large contribution of matrix erosion mechanism.

3.6. Use of percolation theory

Percolation theory is based on the existence of clusters of like molecules formed in a lattice by site and/or bond percolation. If a system can be sufficiently well described by a lattice, then percolation theory can be applied to describe the formation of an infinite cluster of occupied sites which is a prerequisite for a percolation process to start taking place (Stauffer and Aharony, 1992). A tablet compressed to a certain porosity represents a three-dimensional lattice of the different components of which it is composed. As the amount of the matrix component added to the drug is increased, the number and the size of the clusters increase until a level of matrix component is reached at which the finite clusters become connected and start to percolate the system. The concentration at which this happens is the first percolation threshold. In previous studies involving caffeine/starch binary systems, percolation theory was employed in order to characterize changes in intrinsic dissolution rates around the critical percolation threshold, p_c; at starch concentration p close to p_c the starch spans the whole system and at $p > p_c$ it percolates the system changing the characteristics of the tablet with regard to dissolution. The caffeine finite clusters become more and more insulated and this continues until a second percolation threshold is reached where the matrix component now predominates the system by completely surrounding the drug (Luginbühl, 1994).

The observed dissolution parameters of caffeine shown in Fig. 2 deviate significantly over the PVP range of 10–30% by weight which corresponds to 12–35% by volume (see Table 1). This can be explained by the fact that at these levels the polymer matrix forms only disconnected finite clusters which are surrounded by the infinite caffeine clusters. Due to its good solubility the polymer dissolves more rapidly and enables dissolution of the poorly water-soluble drug within the clusters. However, the drug diffuses slowly from the PVP regions due to high viscosity of the PVP solution and this gives slow release rate and low b' values. As the PVP concentration is increased to 30% w/w ($\Rightarrow$ 35% v/v) an infinite cluster of polymer can be formed, spanning the tablet and

Table 6
Dissolution parameters for PVP obtained by linear regression based on: $Q(t) = a' + b't$

Amount of PVP		$a' \pm$ SE	$b' \pm$ SE (mg cm^{-2} min)	$b'_{theor.}$	n (data points)	r^2
% w/w	% v/v					
10	15.76	7.25 ± 2.49	1.46 ± 0.25	0.29	8	0.854
30	41.79	−11.18 ± 1.37	7.08 ± 0.14	0.86	6	0.998
50	62.78	−19.15 ± 2.14	8.13 ± 0.16	1.43	9	0.997
70	79.74	−6.50 ± 1.26	5.26 ± 0.04	2.0	16	0.999
90	93.82	8.82 ± 2.3	3.18 ± 0.06	2.57	23	0.994
100	100	12.49 ± 2.3	2.86 ± 0.05	2.86	26	0.994

changing the release kinetics which is now dominated by the erosion of the matrix. If this concentration coincides with the first percolation threshold, exceeding it, at $p > p_c$ brings further decrease in the b' parameter along the predicted values. The decrease is (now) due to increase in viscosity of the PVP layer but is undermined (counteracted) by the erosion of the matrix.

3.7. Dissolution behaviour of matrix material

In Fig. 3 are shown the changes in the dissolution parameter b' for KCl at different drug loadings. Although deviations from the predicted values are observed over the whole range of drug/matrix ratios investigated, b' increased faster at drug loadings exceeding 70% by weight. In order to determine this turning point more accurately, the data obtained from the measurement of the dissolution rates of the matrix itself were employed. In Table 6 are given the regression parameters obtained from the plots of the amount of PVP released (in mg/cm^2) vs time (in min) for different weight percentages of PVP calculated using Eq. 2, together with the squared correlation coefficients. It can be seen from Table 6 that, with the exception of the mixture of low polymer concentration, good fits to the model used were obtained giving $r^2 > 0.994$. As also seen from Table 6, the dissolution parameter b' reaches a maximum at PVP concentration between 30 and 50% by weight which corresponds to 41–62% v/v. Thereafter, it decreases to attain its minimum value at 100% polymer. A comparison between the experimentally obtained b' values and the normalized values, $b'_{\text{theor.}}$, obtained by means of Eq. 4 (see Table 6) shows that the maximum deviation occurs within the 30–50% w/w range. Fig. 4 shows the dissolution parameters of both drug and matrix plotted together vs drug (or polymer) concentration. It can be seen from Fig. 4 that the two curves intersect at a point corresponding to 1:1 weight ratio of KCl to PVP. Analysing Fig. 4 it can be concluded that upon addition of 10% w/w PVP, there is a significant decrease in the dissolution parameter of KCl but the release of the polymer did not improve when compared to its 100% value in spite

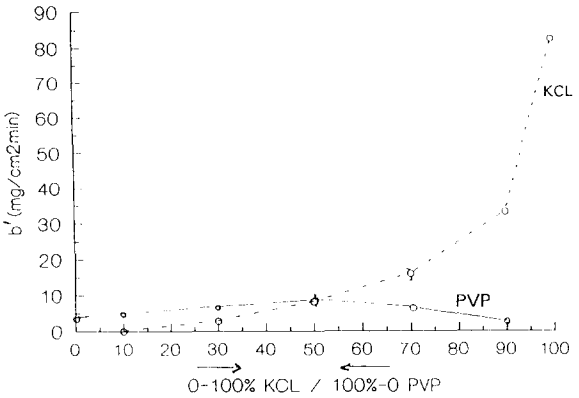

Fig. 4. Dissolution parameter b' based on model: $Q(t) = a' + b't$ for KCl (broken line) and PVP (full line).

of the large amount of readily soluble KCl present. The polymer forms disconnected clusters which, by dissolving, like in the caffeine/PVP tablets, increase the viscosity of the system slowing down the release of KCl. Further addition of PVP (> 30% w/w) increases the dissolution parameter of the polymer and continues to slow down the release of KCl although at a slower rate. This can be interpreted with the increase in PVP clusters in which erosion counteracts the viscosity effect on the release of KCl. At the same time the clusters are more readily wetted which gives rise to the dissolution parameter of the polymer (Fig. 4). The maximum dissolution of the matrix is observed at a 1:1 weight ratio of drug and polymer and it is possible that in the vicinity of this point PVP percolates the system. Upon further increase in concentration the polymer behaviour dominates the system. This inversion point corresponds to approx. 37% by volume of KCl or about 63% by volume of PVP which is much higher than the critical threshold observed in the caffeine/PVP system (see Fig. 2). This discrepancy may be due to the much larger particle size of KCl (mean particle size, 388 μm) compared to that of caffeine (mean particle size, 47 μm). Bonny (1992) observed a p_c around 70 and 80% w/w of caffeine in ethylcellulose matrices at which the Fickian diffusion becomes zero-order transport; Luginbühl (1994) determined a critical range of 20–30% w/w (15–25% v/v) of starch in tablets compressed from binary mixtures

of caffeine and StaRX1500®. In both systems quoted above, the particle sizes of the components lay within similar particle size ranges. Introducing particles of largely differing size characteristics might affect the percolation behaviour as seen in the KCl/PVP system were the KCl particles were in a range 7–8-fold that of the caffeine particles.

4. Conclusions

The release kinetics of a poorly soluble drug (caffeine) and a water-soluble drug (KCl) from PVP matrices was characterized using different mathematical models. It was found that to some extent the KCl/PVP system can be described with the √time law, whereas the release kinetics of the system containing caffeine showed strong deviation from the root of time equation, indicating non-Fickian transport and an increase in lag time periods needed before the system starts to follow linear release.

The effect of the amount of drug present in the matrix on the release kinetics was determined by comparing the experimentally obtained dissolution parameters to their normalized values. It was shown that the discrepancies between the obtained and the expected values depended not only on the type of drug but also on the critical concentration of the matrix material. The behaviour around this critical concentration could be explained using the concepts of percolation theory. This and the data obtained from the measurements of the dissolution kinetics of the polymer matrix itself can be useful tools in establishing the percolation phenomena responsible for the critical changes in the release behaviour of drugs from PVP matrices.

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