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Study of gel-forming properties of sucrose esters for thermosensitive drug delivery systems

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ABSTRACT

Sucrose esters (SEs) are non-toxic, biodegradable, non-ionic surfactants. They have a wide range of hydrophilic–lipophilic balance values (1–16) and are usually applied as surfactants, or as solubility or penetration enhancers. The aims of this work were to study the gelling behaviour of SEs and the effects of this property on drug release. The gelling characteristics of two different SEs (P1670 and S970) were investigated by rheological measurements, and compared with each other. The effects of the gel-forming SEs on model drug (paracetamol) release were evaluated by *in vitro* drug release studies. The kinetics of the dissolution process were studied by analysing the dissolution data through the use of various kinetic equations. The results revealed that the gelling of the SEs is temperature- and concentration-dependent. The examined sucrose stearate (S970) has a stronger gel structure than that of sucrose palmitate (P1670) and this behaviour has a significant effect on the drug release. The analysis of the dissolution kinetic data in this study revealed that the dissolution follows the Korsmeyer–Peppas (paracetamol–P1670) or Higuchi (paracetamol–S970) equations.

1. Introduction

Sucrose esters (SEs) are non-ionic surface-active agents consisting of sucrose as hydrophilic moiety and fatty acids as lipophilic groups. Through variation of the type or number of the fatty acid groups, a wide range of hydrophilic–lipophilic balance (HLB) values can be obtained (Mitsubishi-Kagaku Foods Corporation, 1982). The most common pharmaceutical application of SEs is for the modification of bioavailability. Due to the wide range of their HLB values, they can increase or decrease drug liberation or absorption.

In most cases, SEs are used to improve the dissolution of drugs. For example, sucrose palmitate with a high HLB value dramatically improved the rate of dissolution of nifedipine, especially when a drug:ester ratio of 1:14 was used (Ntawukulilyayo et al., 1993). Sucrose stearate S-1670 (HLB = 16) improved the rates of dissolution of phenytoin (Otsuka and Matsuda, 1995) and glybuzole (Otsuka et al., 1998). In the case of spironolactone, three SEs with an HLB value of 16 (S-1670, L-1695 and M-1695) were applied to increase the rate of dissolution (Marton et al., 2005).

There are some literature data about the applicability of SEs as permeation enhancers through the skin or mucosa. For example, L-595 and L-1695 have been used in microemulsions to improve the penetration of hydrocortisone through the stratum corneum (Lehmann et al., 2001). For the oral mucosal permeation of lidocaine hydrochloride, four SEs (S-1670, O-1570, P-1670 and L-1695) were studied as absorption enhancers (Ganem Quintanar et al., 1998). They observed an increase in the passage of lidocaine through the mucosa only for L-1695; the other SEs did not display any promoting effect. The applicability of different SEs (S-370, S-970, S-1670, O-1570, P-1670, L-1695 and M-1695) was examined also as drug delivery agents in transdermal therapeutic systems (Csóka et al., 2007). They demonstrated that all SEs increased the drug (metoprolol tartrate) release, but this effect depended on the HLB value and the C atom number of the fatty acid chain in the SE.

SEs are often also used in controlled drug delivery systems, with the use of other excipients. For example, S-1570 and P-1570 have been applied with microcrystalline cellulose as tablet matrix-forming agents (Ntawukulilyayo et al., 1995). The authors attributed the matrix-forming property to the H-bonds formed between the SE and the cellulose molecules present in the formulated product. Mostly the surfactant properties of SEs are utilized to form controlled delivery systems. For instance, sucrose erucate (ER-290) and sucrose laurate (L-1695) have been applied to prepare an enteric-coated dry emulsion system for oral insulin delivery (Toorisaka et al., 2005). Sucrose erucate was used to prepare a solid-in-oil nanodispersion for transcutaneous protein delivery (Tahara et al., 2008), while sucrose stearates (S-1170 and S-1670) were applied to develop controlled-release proniosome-derived niosomes (Abd-Elbary et al., 2008).

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We earlier studied the structures of some SEs in order to predict their applicability in the hot melt method (Szűts et al., 2007). During our examinations, we found that the P1670 sucrose palmitate and the S970 sucrose stearate form gels in water, this behaviour depending on the temperature (Szűts et al., 2008). As they can be usable thermosensitive materials in controlled drug delivery systems, therefore the objective of this study was the further examination of these SEs.

Rheological studies of the temperature-dependent gelling characteristics have been already described for different types of polymer such as gelatine, agar-agar, poloxamers (Chang et al., 2002; Li et al., 2008; Cabana et al., 1997; Ma et al., 2008; Koffi et al., 2006), starch (Rosalina and Bhattacharya, 2002) and curdlan (Funami et al., 1999; Funami et al., 2000; Funami and Nishinari, 2007). The most common thermosensitive polymers are the poloxamers, the gelation of which depends strongly on temperature, the concentration of polymer or other additives such as other polymers and salts (Miller and Drabik, 1984; Vadnere et al., 1984; Edsman et al., 1998; Bonacucina et al., 2007; Liu et al., 2009). However, as the modern pharmaceutical industry displays an increasing preference for biomaterials and green technology, it is reasonable to seek new types of thermosensitive non-toxic biomacromolecules. Due to the non-toxic, biodegradable and gel-forming properties of SEs, they are promising materials with which to form thermosensitive delivery systems.

One aim of the present work was to study the gel structures of two different SEs (sucrose palmitate and sucrose stearate), and the temperature and concentration dependences of their gelling. Another aim was to demonstrate the applicability of gel-forming SEs to sustain drug release.

2. Materials and methods

2.1. Materials

Sucrose palmitate P1670 (HLB = 16), and sucrose stearate S970 (HLB = 9) were kindly provided by Syntapharm GmbH (Germany).

Paracetamol was supplied by Hungaropharma Ltd. (Hungary).

2.2. Rheological measurements

The gelling characteristics and rheological properties were studied with a Physica MCR101 rheometer (Anton Paar, Austria). The measuring system was of plate and plate type (diameter 50 mm, gap 0.1 mm).

Dynamic frequency sweep tests were carried out at 37 °C, at 1.0 Pa in the limit of the linear viscoelastic region. From these measurements, storage modulus (G') and loss modulus (G'') were determined for frequencies between 0.1 and 100 Hz.

The gelling characteristics were measured at a constant frequency of 1.0 Hz at a constant strain of 1.5% (this strain was within the linear viscoelastic range of the SE gels; as an example, Fig. 1 shows the strain-sweep graph of 5% P1670/water dispersion). The heating rate was 2 °C/min. The gelling temperature of an SE was defined as the temperature where the storage modulus was half way between G' for the SE dispersion and G' for the SE gel (Fig. 2) (Edsman et al., 1998).

Each measurement was carried out on a freshly made sample and was repeated three times.

2.3. Contact angle measurements

The contact angle (Θ) of a solid was determined by the sessile drop technique, using the OCA 20 Optical Contact Angle Measuring System (Dataphysics, Filderstadt, Germany), and the method of Wu (1971). The solid surface free energy is the sum of the polar (γ^p) and non-polar (γ^d) components, and is calculated according to Eq. (1):

$$(1+\cos\Theta)\gamma_l = \frac{4(\gamma_s^d\gamma_l^d)}{\gamma_s^d+\gamma_l^d} + \frac{4(\gamma_s^p\gamma_l^p)}{\gamma_s^p+\gamma_l^p} \quad (1)$$

where Θ is the contact angle, γ_s is the solid surface free energy and γ_l is the liquid surface tension.

The liquids used for contact angle measurement were bidistilled water ($\gamma^p = 50.2\ \mathrm{mN\,m^{-1}}$, $\gamma^d = 22.6\ \mathrm{mN\,m^{-1}}$) and diiodomethane ($\gamma^p = 1.8\ \mathrm{mN\,m^{-1}}$, $\gamma^d = 49\ \mathrm{mN\,m^{-1}}$). The polarity percentage was calculated from the γ^p and γ values: $(\gamma^p/\gamma)\times 100$ (Bajdik et al., 2009).

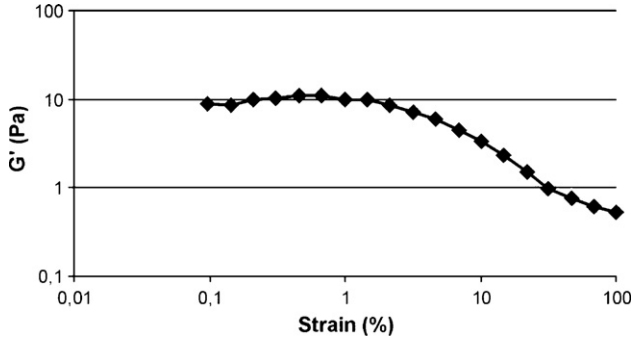

Fig. 1. Strain-sweep graph of 5% P1670/water dispersion.

2.4. Dissolution studies

For the dissolution tests, paracetamol–SE physical mixtures were filled into hard gelatine capsules (N^0 0). The capsules contained 50 mg of paracetamol and 50 mg of SE.

The release of the model drug was studied by using Pharmatest equipment (Hainburg, Germany) at a paddle speed of 100 rpm. 900 ml artificial gastric juice with a pH of 1.2 (±0.05) at 37 °C (±0.5 °C) was used. The drug contents of the samples were measured spectrophotometrically (λ = 244 nm) (Unicam UV/vis spectrophotometer). The dissolution experiments were conducted in triplicate.

2.5. Drug release kinetics

In order to describe the kinetics of the drug release from the formulations, the following mathematical equations were used:

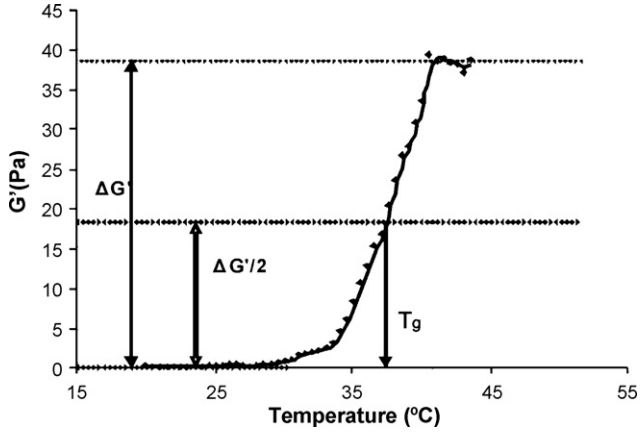

Fig. 2. Gelling profile of 10% P1670/water dispersion.

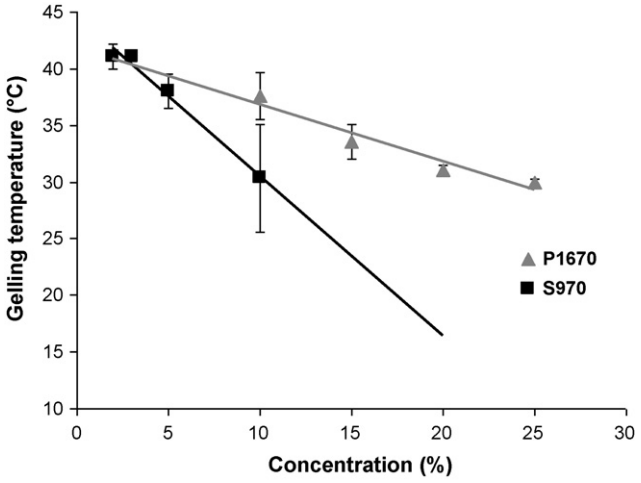

Fig. 3. Concentration dependence of gelling temperatures of SE dispersions.

Zero-order kinetic model

$$M_0 - M_t = k_0 t \quad (2)$$

First-order model

$$\ln\left(\frac{M_0}{M_t}\right) = k_1 t \quad (3)$$

Higuchi model

$$M_t = K_H\, t^{1/2} \quad (4)$$

Hixson–Crowell cube root model

$$(Q_0)^{1/3} - (Q_t)^{1/3} = k_{HC} t \quad (5)$$

Korsemeyer–Peppas model

$$\frac{M_t}{M_\infty} = K\, t^n \quad (6)$$

where M_0, M_t and M_∞ correspond to the amount of drug taken at time zero, or dissolved at a particular time t, and at infinite time, respectively. Q_t is the amount of drug released in time t, and Q_0 is the initial amount of the drug. k_0, k_1, k_{HC}, K_H and K are the release kinetic constants obtained from the linear curves of the zero-order, first-order, Hixson–Crowell cube root law, Higuchi model and Korsmeyer–Peppas model, respectively (Ahuja et al., 2007; Costa and Lobo, 2001). In the case of the Korsmeyer equation, n is the diffusional exponent, which can range from 0.43 to 1; it depends on the release mechanism and the shape of the drug delivery device (Baumgartner et al., 2006).

3. Results and discussion

3.1. Rheological measurements

The gelling temperatures of different dispersions were established as described above (Section 2.2). As an example, Fig. 2 depicts the gelling temperature of 10% P1670.

The concentration dependences of the gelling temperatures of the SE dispersions can be seen in Fig. 3. Both reveal a correlation with the concentration, but it is clear that the dependence is more marked for S970 (indicated by the slope).

The basis of the changes in their viscoelastic properties is micelle formation, which can involve spherical or worm-like micelles, with a hexagonal or lamellar liquid crystal structure. The type of the association depends on the molecular geometry and the packing parameter (the ratio of the volume of the hydrophobic group to the product of the length of this group and the cross-sectional area of the hydrophilic group) (Yang, 2002).

It has been established that the temperature rise progressively breaks down the H-bonds between the SEs and the water, which favours the growing of the micelles (Berjano et al., 1993). This increased micellar size or the transition from spherical to worm-like micelles can improve the viscosity of the systems. Besides the temperature, other factors can also influence the rheological behaviour of SEs, such as the SE concentration, the presence of cosurfactants or oil, or the preparation mode. It has been reported that the SE concentration can modify the micellar hydration, which leads to micellar growth or a micellar shape change (from spherical to worm-like), and accordingly changes in the viscous behaviour can be observed (Madiedo et al., 1994; Berjano et al., 1993). The addition of a lipophilic cosurfactant also induces micellar growth, and the formation of a worm-like micelle results in a viscosity increase, but over a critical value micelle disruption can occur. If the system contains oil too, the oil can solubilize the cosurfactant or can penetrate into the surfactant palisade, resulting in changes in the micellar size (Rodriguez-Abreu et al., 2005). Finally, the different modes of fabrication (e.g. cold or hot dispersed samples) can lead to alterations in the viscosity, which should also be considered during the preparation (Ullrich et al., 2008).

During our studies, the rheological properties of SE/water dispersions were investigated with oscillation tests at body temperature (37 °C). Frequency sweeps were recorded to study the gel strengths of the dispersions. In rheological terms, for a gel the storage (G') and the loss (G'') modulus are frequency-independent and $G' > G''$. Gels can usually be classified into two categories (Lapasin and Pricl, 1995): weak gels, where the moduli (G' and G'') depend slightly on the frequency; and strong gels, where the moduli are relatively independent of frequency. Under small deformation, strong gels exhibit viscoelastic solid behaviour, while weak gels resemble strong gels in their mechanical properties. Under increased deformation or continuous flow conditions, strong gels rupture into small gel regions rather than flow, while the weak gel network breaks down into smaller flow units and may flow homogeneously (Lapasin and Pricl, 1995; Rosalina and Bhattacharya, 2002).

Frequency sweep tests were carried out in the linear viscoelastic region to examine the frequency dependences of the storage and the loss moduli. The frequency dependencies of G' and G'' at the same SE concentration can be seen in Fig. 4. Both dispersions display gel characteristics, because the storage moduli are higher than the loss moduli at all frequencies, although the moduli of the S970 dispersion are higher than those of P1670 at all frequencies. These results indicate that S970 dispersions have more elastic behaviour (higher G' values) and better gel characteristics (lower slopes of the curves).

The frequency dependence can be studied via the slopes of the $\log G'$ and $\log G''$ versus $\log f$ curves (Lapasin and Pricl, 1995; Rosalina and Bhattacharya, 2002). The lower the slope is, the stronger the gel structure. If only the slope is regarded, the moduli show a slight dependence on the frequency, which indicates that the S970 dispersions are weak gels at low concentrations and may assume structures close to those of strong gels above about 20%. The moduli of P1670 dispersions are strongly dependent on the frequency, mainly at low concentration, but on increase of the concentration they demonstrate a more marked gel structure (Fig. 5). These results indicate that the S970 dispersions have a stronger gel structure than P1670, and it may modify the dissolution profile of the systems, because S970 is prone to form a gel at body temperature even in low concentration.

3.2. Contact angle measurements

The results of contact angle measurements, which provide information on the surface free energies and polarities of the samples, are presented in Table 1. The different HLB values are manifested

Table 1
Contact angles, surface free energies and polarities of the materials.

Materials	θ_{water} (°)	$\theta_{diiodomethane}$ (°)	γ^d (mN m^{-1})	γ^p (mN m^{-1})	γ (mN m^{-1})	Polarity (%)
P1670	18.49 ± 0.85	58.76 ± 0.72	27.37	42.73	70.10	60.96
S970	46.79 ± 1.76	62.99 ± 1.10	25.50	29.75	55.25	53.85
Paracetamol	39.32 ± 1.77	28.72 ± 2.42	40.42	27.54	67.96	40.52
Paracetamol–P1670	23.11 ± 1.83	47.13 ± 1.46	32.73	37.82	70.55	53.61
Paracetamol–S970	37.19 ± 1.13	54.74 ± 1.81	29.27	33.09	62.37	53.05

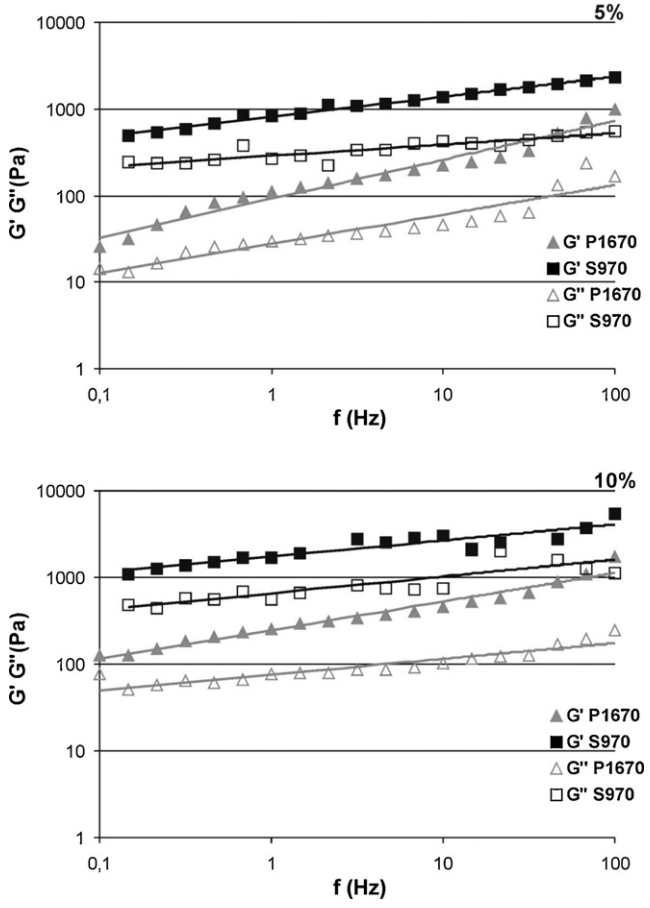

Fig. 4. Frequency dependence of 5% and 10% aqueous dispersions of P1670 and S970.

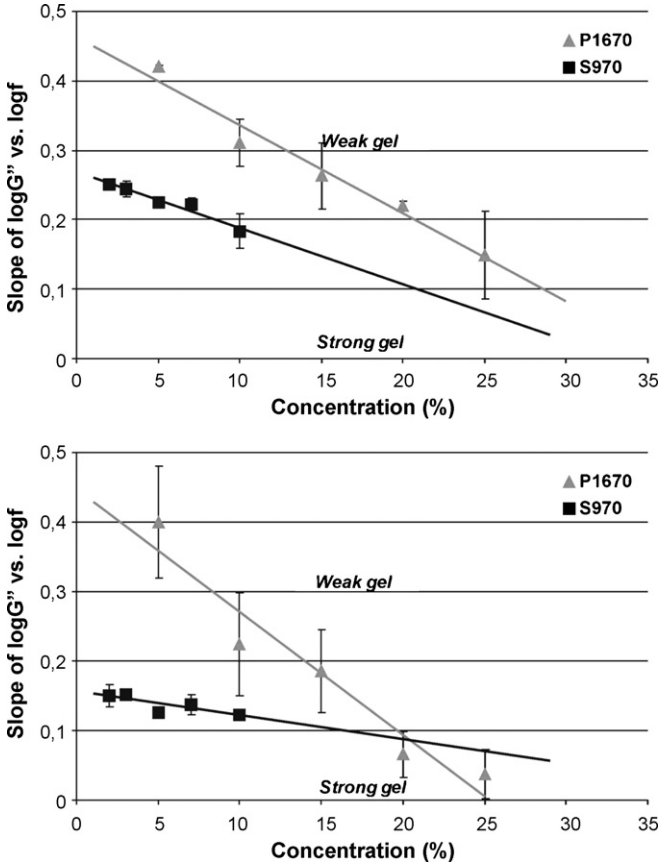

Fig. 5. Slopes as functions of the SE concentration.

in the various polarity values of the SEs. The contact angles of mixtures with water were decreased and the polarities were increased compared with those of the pure drug. In spite of these results, the two SEs sustained paracetamol release (Fig. 6).

3.3. Dissolution studies

The *in vitro* drug release results confirmed the rheological measurements. Paracetamol is rapidly released in gastric juice: most of the drug was dissolved after 10 min. Due to the swelling properties of the SEs, they sustained the drug release. In the case of the P1670-containing sample 79% of the drug, whereas for the S970-containing sample only 20% of the paracetamol was dissolved after 180 min (Fig. 6).

For paracetamol–P1670, the contact angle with water decreased from 39.32° (pure drug) to 23.11°, but the paracetamol dissolved more slowly than without P1670. Thus, the sustained drug release was caused unambiguously by the swelling of the sucrose palmitate. The drug release from the S970-containing product was significantly slower than from the P1670-containing system, which can be due to two reasons. Our rheological studies indicated that S970 has a stronger gel structure than P1670 (Fig. 5), and the lower polarity of this SE (Table 1) also resulted in a slower drug release.

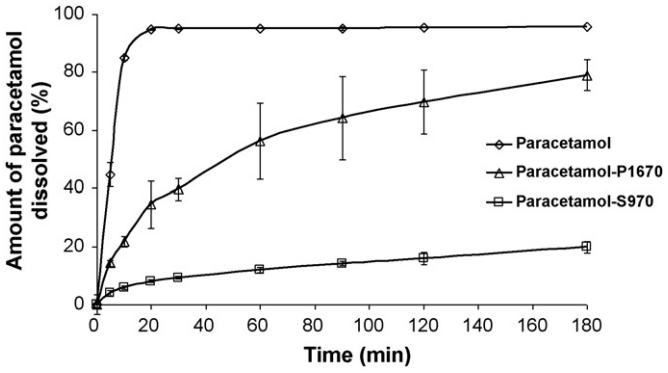

Fig. 6. Dissolution curves of paracetamol and paracetamol–SE samples.

Table 2
Correlation coefficients of the linearization of drug release plots.

Sample	Zero-order	First-order	Higuchi	Hixson–Crowell	Korsmeyer–Peppas
Paracetamol–P1670	0.8760	0.9703	0.9740	0.9444	***0.9816***
Paracetamol–S970	0.9497	0.9604	***0.9953***	0.9570	0.9944

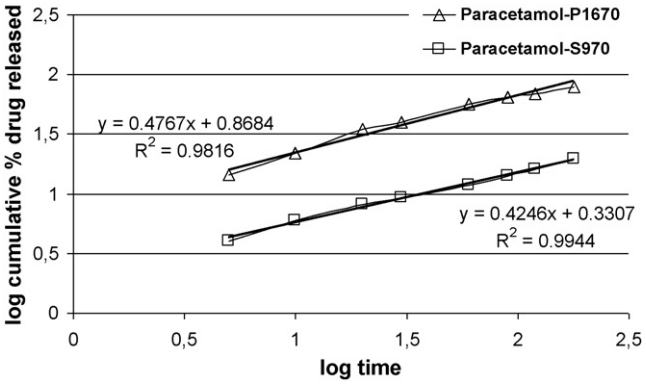

Fig. 7. Korsmeyer–Peppas plots of paracetamol–SE samples.

3.4. Drug release kinetics

The dissolution kinetics of the drug release were studied in the SE containing systems. Table 2 shows the correlation coefficients (r^2) of the formulations. As concerns the correlation coefficients, the best fit was that with the Korsmeyer–Peppas model for paracetamol–P1670 (r^2 = 0.9816), and with the Higuchi model for paracetamol–S970 (r^2 = 0.9953). The drug release was also found to be very close to the Korsmeyer–Peppas equation in the S970-containing system (r^2 = 0.9944).

In the Korsmeyer equation, the diffusional exponent n is an important indicator of the mechanism of transport of the drug through the gel layer. If Fickian diffusion takes place, n is equal to 0.5, 0.45 and 0.43 for a thin film, a cylinder and a sphere, respectively. When n exceeds these thresholds, non-Fickian release takes place (Grassi and Grassi, 2005). The release exponent n was 0.48 for paracetamol–P1670 and 0.42 for paracetamol–S970, which appears to indicate that the drug release mechanism involves Fickian diffusion (Fig. 7).

4. Conclusion

These results showed that SEs are appropriate excipients with which to sustain the drug release. S970 has a stronger gel structure, and can sustain drug release to a great extent at low concentration. P1670 also exhibits gel-forming behaviour, but this is not so marked as in the case of S970. The gelling temperatures of SE dispersions depend on the concentration and the type of the SE. Due to their temperature-dependent viscoelastic properties, the SEs allow the formulation of temperature-sensitive controlled drug delivery systems.

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