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Hydrotrope-gelled starch: Study of some physicochemical properties

L.K. El-Khordagui

Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Khartoum Square, Alexandria (Egypt)

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Summary

A starch gel has been prepared without heat treatment or chemical modification, using a typical hydrotropic salt (sodium salicylate) as a gelling agent. This gel has the advantage of retaining the marked solubilizing capacity of sodium salicylate. Swelling of dried starch-sodium salicylate gels is affected by the concentration of both starch and sodium salicylate as well as the presence of additives in the swelling medium. Study of the release characteristics of the gel using riboflavin as a model solubilized drug indicated consistent diffusion-controlled kinetics. Drug release is influenced by initial loading levels, starch content of the gel and, to a lesser extent, concentration of the gelling agent. Hydrotrope-gelled starch offers promise as a vehicle for topical drug delivery.

Introduction

Hydrotropes are recognized as a class of compounds which, in fairly high concentrations, increase the solubility of a variety of poorly soluble drugs in water (Neuberg, 1916; Badwan et al., 1983; Darwish et al., 1989) and the solubility of water in organic solvents (Saleh et al., 1983, 1986). Another feature of hydrotropes, although less extensively investigated, is their effect on biocolloids. For instance, hydrotropic agents were shown to inhibit the gelling of gelatin solutions (Feigen and Trapini, 1954), denature haemoglobin (Saleh et al., 1987a), induce haemolysis in hypertonic solutions (El-Khordagui et al., 1980; Saleh et al., 1987b) increase liposomal membrane permeability (Darwish et al., 1988) and considerably affect the properties of albumin in different systems (Neuberg, 1916; Saleh et al., 1989a,b).

As far as starch is concerned, hydrotropic salts were reported to induce swelling and gelatinization of starch without the use of heat, i.e. decrease the gelatinization temperature, the effect being structure and concentration dependent (Neuberg, 1916; Kohn and Rekker, 1978).

As part of trials of explore new pharmaceutical applications of hydrotropy, the present work reports on some properties of hydrotrope-gelled starch, particularly release of solutes. This gel may

Correspondence: L.K. El-Khordagui, Dept. of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Khartoum Square, Alexandria, Egypt.

be of pharmaceutical interest because of the high solubilizing capacity conferred by the hydrotropic gelling agent.

Materials and Methods

Sodium salicylate (Riedel-De Haën AG, Seelze-Hannover, Germany), riboflavin (Sigma) and maize starch B.P. (El-Nasr Pharmaceutical Chemicals, Cairo, Egypt) were used in the study.

Preparation of hydrotope-gelled starch

A typical hydrotropic salt, sodium salicylate, was used as the gelling agent. Preliminary trials were carried out using different concentrations of maize starch (2–30% w/v) and sodium salicylate (2–30% w/v) in order to determine the concentration of either ingredient required to obtain a satisfactory gel in terms of complete gelatinization with loss of birefringence of starch granules under the polarized-light microscope. Gels were prepared by adding the required amount of starch to sodium salicylate solution of predetermined concentration at ambient temperature with constant stirring until complete gelatinization was achieved.

For the preparation of drug-loaded gels, a model drug (riboflavin) was solubilized in the sodium salicylate solution prior to the addition of starch. Complete solubility of riboflavin in the gel was confirmed by microscopic examination.

Scanning electron microscopy

A specimen of a gel composed of 10% starch in 20% sodium salicylate solution was freeze-dried and examined on a Philips 500 model scanning electron microscope.

Swelling experiments

Portions of starch-sodium salicylate gels of different composition were dried in tared 25 ml beakers in a vacuum oven at 27 °C. The calculated mean residual moisture content ± S.D. of 12 samples of dried gels was 17.4 ± 2.4. The required swelling medium (10 ml) was added and the percentage increase in the gel dry weight was determined at different time intervals after carefully wiping off excess water from the surface. Two samples of dried gel were used in each experiment.

Release experiments

Solute release from the starch gel under study was assessed at 30 ± 0.2 °C using a membrane-less model system under sink conditions. Petri dishes (3.90 cm in diameter and 1.22 cm deep) were filled with gel (approx. 12 g) and the excess was removed with a spatula to produce an even uniform surface. Each dish was fixed in the bottom of a 150 ml beaker with melted wax. To start the run, 50 ml of distilled water previously equilibrated at the temperature of the study was carefully layered over the gel. The beakers were agitated in a constant-temperature water bath at a speed not disturbing the gel (120 strokes/min). At appropriate time intervals, 25 ml of the release medium was removed and replaced by an equal volume of water equilibrated at the same temperature. Samples were filtered using a 0.22 μm Millipore filter and assayed after suitable dilution for riboflavin or sodium salicylate at 445 and 298 nm, respectively, using a Unicam SP 1800 spectrophotometer. All experiments were carried out at least in duplicate and the results were averaged. This method was used to study the release of incorporated riboflavin from the starch gel as a function of initial loading level, concentration of starch and sodium salicylate. The release of sodium salicylate from drug-free gels was studied similarly. The effect of temperature (30, 37 and 45 °C) on the release properties of the gel was also investigated.

Results and Discussion

Preliminary results on the preparation of sodium salicylate-gelled starch indicated that the minimum hydrotrope concentration required to produce complete gelatinization of maize starch without heating was 18% w/v whilst the minimum starch concentration in this solution was 8% w/v. An optically clear gel could be obtained reproducibly within a few minutes at a starch concentration of 10% in 20% (1.25 M) sodium salicylate solution. Sodium chloride in a wide concentration range (0.2–2.0 M) did not induce starch

gelling, thus indicating the non-osmotic nature of the hydrotropic effect. Sodium chloride was reported previously to raise the gelatinization temperature of starch (Oosten, 1979).

In the absence of additives, starch granules swell upon heating and undergo complete rupture at a specific gelatinization temperature (T_{gel}), losing birefringence and releasing two D-glucose macromolecular compounds: amylose and amylopectin (Lelievre, 1976). Organic solutes were shown to affect T_{gel}, its value being raised by saccharides and polyols and lowered by alcohols and salts of carboxylic acids (Lelievre, 1976; Oosten, 1984). These effects can generally be ascribed to various solute-water and solute-starch interactions (Busk, 1984; Oosten, 1984). Although gelatinization of starch in hydrotropic systems is not yet fully understood, the phenomenon can be related to the solvent action of hydrotropes on amylopectin (Ulmann, 1959) and their influence on water structuring. It has been postulated that hydrotropic agents increase the structuring and hydrophobicity of water as indicated by near-infrared data and solubilization of water in organic solvents (Saleh et al., 1983, 1986). Changes in the characteristics of water induced by hydrotropes results in a medium with a marked solubilizing power (Huttenrauch and Fricke, 1982). This appears to modify strongly the structure of starch, increasing the solubility of hydrophobic moieties and enhancing

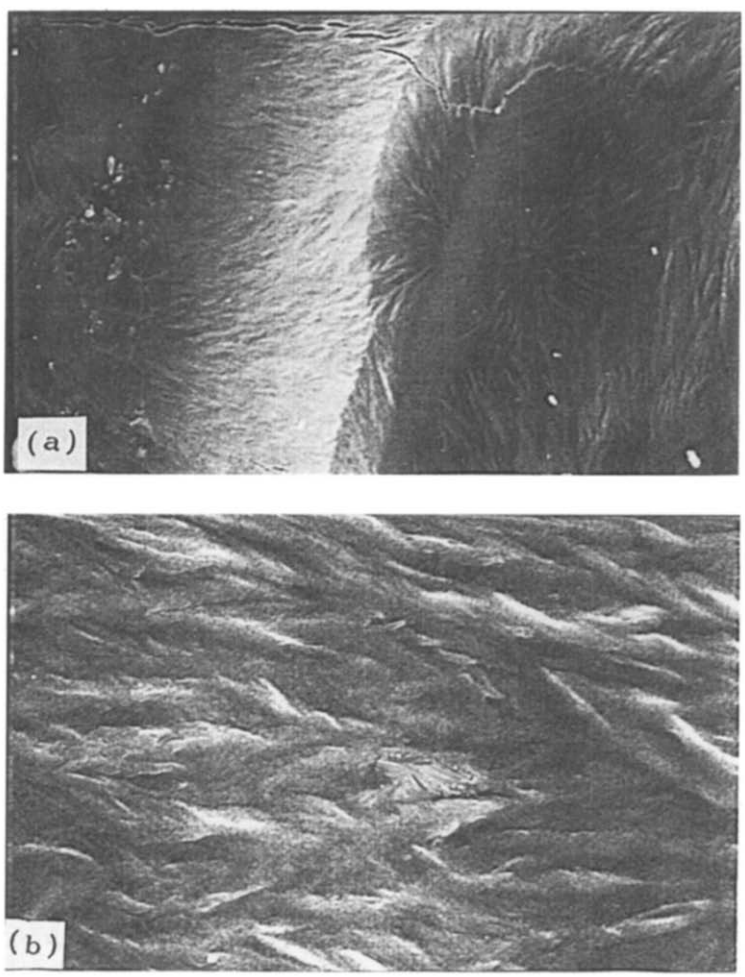

Fig. 1. SEM photographs of freeze-dried 10% starch-20% sodium salicylate gel. Magnification: (a) 1 × 100; (b) 1 × 600.

disruption of starch granules without heat treatment. The formed gel may be further stabilized by the more structured weater-hydrotrope phase of the gel.

Scanning electron photographs of freeze-dried 10% starch in 20% sodium salicylate solution gel are shown in Fig. 1a and b. The gel appears as a continuous phase with no characteristic structural features.

Swelling of dried gels

Fig. 2a and b shows the effect of the composition of the gel under study and swelling medium, respectively, on the rate of gel hydration. The relatively high swelling ability of the gel is due to its hydrophilic nature. The increase in dry weight of a gel composed originally of 10% starch in 20% sodium salicylate solution (28.5% starch and 57% sodium salicylate in the dried gel, gel A) was 130% in 5h. Whilst the presence of embedded riboflavin in the dried gel did not affect the rate of water uptake, hydration of gel A increased with increasing starch concentration and decreased at higher sodium salicylate concentration (Fig. 2a). A higher volume fraction of hydrophilic segments of macromolecular components of gelatinized starch may account for increased water uptake at the higher starch concentration. Gels prepared using higher sodium salicylate concentration were expected to imbibe water at a higher rate due to osmotic activity. However, the hydrotrope concentration appears to affect eventually the gel properties and the structuring of water in the fluid phase of the gel. It has been pointed out in this study and elsewhere (Kohn and Rekker, 1978) that the swelling of starch by hydrotropes is concentration dependent. The presence of NaCl and ethanol in the swelling medium decreased the rate of hydration (Fig. 2b), an effect attributable to their dehydrating properties. A similar observation has been reported for the swelling of poloxamer hydrogels (Al-Saden et al., 1980). These results may be of importance when the dried hydrotrope-gelled starch is considered for use.

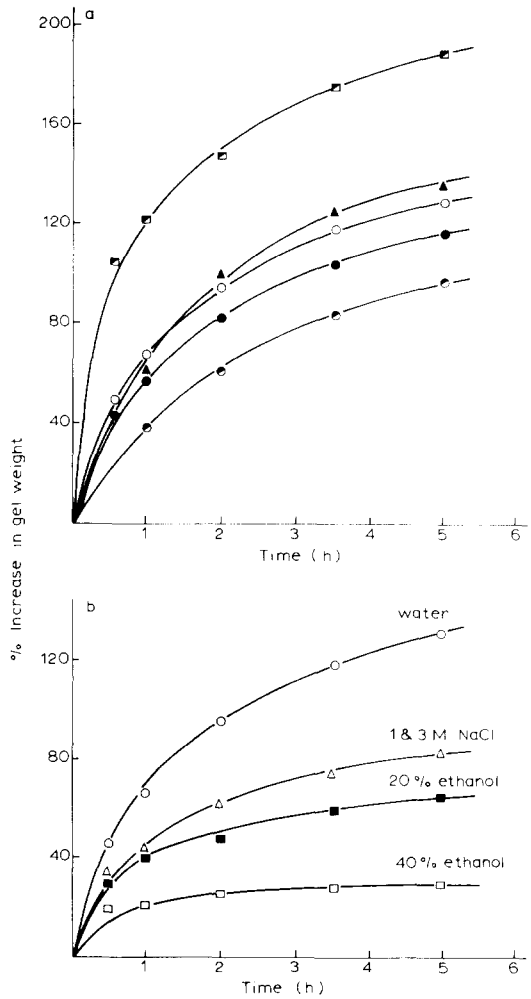

Fig. 2. (a) Effect of gel composition on the hydration rate of dried sodium salicylate-gelled starch at 27 °C. (○) 28.5% starch-57% sodium salicylate (gel A); (●) 22.8% starch-57.1% sodium salicylate; (◐) 20.8% starch-62.5% sodium salicylate; (▲) gel A containing 0.044% riboflavin; (◩) 51.5% starch-34.4% sodium salicylate. (b) Effect of additives in the medium on the hydration rate of gel A.

Release of solutes

The release characteristics of sodium salicylate-gelled starch were investigated in order to assess its potential usefulness as a vehicle with non-surfactant solubilizing properties for topical drug delivery. Riboflavin was used as a model solubilized drug. Reproducibility of release data was tested by determining the release rate of riboflavin, 0.044% w/w, from seven different samples of gel A. The standard deviation of fractional release was within $\pm 10\%$ of the respective means

TABLE 1

Reproductibility of data for solute release from 10% starch-20% sodium salicylate gel (gel A) at 30 °C

Time (h)	Mean % release ± S.D.		
	Riboflavin 0.044% w/v ($n = 7$)	Sodium salicylate (drug-free gel) ($n = 3$)	sodium salicylate (drug-loaded gel) ($n = 3$)
1/2	7.0 ± 0.8	10.7 ± 0.5	10.5 ± 0.4
1	10.6 ± 0.9	15.4 ± 1.1	15.7 ± 0.9
2	14.6 ± 1.3	21.7 ± 1.5	22.3 ± 0.8
3	18.1 ± 1.1	26.3 ± 1.9	26.9 ± 0.8
4	20.9 ± 1.3	30.5 ± 1.5	31.8 ± 1.8
5	23.4 ± 1.4	34.8 ± 3.0	35.5 ± 1.4
6	25.4 ± 1.2	37.1 ± 2.6	38.4 ± 1.5
8	28.5 ± 1.7	43.2 ± 3.3	44.2 ± 2.5

in most cases (Table 1), indicating consistency of the release kinetics.

The following equation (Higuchi, 1962) was used for data treatment:

$$Q = 2C_0\left(\frac{D_{app} \cdot t}{\pi}\right)^{1/2}$$

where Q denotes the amount released per unit area, D_{app} is the apparent diffusion coefficient of solute in the vehicle, C_0 represents the initial solute concentration in the vehicle and t is time.

Release of solubilized riboflavin Fig. 3 shows the effect of initial riboflavin concentration (C_0 ranging from 0.022 to 0.088% w/w) on the release from gel A at 30 °C. The highest concentration of riboflavin used was well below its solubility in 20% sodium salicylate solution (Ueda, 1966). Linearity of Q vs $t^{1/2}$ plots indicates a diffusion-controlled process. Values of the regression slopes of these lines increased linearly with increasing C_0 (Fig. 4). This implies that drug release is independent of factors other than C_0 and that D_{app} is independent of initial drug loading. These results indicate complete solubility of riboflavin in the gel and adherence of the release process to the theoretical model (Bottari et al., 1979). The mean ± S.D. value calculated for D_{app} was $(2.66 \pm 0.12) \times 10^{-6}$ cm^2/s. Increased drug release as a function of C_0 has been reported for the release of relatively low molecular weight drugs from different gel matrices (Bottari et al., 1979; Chen-Chow and Frank, 1981; Al-Khamis et al., 1986).

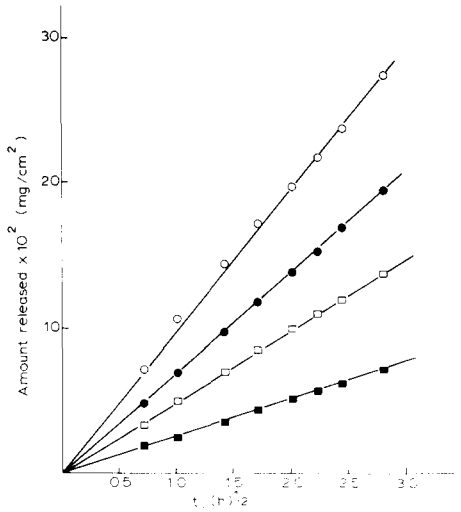

Fig. 3. Effect of initial riboflavin concentration on the release from 10% starch-20% sodium salicylate gel (gel A) at 30 °C. (■) 0.022; (□) 0.044; (●) 0.066 and (○) 0.088% w/w.

Release of sodium salicylate The release of the swelling agent, sodium salicylate, was assessed

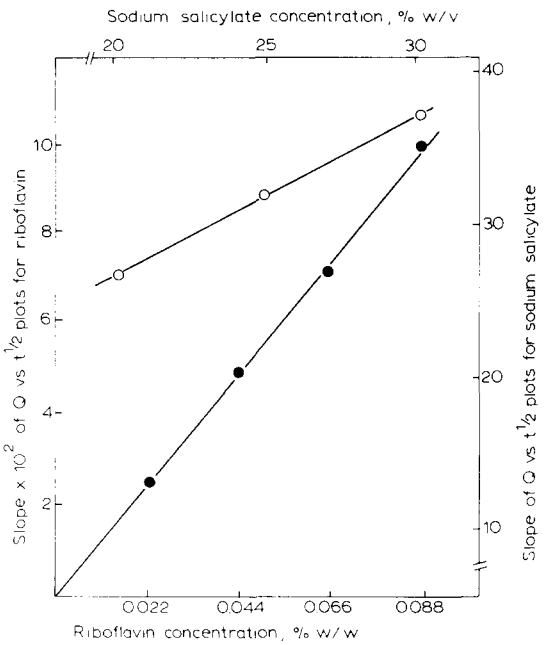

Fig. 4. Relationships between the slopes of Q vs $t^{1/2}$ plots and initial concentrations of riboflavin (●) and sodium salicylate (○) in 10% starch gels.

TABLE 2

Effect of gel composition on the apparent diffusion coefficients (±SE) of sodium salicylate and riboflavin

Starch (% w/v)	Sodium salicylate (% w/v)	D_{app} (cm^2/s)($\times 10^6$)	
		Sodium salicylate [a]	Riboflavin
10	20	3.63 ± 0.32 ($n = 3$)	2.66 ± 0.12 ($n = 8$)
10	25	3.61 ± 0.23 ($n = 4$)	2.25 ± 0.12 ($n = 4$)
10	30	3.58 ± 0.30 ($n = 4$)	1.98 ± 0.08 ($n = 4$)
20	20	3.00 ± 0.22 ($n = 3$)	1.75 ± 0.15 ($n = 3$)
30	20	2.28 ± 0.13 ($n = 3$)	1.09 ± 0.13 ($n = 3$)

[a] Data obtained using riboflavin-free gels.

using riboflavin-free gels. Linear Q vs $t^{1/2}$ plots were obtained at different vlaues of C_0 (20, 25 and 30% w/v) with slopes increasing linearly as a function of sodium salicylate concentration (Fig. 4). The mean $D_{app} \pm$ S.D. from the values in Table 2 was $(3.61 \pm 0.03) \times 10^{-6}$ cm^2/s. As shown in Table 1, release of sodium salicylate from gel A was almost unaffected by the presence of riboflavin (0.044% w/w) in the gel, probably due to the low riboflavin: sodium salicylate molar ratio (1 : 1068). The mean percentage of sodium salicylate released after 8 h was 43.7%. The calculated amount of sodium salicylate released at any time was sufficient to maintain complete solubility of riboflavin in the release medium.

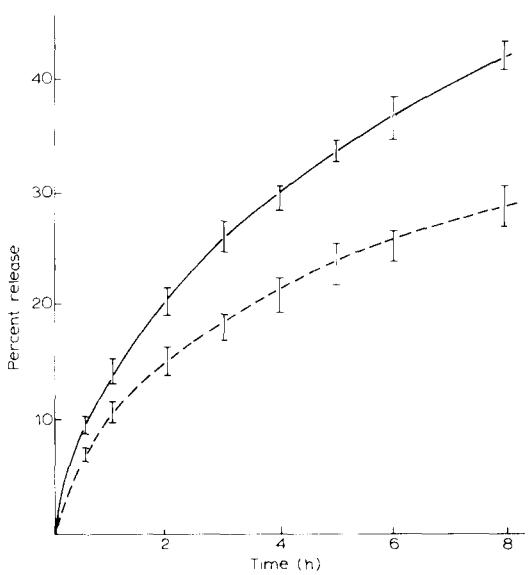

Fig. 5. Composite curves for the % riboflavin (— — —) and sodium salicylate (———) released at 30 °C from 10% starch gels with different concentrations of riboflavin (0.022, 0.044, 0.066 and 0.088% w/w) and sodium salicylate (20, 25 and 30% w/v). Bars represent the range.

Plotting the percentage release of either riboflavin or sodium salicylate rather than the cumulative amount released vs time at different loading levels showed that the fractional release was independent of the respective initial concentrations (Fig. 5). These results are consistent with the mechanism of release of dissolved drugs from polymer matrices described by Baker and Lonsdale (1974).

Effect of sodium salicylate concentration on drug release

Linear Q vs $t^{1/2}$ relationships were obtained for the release of riboflavin from 10% starch gels as a function of sodium salicylate concentration (20, 25 and 30%). The values of D_{app} calculated from the slopes of these lines are listed in Table 2. Increasing sodium salicylate concentration slightly decreased the release rate and D_{app} of riboflavin. Such a reduction in drug diffusivity may result from the reduced thermodynamic activity of riboflavin molecules, markedly solubilized at higher hydrotropic concentrations (Ueda, 1966) and increased microviscosity of the gel water phase. Microviscosity is a parameter reported to influence drug release from gel formulations (Al-Khamis et al., 1986).

Effect of starch concentration on solute release

The release profiles of riboflavin from starch gels prepared in 20% sodium salicylate showed a reduction in release rate as a function of the starch concent of the gel (10, 20 and 30%). Similar results were obtained for the release of sodium salicylate from plain gels. The D_{app} values are shown in Table 2. Since in gelatinous media diffusion occurs only in the fluid aqueous phase, solute diffusivity is influenced by the volume fraction of the polymer (Flynn et al., 1974). At higher starch concentrations, the number and dimensions of aqueous regions available for diffusion are reduced with a possible increase in microviscosity.

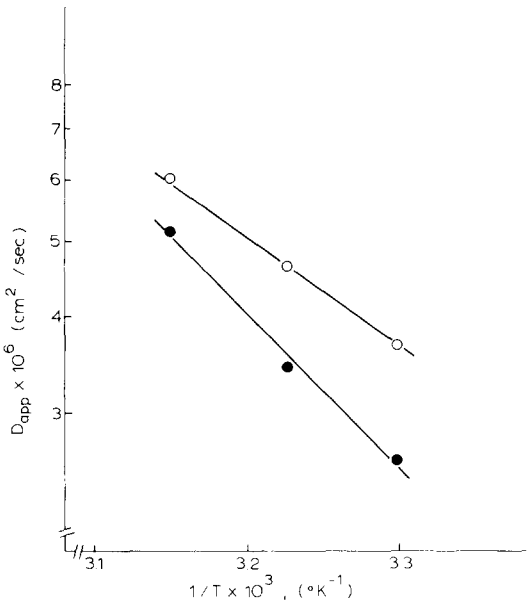

Fig. 6. Apparent diffusion coefficient (D_{app}) for riboflavin (●) and sodium salicylate (○) release from gel A as a function of the reciprocal of absolute temperature.

From these results, release of solutes from hydrotrope-gelled starch appears to be affected by initial loading levels, starch concentration and, to a lesser extent, the hydrotrope concentration. Different release rates can be achieved by controlling these factors.

Effect of temperature on solute release

Increasing temperature enhanced the release of riboflavin and to a, lesser extent that, of sodium salicylate from gel A. Such enhancement is expected as the diffusion of small molecules in a polymer structure is an energy-activated process. The temperature dependence of solute diffusion is shown in Fig. 6 where D_{app} values for riboflavin and sodium salicylate are plotted vs temperature according to the Arrhenius equation. The calculated energy of activation for diffusion of riboflavin and sodium salicylate was 37.5 and 29.4 kJ/mol, respectively. The lower value for sodium salicylate can be attributed to its smaller molecular size and greater diffusivity. The values of E_a obtained compare favourably with those reported for the diffusion of relatively small molecules from different hydrogels (Chen-Chow and Frank, 1981; Hadgraft and Howard, 1982; Al-Khamis et al., 1986).

From the data presented, it would seem that hydrotrope-gelled starch offers promise as a vehicle for the topical application of drugs. It has the advantage of incorporating water-soluble drugs or hydrotrope-solubilized poorly soluble drugs, consistent release properties, ease of preparation and low cost. Moreover, a wide range of hydrotropic agents can be used to induce starch gelling.

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