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Percutaneous absorption of non-steroidal anti-inflammatory drugs from in situ gelling xyloglucan formulations in rats

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Abstract

The potential of gels formed in situ by dilute aqueous solutions of a xyloglucan polysaccharide derived from tamarind seed as sustained release vehicles for percutaneous administration of non-steroidal anti-inflammatory drugs has been assessed by in vitro and in vivo studies. Chilled aqueous solutions of xyloglucan that had been partially degraded by β-galactosidase formed gels at concentrations of 1–2% w/w when warmed to 37 °C. The in vitro release of ibuprofen and ketoprofen at pH 7.4 from the enzyme degraded xyloglucan gels and the subsequent permeation of these fully ionized drugs through cellulose membranes followed root-time kinetics over a period of 12 h after an initial lag period. Diffusion coefficients were appreciably higher when the drugs were released from 1.5% w/w xyloglucan gels than when released from 25% w/w Pluronic F127 gels formed in situ under identical conditions. The difference in release rates was attributed to differences in the structure of the gels. The permeation rate of ibuprofen through excised skin was higher than that of ketoprofen when released from both gels, but of similar magnitude through cellulose membranes. Plasma concentrations of ibuprofen and ketoprofen from gels formed in situ following topical application of chilled aqueous solutions of xyloglucan and Pluronic F127 to the abdominal skin of rats were compared. The bioavailabilities of ibuprofen and ketoprofen were significantly higher when released from xyloglucan gels compared to Pluronic F127 gels. Occlusive dressing techniques had a greater enhancing effect on the bioavailability of ibuprofen when released from Pluronic gels.

Keywords: Percutaneous absorption; Non-steroidal anti-inflammatory drugs; Xyloglucan gels; In situ gelation; Sustained release

1. Introduction

The topical delivery of non-steroidal anti-inflammatory drugs (NSAIDs) has been explored as a potential method of avoiding the first pass effects and the gastric irritation that may occur when these drugs are administered orally. It is well

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known that the vehicle composition can affect both drug release and skin permeability properties and a number of vehicles, including simple creams and gels, have been utilized in topical preparations. Several workers have used poloxamer gels, particularly those formed by Pluronic F127, as vehicles for the topical delivery of NSAIDs (Chi and Jun, 1990; Miyazaki et al., 1995; Lee et al., 1997; Shin et al., 1999, 2000) and other bioactive agents (Miyazaki et al., 1984; Bonina and Montenegro, 1994; Liaw and Lin, 2000).

Pluronic F127 is a high molecular weight poly(oxyethylene)/poly(oxypropylene)/poly(oxyethylene) triblock copolymer, aqueous solutions (typically 20–30% w/w) of which form thermally reversible gels on warming to body temperature. In the present paper we have explored the potential of an alternative in situ gelling material of natural origin, xyloglucan, for the topical delivery of NSAIDs. Xyloglucan is a polysaccharide derived from tamarind seeds, which when partially degraded by β-galactosidase exhibits thermally reversible gelation in dilute aqueous solution, the sol–gel transition temperature varying with the degree of galactose elimination. The material used here had a percentage of galactose removal of 44% and exhibited a thermally reversible transition from sol to gel at temperatures of between 22 and 27 °C. We previously investigated the potential use of xyloglucan gels for rectal (Miyazaki et al., 1998), intraperitoneal (Suisha et al., 1998) and oral drug delivery (Kawasaki et al., 1999; Miyazaki et al., 2001). We now compare the potential of xyloglucan and Pluronic F127 gels as vehicles for the transdermal delivery of the NSAIDs ibuprofen and ketoprofen using both in vitro and in vivo assessment methods.

2. Materials and methods

2.1. Materials

Xyloglucan with a percentage of galactose removal of 44% (Lot. 9530L) was prepared as described previously (Shirakawa et al., 1998) and supplied by Dainippon Pharmaceutical Co., Osaka. Pluronic F127 and ibuprofen sodium were obtained from Sigma Chemicals (St. Louis, MO, USA), and ketoprofen was obtained from Wako Pure Chemical Industries (Tokyo).

2.2. Preparation of drug formulations

Xyloglucan sols of concentrations 1.0, 1.5 and 2.0% w/w were prepared by slowly adding a weighed amount of the enzyme-degraded xyloglucan to cold phosphate buffer pH 7.4. The mixture was slowly homogenized (automatic homogenizer CM-200, Iuchi, Osaka) and an appropriate amount of drug was then dissolved in the resulting solution to produce a final drug concentration of 1% w/v. Pluronic F127 sols (25% w/w) were prepared in a similar manner but stored overnight at 5 °C to ensure complete dissolution before the addition of the drug.

2.3. Animal experiments

Male Wistar rats weighing 280–380 g were used in the in vitro permeation and in vivo percutaneous absorption studies. The experiments were performed in a constant temperature room (21–22 °C). The day before the experiment the hair of the abdominal parts was carefully removed with an electric clipper and a razor without breaking the skin.

2.4. In vitro permeation study

The in vitro permeation of drugs was studied by using a plastic dialysis cell similar to that described previously (Miyazaki et al., 1984). The capacity of each half-cell was 2 ml and the surface area of the membranes was 2.0 cm^2. The xyloglucan and Pluronic F127 formulations, prepared in pH 7.4 buffer and loaded with a known weight of drug, were placed in the donor compartment and an equal volume of the pH 7.4 buffer was placed in the receptor compartment. The gel donor and the aqueous receptor compartments were separated by either the freshly-excised, full-thickness, rat skin or cellulose membrane (Viskase Sales Co., Chicago, USA, size 36/32). The assembled cell was shaken horizontally at the rate of 60 strokes/min in an incubator. The total volume of the receptor

solution was removed at intervals throughout the release period and replaced by fresh medium. Drug concentrations were determined by high-performance liquid chromatography as described previously (Miyazaki et al., 1986).

2.5. In vivo percutaneous absorption study

The rats were anaesthetized with an i.p. injection of urethane, 1 g/kg, and the jugular vein was cannulated to facilitate removal of blood sample. The sol formulation (1 g) was applied to a 3-cm diameter circular site, (surface area 7.1 cm^2), on the abdominal skin. At hourly intervals after drug administration, a blood sample (0.5 ml) was collected from the jugular vein and centrifuged at 3000 rpm for 10 min. The plasma concentration of drugs was determined by high-performance liquid chromatography. The area under the plasma concentration curve (AUC) up to 4 h post-administration, was calculated by moment analysis (Yamaoka et al., 1981).

The effect on percutaneous absorption of the application of an occlusive dressing technique (ODT) was investigated by covering the area around the application site with Saran Wrap film (Asahi-Dow Co., Japan) as described previously (Miyazaki et al., 1995).

3. Results and discussion

3.1. In vitro diffusion through excised rat skin and cellulose membranes

The influence of the gel vehicle on the release of drug was investigated by comparing permeation rates of the drugs through each gel using cellulose membranes to divide the donor and receptor compartments of the diffusion cell. Fig. 1 shows the cumulative permeation of ibuprofen (1.0% w/v) through 1.5% w/w xyloglucan gels and 25% w/w Pluronic F127 gels over a 12 h time period plotted in accordance with the diffusion model proposed by Higuchi (1962),

$$Q = 2C_0(Dt/\pi)^{1/2}, \quad (1)$$

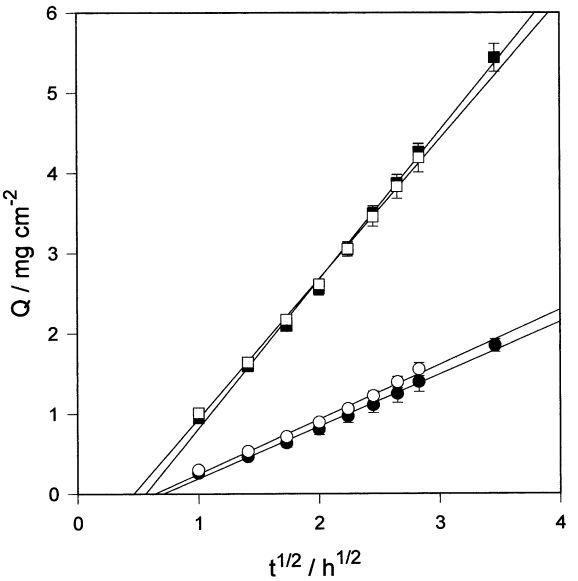

Fig. 1. Cumulative amount of drug (initial loading 1% w/v) per unit area, Q, permeating through cellulose membranes as a function of square root of time when released from gels of 1.5% w/w xyloglucan (squares) and 25% w/w Pluronic F127 (circles). Closed symbols are for ibuprofen; open symbols are for ketoprofen. Each value is the mean ± S.E. of four determinations.

where Q is the cumulative amount of drug released per unit surface area, C_0 is the initial drug loading, D is the diffusion coefficient and t is the time after commencement of diffusion.

The plots were linear after an initial lag time indicative of diffusion-controlled release from the gels. Diffusion coefficients calculated from the gradients of the linear Higuchi plots are compared in Table 1 and show significantly higher values when ketoprofen and ibuprofen were released from xyloglucan gels compared to their release from gels of Pluronic F127. The pK_as of the two drugs are similar [ibuprofen 4.45 (Avdeef et al., 1998), ketoprofen 5.0 (Jeong et al., 2000)] and indicate complete ionization of each drug at the pH of the in vitro permeability experiments (pH 7.4). Diffusion of these ionized drugs through the gel will be through water channels and consequently will be influenced by the gel structure and concentration. The significantly higher permeabilities through cellulose membranes when drug is released from xyloglucan rather than Pluronic

Table 1
Comparison of apparent diffusion coefficients, D, for in vitro release of ibuprofen and ketoprofen from gels of xyloglucan and Pluronic F127 and transfer through excised rat skin and cellulose membranes

Dosage form	10^7 D (cm^2/s)	
	Ibuprofen	Ketoprofen
Skin[a]		
Xyloglucan		
1.0% w/w	9.36	–
1.5% w/w	7.16	0.34
2.0% w/w	7.46	–
Pluronic F127 25%	0.24	0.03
Cellulose membrane		
Xyloglucan 1.5% w/w	74.8	66.0
Pluronic F127 25%	9.18	10.1

[a] Diffusion coefficients for the skin model have little intrinsic meaning and are intended for comparative purposes only.

F127 gels is a consequence both of the very much higher concentration of the latter and also of the very different structures of the gels. The Pluronic F127 gels are cubic gels formed by the packing of the micelles of this poly(oxyethylene)/poly(oxypropylene)/poly(oxyethylene) triblock copolymer (Booth and Attwood, 2000), whereas the thermally reversible gelation of xyloglucan is a consequence of the lateral stacking of rod-like chains (Yuguchi et al., 1997). A significant proportion of the water in the Pluronic F127 gels is retained between the polyoxyethylene chains forming the micelle fringe or hydrogen-bonded to the ether oxygens of these chains, and does not constitute bulk water through which the drug is able to readily diffuse. In contrast, the xyloglucan gels have a much higher water content (98.5%), and our results suggest that there is a lower resistance to the diffusion of the ionized drugs through water channels between the laterally stacked chains than between the micelles of the Pluronic gel. In addition, it is probable that the thermodynamic activities (and hence the chemical potentials) of drug in the two gels will be different so influencing diffusional release from these vehicles, although the influence of this cannot be quantified from the present study.

Experimental results for release of drug from each vehicle and its passage through excised skin were treated in a similar manner. Although linear plots were obtained when permeation rates were plotted as a function of root time, it is stressed that the linearity of these plots may be fortuitous since Eq. (1) is strictly only valid when the vehicle is exerting considerably more resistance to diffusion than the membrane. In this respect it should be noted that there is a difference of one to two orders of magnitude between apparent diffusion coefficients through skin and cellulose membranes, the lower permeation rates through skin reflecting the greater resistance to the passage of these ionized drugs through this more complex structure. Permeation through skin is predominantly by intercellular and transcellular routes and there is evidence to suggest that even small polar molecules diffusing in the intercellular channels are transferred along a tortuous pathway (Hadgraft, 2001). Although apparent diffusion coefficients were calculated from the gradients of the plots (see Table 1), the values obtained when the barrier was skin should be treated with caution, and serve only as a qualitative indication of the factors influencing permeation rates through skin.

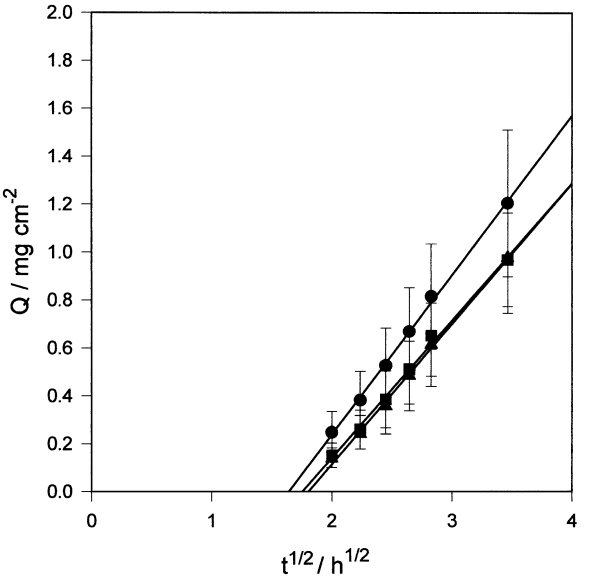

Fig. 2. Cumulative amount of ibuprofen (initial loading 1% w/v) per unit area, Q, permeating through excised rat skin as a function of square root of time when released from xyloglucan gels of concentrations (▲) 2.0, (■) 1.5 and (●) 1.0% w/w. Each value is the mean ± S.E. of four determinations.

Fig. 2 compares the cumulative permeation through skin of ibuprofen (1.0% w/v) released from xyloglucan gels of concentrations 1.0, 1.5 and 2.0% w/v. Apparent diffusion coefficients calculated from the gradients of the plots (see Table 1) were independent of gel concentration within the limits of error of measurement, and 1.5% w/w xyloglucan was selected as a representative gel.

Fig. 3 compares the cumulative permeation of each drug following release from 1.5% w/w xyloglucan and 25% w/v Pluronic F127 gels. The results of our study show a significantly higher rate of transport of ibuprofen through skin compared to that of ketoprofen, for both gel systems. Transport of drug dissolved in the gel vehicle across the skin or cellulose membrane involves the initial diffusion of drug through the gel to the surface of the barrier and the subsequent diffusion through the barrier membrane of drug that has partitioned into it from the vehicle. As no significant difference in D values for these drugs is observed when the barrier is a cellulose membrane (see Table 1), it may be concluded that there are no significant differences between the diffusion rates of ibuprofen and ketoprofen through each of the two gel vehicles. The observed higher rate of ibuprofen transport may be attributed, therefore, to differences in the partitioning of drug from the vehicle into the skin and its subsequent transport through this barrier.

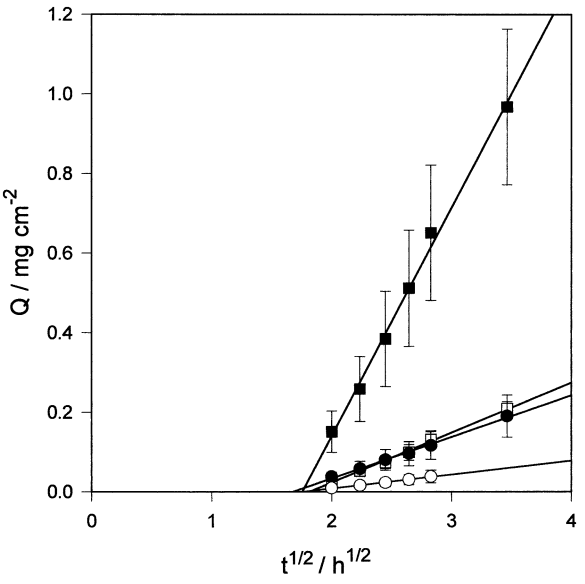

Fig. 3. Cumulative amount of drug (initial loading 1% w/v) per unit area, Q, permeating through excised rat skin as a function of square root of time when released from gels of 1.5% w/w xyloglucan (squares) and 25% w/w Pluronic F127 (circles). Closed symbols are for ibuprofen; open symbols are for ketoprofen. Each value is the mean ± S.E. of four determinations.

Several attempts have been made to establish correlations between the physicochemical parameters of NSAIDs and their transdermal permeation (Cordero et al., 1997; Hadgraft and Valenta, 2000; Hadgraft et al., 2000; Hadgraft, 2001). The total flux of weak acids or weak bases through skin is primarily determined by pH (through its affect on the relative amounts of ionized and non-ionized species), the drug concentration or saturated solubility, the molecular weight, and the extent of partitioning into the lipoidal components of the skin. The latter is usually assessed by the octanol/water distribution coefficient, although a liposomal membrane/water partition coefficient has been proposed as a more reliable indicator of the partitioning of ionizable species (Avdeef et al., 1998). The successful modeling of skin permeability using these parameters suggests that there is no specific pathway through which organic ionized species transfer (Hadgraft and Valenta, 2000). Since the two drugs of the present study have similar molecular weights, are both fully ionized at the pH of the measurements, and are present in solution at the same concentration, the main indicator of their skin permeability is their octanol/water distribution coefficient, D_{oct}. Cordero et al., (1997) report a D_{oct} value of 5.2 for ketoprofen at pH 6.6 (99.0% ionized) which compares with a value of approximately 60 for ibuprofen at this pH as interpolated from a plot of the variation of log D_{oct} against pH reported by Avdeef et al. (1998). There is a direct relationship between skin permeation and D_{oct} from which it may be inferred that the higher lipophilicity of ibuprofen compared to ketoprofen is the probable cause of the higher rate of transfer of this drug through skin as observed in Fig. 3 and Table 1.

3.2. In vivo drug release

The release of ibuprofen and ketoprofen from gels of 1.5% w/w xyloglucan and 25% w/w Pluronic F127 formed in situ following the application of 1 g of sol containing 1% w/v drug to a defined area of the abdominal rat skin was monitored by the determination of plasma drug levels. Fig. 4 compares the plasma concentrations achieved following release from each gel for the two drugs up to 4 h post-administration. Table 2 summarizes the AUC values calculated from the plasma concentration–time data using a model-independent analysis (Yamaoka et al., 1981). The lower T_{max} of ibuprofen observed for release from each gel vehicle is in agreement with the in vitro results, which show a higher diffusion rate for this drug through excised rat skin compared to that of ketoprofen.

Fig. 4 and Table 2 show considerably higher bioavailabilities for the release of both drugs from the xyloglucan gels compared to that from the

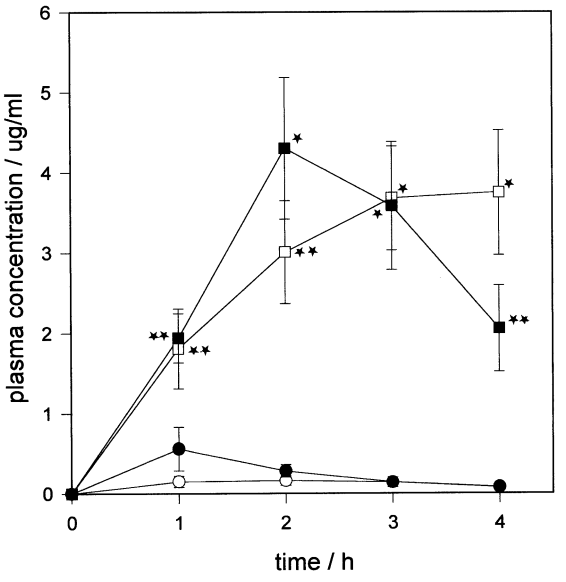

Fig. 4. Percutaneous absorption in rats of ibuprofen (closed symbols) and ketoprofen (open symbols) from gels formed by in situ gelation of sols of 1.5% w/w xyloglucan (squares) and 25% w/w Pluronic F127 (circles) loaded with an initial drug concentration of 1% w/v. Each value is the mean ± S.E. of 4–5 determinations. *$P < 0.005$, **$P < 0.01$ compared with Pluronic F127.

Table 2
Comparison of bioavailability parameters of ibuprofen and ketoprofen following administration to rat skin in gels formed in situ by gelation of sols of xyloglucan (1.5% w/w) and Pluronic F127 (25% w/w), and the influence of ODT on skin transport

Dosage Form	T_{max} (h)	C_{max} (μg/ml)	AUC (0–4 h) (μg h/ml)
Ibuprofen			
Xyloglucan	2.20 ± 0.20	4.47 ± 0.94*	10.81 ± 2.06*
Pluronic F127	1.60 ± 0.24	0.59 ± 0.27	1.02 ± 0.32
Ketoprofen			
Xyloglucan	3.5 ± 0.3**	3.86 ± 0.77*	10.38 ± 2.15*
Pluronic F127	1.8 ± 0.5	0.17 ± 0.06	0.47 ± 0.19
Ibuprofen (ODT)			
Xyloglucan	2.67 ± 0.33	5.12 ± 0.52	15.55 ± 2.06
Pluronic F127	2.33 ± 0.58	0.75 ± 0.17	2.28 ± 0.58

Each value represents the mean ± S.E. of 4–6 experiments.
* $P < 0.005$;
** $P < 0.05$.

Pluronic F127 gels. A major factor contributing to the very much lower bioavailability following release from the F127 gels is clearly the low rate of diffusion of the ionized drugs through their cubic gel structure as discussed above. Our previous histological studies have shown that neither Pluronic F127 (Miyazaki et al., 1987) nor xyloglucan (Miyazaki et al., 1998) cause any measurable changes in the structure of mucous membranes and it is thought unlikely that the observed differences in in vivo permeability of the two drugs arise from the influence of the gel vehicles on skin structure. Further insight into other possible causes of the lower bioavailability was seen from an examination of the influence of an ODT on the observed bioavailability of ibuprofen from the two vehicles. Fig. 5 and Table 2 show a greater influence of the ODT on the plasma concentration profile for release of ibuprofen from the Pluronic gels (increase of AUC by a factor of 2.2) than from xyloglucan gels (increase of AUC by a factor of 1.4). We have noted a similar enhancement of the bioavailability of indomethacin when released from 20% w/w Pluronic F127 gels (a 2.0-fold increase) following the application of an ODT using an identical rat model (Miyazaki et al., 1995). These findings

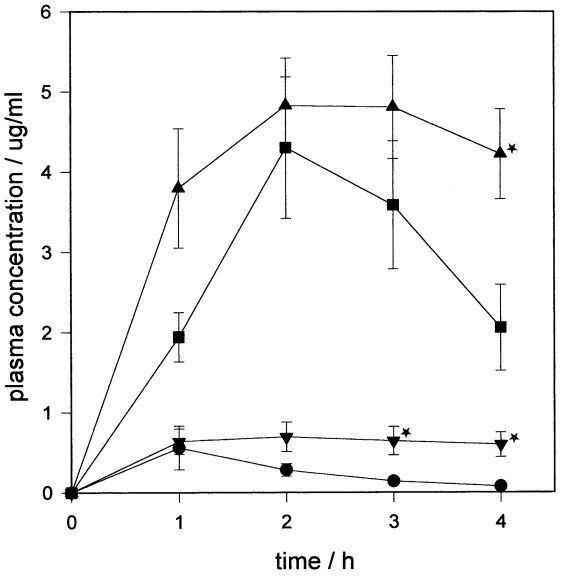

Fig. 5. Effect of occlusive dressing on the percutaneous absorption in rats from gels formed by in situ gelation of sols of 1.5% w/w xyloglucan and 25% w/w Pluronic F127 loaded with an initial concentration of 1% w/v ibuprofen. (▲) xyloglucan with occlusive dressing; (■) xyloglucan without occlusive dressing; (▼) Pluronic F127 with occlusive dressing; and (●) Pluronic F127 without occlusive dressing. Each value is the mean ± S.E. of 5–6 determinations. $^{*}P < 0.05$ compared with non-occlusive dressing.

suggest that prevention of water loss by occlusion may influence the gel structure and skin hydration to differing extents for the two gel vehicles. The gels of Pluronic F127 form as thin, smooth films within minutes of application of sol to the skin surface. Water loss from these gels increases the resistance to drug transport through the gel network and may also be accompanied by dehydration of the skin surface as water migrates into the gel. Prevention of water loss by the occlusive dressing would be expected to minimize these processes thus explaining the observed enhanced bioavailability. The xyloglucan gels initially have a higher water content (98.5% w/w) and form more slowly than the Pluronic gels. Our results suggest that any changes of the water content of these gels by evaporation has less influence on drug transport or skin hydration and hence occlusion techniques might be expected to have little effect on bioavailability as was observed.

4. Conclusion

Our study has demonstrated the potential of the gels formed by in situ gelation of xyloglucan sols as sustained-release vehicles for percutaneous delivery of NSAIDs. The bioavailabilities of ibuprofen and ketoprofen in rat when administered at a pH at which they are fully ionized are enhanced 10- and 20-fold, respectively compared to their release from a Pluronic F127 gel under identical conditions. In addition, xyloglucan has recognized non-toxicity and a lower gelation concentration compared to that of the Pluronic.

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