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The use of colloidal microgels as a (trans)dermal drug delivery system

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Abstract

A co-polymer of poly(*N*-isopropylacrylamide) (85%) co-butyl acrylate (10%) co-methacrylic acid (5%) (NIPAM/BA/MAA) (85/10/5) microgel was synthesised and investigated as a potential pH and temperature sensitive transdermal delivery device. Three compounds having different octanol/water partition coefficients and solubilities were incorporated into the microgel, namely: salicylamide (SA), methyl paraben (MP) and propyl paraben (PP). Physico-chemical characterisation of these microgel–drug complexes showed that microgels incorporating MP and SA have smaller volumes after changing environmental pH or temperature when compared with the co-polymer NIPAM/BA/MAA (85/10/5) alone. This reduction in volume could be attributed to the incorporation of the compounds into the microgel particles, having a shielding effect on the charged groups present within the network. Diffusion studies, across human skin, were performed at 305 K in the range of pH 3–7 for saturated solutions of SA, MP and PP, and for microgel particles incorporating the three compounds. The transport rate for these microgels incorporating MP was reduced by 2/3-fold compared to the saturated solution, by one order of magnitude for PP, meanwhile the transport rate for these microgels incorporating SA is the same order of magnitude as that for the corresponding saturated solutions. Transdermal release studies of the saturated colloidal dispersions indicated that pH control of the drug release was marginal. The incorporation of compounds into the pH/temperature sensitive co-polymer NIPAM/BA/MAA (85/10/5) and the subsequent release depends on the octanol/water partition coefficient and solubility of the respective compound.

Keywords: Microgel particles; pH/temperature sensitive; Transdermal drug delivery; Octanol/water partition coefficient; Solubility

1. Introduction

Conventional delivery systems suffer from the limitations of minimal synchronization between the required time for therapeutically effective drug plasma concentrations and the actual drug release profile ex-

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hibited by the dosage form. With an increase in the understanding of the concept of chronopharmacokinetics and variations in disease symptoms, Gupta et al. (2002) have said that the focus of pharmaceutical scientists is shifted towards an idealized drug delivery system wherein the required amount of active agent is made available at the desired time and at a specific site of action in the body, i.e. releasing certain drugs in a patterned manner, responding to the body's need for the drug.

The design of a drug delivery system is usually based on the drug's physicochemical and pharmacokinetic properties. Current investigations are ongoing with respect to developing controlled release devices that can control the release of rapidly metabolised drugs and/or have the ability to also protect sensitive drugs. For example some research related to this is in the use of hydrogels for a pulsatile local delivery of thrombolytic and antithrombotic agents (Brazel and Peppas, 1996) and the use of pH-thermosensitive polymeric beads for modulating insulin release using a pH trigger (Ramkisson-Ganorkar et al., 1999). Swelling controlled release systems (for example, microgels) seem to fulfill these aforementioned requirements. They have been used to achieve both zero order, when water is absorbed, and pulsatile release patterns, when certain environmental conditions, such as temperature, pH or ionic strength are met to obtain a responsive release (Sahoo. et al., 1998; Soppimath et al., 2001; Bharali et al., 2003).

Different names and definitions have been used to define and describe colloidal microgels. Some ambiguity arises as these terms are not always restricted to cross-linked structures and consequently cause confusion with respect to the exact nature of the systems under study. In this paper, colloidal microgels may be defined as a disperse phase of discrete polymeric gel particles, which are typically in the size range of 1 nm to 1 μm uniformly dispersed in a continuous solvent medium, which is swollen by a good solvent (Murray and Snowden, 1995).

Microgels are classified as "smart materials" because of their conformation changes in response to changes in environmental conditions such as temperature (Senel et al., 1997), pH (Sen et al., 1999) or ionic strength (Akkas et al., 1999). The extent of swelling (or de-swelling) is an interesting property of microgel particles (Benee et al., 2002).

A common misinterpretation is the use of the terms hydrogels and microgels. They have similar polymer chemistry, but their physical molecular arrangements are different (Benee et al., 2002). Microgels, defined as "discrete gel like particles", compared with hydrogels (they could be imagined as a "bowl of jelly") have the following physico-chemical properties: much lower viscosity, very high surface area, rapid thermal response and rapid "solution" response.

Their properties make them useful in a variety of fields including paint industry, in ink jet printing, cements, enzyme immobilization, oil recovery, molecular separation and environmentally sensitive display devices (Murray and Snowden, 1995). Also, microgels have many potential uses as drug delivery devices in the biomedical field, and have been used as on/off switches, responding to small changes in physiological conditions.

The development of microgels responding simultaneously to temperature and pH stimuli, is a wide and interesting area of research for the development of specific drug carriers, mainly for oral delivery (Yoshida et al., 1999; Zahirul et al., 1999; Yildiz et al., 2002; Ramkisson-Ganorkar et al., 1999). The use of these systems for topical applications has not been widely studied. One of the few examples was the development of a novel drug-loaded wound dressing having thermoresponsive, adhesive, absorptive an easy peeling functions (Lin et al., 2001).

In this study, microgels will be used as novel drug carriers for either dermal or transdermal delivery. The reason for investigating the use of microgels as transdermal delivery systems is based on the advantages that the transdermal drug delivery route has over the oral administration of drugs (Ranade, 1991) and because of the small number of studies done using this system. A comparatively smaller number of drugs are marketed using this route of delivery, compared to oral dosage forms, as drug absorption across the skin is very low because of the stratum corneum (the main barrier for drug absorption across the skin). Several techniques have been developed, or are currently under development, to overcome the stratum corneum (Higaki et al., 2003).

Despite the heterogeneity in the structure of the barrier function, diffusion experiments show that permeation is well described according to Fick's first law of diffusion, where the transport of drugs across the skin

via passive diffusion at steady state can most simply be described by Eq. (1) (Hadgraft, 2001):

$$J = \frac{DK\Delta c}{h} \quad (1)$$

where J is the flux per unit area, D the diffusion coefficient in the skin, K the skin-vehicle partition coefficient, Δc the concentration gradient across the skin and h the diffusional pathlength.

Another problem in transdermal delivery is skin toxicity. Drug molecules are required that are innocuous, neither creating irritancy nor allergenicity so, in some circumstances using a larger patch area can alleviate the problem. Because of this issue and taking into consideration one of the possible practical applications of "smart materials" in wound treatment (Isahara et al., 2002; Lin et al., 2001), the idea of using pH/temperature sensitive microgels as (trans)dermal drug delivery systems was considered.

This paper describes the synthesis, physico-chemical properties and transdermal drug delivery of a thermo- and pH-responsive co-polymer of poly(*N*-isopropylacrylamide) (85%) co-butyl acrylate (10%) co-methacrylic acid (5%) (NIPAM/BA/MAA) (85/10/5) microgel, incorporating three different compounds: salicylamide (SA), methyl paraben (MP) and, propyl paraben (PP) with $\log K_{oct/w}$ 1.28, 1.89 and, 2.83, respectively. These three model compounds, having different octanol/water partition coefficients and solubilities in water, were incorporated into the microgel to determine if there is any relationship between the uptake and release of these compounds from the colloidal microgel particles and their physico-chemical properties.

2. Materials and methods

2.1. Materials

Chemical products have been provided as follows: *N*-isopropylacrylamide 97% (Aldrich, UK), *N*,*N*′-methylenebisacrylamide 99% (Aldrich, UK), potassium persulphate 98% (BDH Laboratory Supplies, UK), butyl acrylate 99% (Acros organics, Belgium), methacrylic acid 99.5% (Acros Organic, Belgium), methyl paraben 99% (Aldrich, UK), propyl paraben 99.5% (a gift from Nipa) and salicylamide 99% (Acros Organic, Belgium). KH_2PO_4 was purchased from BDH Laboratory Supplies (UK), NaH_2PO_4 and Na_2HPO_4 were purchased from Fisher Scientific (UK) and NaCl 99% was obtained from Aldrich (UK). 0.1 M NaOH, 0.1 M $HClO_4$, and $NaClO_4$ were purchased from Aldrich (USA). HPLC grade phosphoric acid was purchased from Sigma (Germany) and HPLC grade acetonitrile was obtained from Fisher Scientific (UK). All chemicals were used without further purification.

Excised human skin (female and male, thigh leg area, age 35 ± 10 years old) was used for all the dermal penetration experiments and, the permeation profiles are given as the mean. Separation of the stratum corneum and epidermis from the dermis was performed using the heat separation technique. After separation the epidermal tissue was wrapped in aluminium foil and stored in polyethylene bags at 255 K until use. Twenty-four hours before the experiments, they were placed in a refrigerator at 277 K.

2.2. Methods

2.2.1. Microgel synthesis

Poly(NIPAM) microgel particles were prepared by surfactant free emulsion polymerisation in deionised water at 343 K, under a nitrogen atmosphere. Potassium persulphate (0.5 g), an anionic free radical initiator, was placed in a 1 L, three-necked round-bottomed flask and stirred continuously at ∼120 rpm. Pre-dissolved NIPAM (4.25 g), BA (0.56 mL) and MAA (0.25 mL) as co-monomers, and *N*,*N*′-methylenebisacrylamide (0.5 g) as a crosslinker, were dissolved in 200 mL deionised water under stirring and then added to the reaction vessel. After 6 h the dispersion was cooled to room temperature and filtered through glass wool. Further purification was done by extensive dialysis against water until the conductivity was less than 1 $\mu S\,cm^{-1}$. These microgels with a NIPAM/BA/MAA mole ratio of 85/10/5 were synthesised to study the incorporation and release of MP, PP and SA over a range of pH (3–7) and temperatures (283–333 K). Dry weight analysis of the NIPAM/BA/MAA microgel showed the dispersion to be of the order of 0.62% (w/w).

2.2.2. Preparation of methyl paraben, propyl paraben and salicylamide loaded microgels

Microgel dispersions of 0.62 (w/w, %) incorporating MP, PP or SA were prepared from freeze dried samples

of NIPAM/BA/MAA (85/10/5) microgel particles, allowing them to swell in the corresponding filtered saturated solutions for 48 h, at different pH values (3–7) in a water bath at 298 K, under continuous stirring. The solutions were adjusted to the required pH by the addition of small quantities of 0.1 M $HClO_4$ and 0.1 M NaOH solutions. A constant ionic strength of 1.5×10^{-4} M was maintained, by supplementing with $NaClO_4$.

2.2.3. Physico-chemical characterisation: dynamic light scattering

Microgel dispersions of 0.15 (w/w, %) by dilution of the stock dispersions were prepared in clean stoppered vials. The hydrodynamic diameter (and hence volume changes) of each microgel dispersion was determined over a temperature range of 283–333 K using a "Malvern Instrument" Zetasizer 3000 instrument, fitted with a 5 mW He–Ne laser ($\lambda = 633$ nm) with a detector placed at 90°.

2.2.4. Solubility studies

Solubility testing involved adding an excess of the compounds to the solution and stirring for 48 h at 305 K. The resulting saturated solutions were centrifuged, the supernatant was diluted and analyzed by UV at 298 K. The molar absorption of the samples was measured at 255 nm for MP and PP, and at 299 nm for using a Cary 100 UV–vis spectrophotometer to collect data.

2.2.5. In vitro permeation

Permeation of MP, PP and SA from saturated solutions of the three solutes in water, in the range of pH 3–7, and from microgels containing saturated concentration of the parabens and salicylamide in the same range of pH (3–7), across human skin, was examined using Franz-type diffusion cells, having a receptor volume of 3.9 mL and diffusional area of ~0.95 cm^2. Phosphate buffered saline (PBS), pH 7.4, was used as the receptor phase.

After preparation, all the samples (saturated solution and microgels) were placed in a thermostated water bath, at the appropriate temperature, 305 K, for 24 h. One milliliter of the sample, either a saturated solution of the different solutes or a microgel containing them, was placed in the donor compartment.

More than 10 experiments were conducted using these systems for a 24 h period. Data analysis showed that the lag times were very short (less than 20 min). Linear regression of the data for the 24 h period produced the same flux as for 5 h. For this reason subsequent experiments were conducted for a shorter time. All the receptor phase was removed and replaced with fresh pre-thermostated receptor phase. The samples were taken after 30 min, 1, 1.5, 2, 3, 4 and 5 h.

HPLC analysis of MP was performed using a SpectraSERIES P100 pump (thermo separation products) set at the flow rate of 1 mL/min, a SpectraSERIES UV 100 detector set at 255 nm and a ChromJet integrator for computing the chromatograms. Samples were injected using SpectraSERIES AS100 autosampler.

The column was an Apex reverse phase ODS 5 μm packed column (250 mm × 4.6 mm) and a mobile phase of acetonitrile/buffer (0.05 M KH_2PO_4) 35:65 (v/v). After mixing, 1% of triethylamine was added, and the pH adjusted to 3.5 with orthophosphoric acid. Calibration curves were constructed on the basis of the peak area measurements using standard solutions of known concentration. The retention time was ~6.1 min.

The HPLC analysis of PP was performed using the same procedure as for MP but the proportions of acetonitrile/buffer (0.05 M KH_2PO_4) in the mobile phase were 50:50 (v/v). The retention time for PP was 6.4 min.

The HPLC analysis of SA was performed using as mobile phase 25:75 (v/v) of acetonitrile/buffer (0.05 M KH_2PO_4), without addition of triethylamine. This time the UV detector was set at 299 nm and the pH was adjusted to 3.3 with orthophosphoric acid. The retention time for SA was 6.3 min.

2.2.6. Statistics

All data were calculated and presented as mean ± S.D. The statistical significance between MP, PP and SA fluxes obtained for saturated solutions and microgels, incorporating those compounds, was determined by two tailed, unpaired test. A value of $P < 0.05$ was considered significant.

3. Results and discussion

3.1. Physicochemical properties of the microgels

The two polymers studied in this work, poly(NIPAM) and MAA, have characteristic temperat

ure- and pH-sensitivity, respectively, with high degrees of swelling in aqueous solutions at low temperatures and high pH values. Thermo-responsive microgel particles based on poly(NIPAM) have been widely investigated because of their ability to undergo conformational changes (Murray and Snowden, 1995; Pelton and Chibante, 1986; McPhee et al., 1993; Snowden and Chowdhry, 1995; Pelton, 2000). MAA polymers are well known for their pH-sensitivity (Seno et al., 1991; Diez-Peña et al., 2002).

Incorporation of co-monomers containing acidic (Snowden et al., 1996) or basic (Loxely and Vincent, 1997; Pinkrah et al., 2003) functionalities into poly(NIPAM) microgels yields particles with pH driven swelling. For example, Snowden et al. (1996) reported the preparation of poly(NIPAM) microgel particles containing acrylic acid groups. It was found that the hydrodynamic diameter (volume change) of the microgel particles increased with a corresponding rise in pH.

Fig. 1 shows that there is an increase in the absolute volume for all the microgels as the pH increases from 3 to 7, at 298 K. The purpose of these experiments was to show size change for the dispersed microspheres. At elevated temperatures the effects are attenuated. Two hundred and ninety eight Kelvin was chosen as a representative temperature to explore size effects. The largest increase in particle volume was found to occur at a pH range of 5–7. This wide change in volume is related to the pK_a of methacrylic acid (∼5.5, Saunders et al., 1997). As dissociation of the methacrylic acid groups occurs, increased charge within the microgel particle causes electrostatic repulsions between the chains. This results in an increases in the hydrophilicity of the network, and therefore, greater swelling ratios. Results similar to these were obtained in previous studies (Brannon-Peppas and Peppas, 1991; Khare and Peppas, 1995).

A second notable observation can be found showing that the volumes occupied by these microgels at pH 3 is the same, within experimental error. As the pH is increased to 7, there are clearly two different behaviours. Microgels incorporating MP and SA have smaller volumes over the range of pH 4–7 when compared with the co-polymer NIPAM/BA/MAA microgel and the microgel incorporating PP. For example, considering the volume values at pH 6, the volumes of the co-polymer NIPAM/BA/MAA and NIPAM/BA/MAA incorporating PP were found to be the same ($\sim 1.25 \times 10^{-13}$ cm^3). Meanwhile, the volumes of NIPAM/BA/MAA incorporating MP and SA were found to be ($\sim 0.9 \times 10^{-13}$ cm^3). This reduction in volume for MP and SA microgel particles, compared with the co-polymer NIPAM/BA/MAA, may be attributed

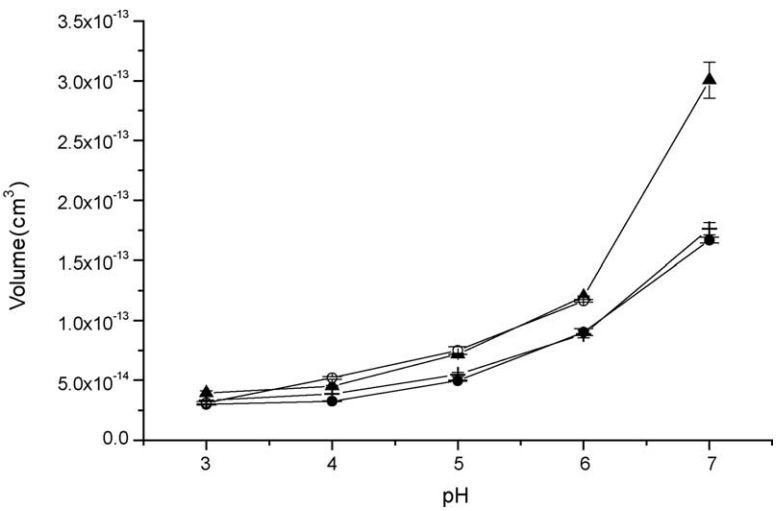

Fig. 1. Hydrodynamic volume vs. pH, measured at 298 K, in a background electrolyte of 1.5×10^{-4} M $NaClO_4$, as a function of the different drugs incorporated into the co-polymer NIPAM/BA/MAA microgels: (▲) NIPAAM/BA/MAA, (●) NIPAAM/BA/MAA incorporating MP, (◯) NIPAAM/BA/MAA incorporating PP, (+) NIPAAM/BA/MAA incorporating SA, at a microgel concentration of 0.10% (w/w).

Table 1
Solubilites of MP, PP, and SA at 305 K over the range of pH 3–7

pH	Solubility of MP at 305 K (mg/mL)	Solubility of PP at 305 K (mg/mL)	Solubility of SA at 305 K (mg/mL)
3	2.37 ± 0.04	0.24 ± 0.02	3.04 ± 0.06
4	2.35 ± 0.05	0.23 ± 0.03	3.05 ± 0.01
5	2.38 ± 0.03	0.25 ± 0.01	3.07 ± 0.01
6	2.43 ± 0.05	0.27 ± 0.01	3.08 ± 0.02
7	2.46 ± 0.01	0.28 ± 0.01	3.44 ± 0.04

Each value represents mean ± S.D. ($n = 4$).

to the incorporation of the compounds into the microgel particles. Incorporation is because of the inherent solubility of the compounds and the degree of swelling of the microgel particles, and also the ability of the drug to interact with the hydrophobic matrix of the particles. The more hydrophilic the drug, the more will be incorporated into the aqueous region of the microgel, and vice versa. The ability to interact with the hydrophobic domains is seen in Table 5. SA and MP, are quite soluble in water (see Table 1) and have a log $K_{oct/w}$ of 1.28 (Merck Index, 1996) and 1.89 (Darwish and Bloomfield, 1995), respectively. Large amounts of these drugs could be incorporated into the microgel having a resultant shielding effect on the charged groups present within the gel network. Shielding results in a reduction of the internal charge repulsion between the ionized methacrylic acid groups, together with a concomitant decrease in polymer–solvent interactions. Therefore, these microgels will adopt a more compact conformation.

For the microgel incorporating PP, the absolute volume at this pH remains constant comparing it with the co-polymer NIPAM/BA/MAA. The log $K_{oct/w}$ of PP is 2.83 (Darwish and Bloomfield, 1995) and it is not very soluble in water (see Table 1). Therefore, not so much of the drug will be incorporated into the microgel particles and as a consequence, it does not have a significant shielding effect between the charged groups.

Fig. 2 shows the change in the volume of the microgels as a function of temperature at pH 3 and 6. There are several observations that can be made here; firstly, it can be seen that at pH 6 the volumes of the microgel particles are larger than at the lower pH values, at all temperatures. This is a consequence of the ionisation of the methacrylic acid groups, as it was explained before.

Secondly, increasing the environmental temperature results in a greater reduction in volume for the most swollen microgels (pH 6). This is not surprising, as the microgels at pH 3 have much more compact conformation as a result of less charge repulsion between the chains. Therefore, there is less scope for conformational change. Similar results were reported for a cationic poly(NIPAM-co-4-vinylpyridine) (Pinkrah et al., 2003).

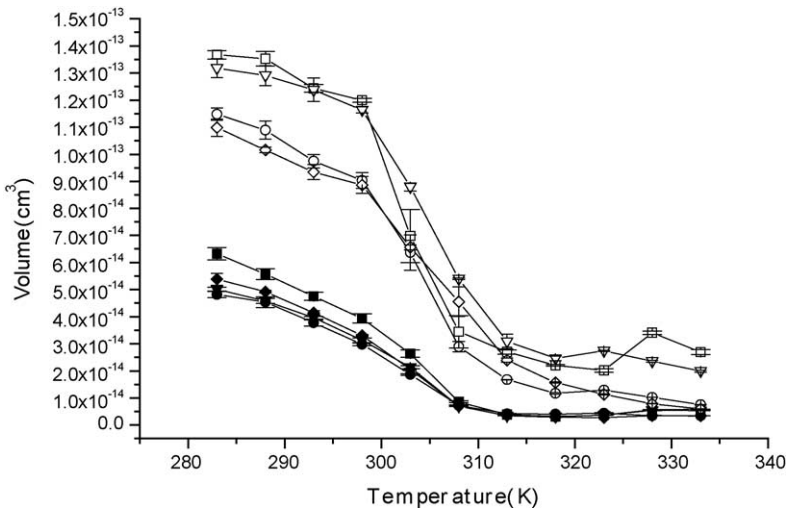

Fig. 2. The change in the volume of the microgels as a function of temperature at pH 3 and 6, in a background electrolyte of 1.5×10^{-4} M $NaClO_4$, at a microgel concentration of 0.06% (w/w). At pH 3: (■) NIPAAM/BA/MAA, (●) NIPAAM/BA/MAA incorporating MP, (▼) NIPAAM/BA/MAA incorporating PP, (♦) NIPAAM/BA/MAA incorporating SA. At pH 6: (□) NIPAAM/BA/MAA, (◯) NIPAAM/BA/MAA incorporating MP, (▽) NIPAAM/BA/MAA incorporating PP, (◇) NIPAAM/BA/MAA incorporating SA.

Table 2
Flux values for MP at 305 K (32 °C) in the range of pH 3–7, through human skin, from saturated solutions with and without microgel (Mg)

pH	Flux saturated MP (μg/cm^2/h)	Flux Mg + MP (μg/cm^2/h)
3	93 ± 9	28 ± 4[a]
4	111 ± 8	35 ± 3[a]
5	116 ± 20	30 ± 1[a]
6	88 ± 6	24 ± 2[a]
7	94 ± 3	39 ± 5[a]

Each value represents the mean ± S.D. ($n = 4$).
[a] Values significantly different to those obtained with saturated solutions ($P < 0.05$).

Table 3
Flux values for PP at 305 K (32 °C) in the range of pH 3–7, through human skin, from saturated solutions with and without microgel (Mg)

pH	Flux saturated PP (μg/cm^2/h)	Flux Mg + PP (μg/cm^2/h)
3	57 ± 6	
4	40 ± 1	6 ± 1[a]
5	44 ± 3	5 ± 1[a]
6	69 ± 4	7 ± 2[a]
7	71 ± 25	8 ± 1[a]

Each value represents the mean ± S.D. ($n = 4$).
[a] Values significantly different to those obtained with saturated solutions ($P < 0.05$).

Table 4
Flux values for SA at 305 K (32 °C) in the range of pH 3–7, through human skin, from saturated solutions with and without microgel (Mg)

pH	Flux saturated SA (μg/cm^2/h)	Flux Mg + SA (μg/cm^2/h)
3	5 ± 1	5 ± 1[a]
4		3 ± 1
5	7 ± 1	5 ± 1[a]
6	6 ± 1	3 ± 1[a]
7	5 ± 1	3 ± 1[a]

Each value represents the mean ± S.D. ($n = 4$).
[a] Values no significantly different to those obtained with saturated solutions ($P > 0.05$).

Thirdly, at both pH values, the microgels incorporating MP, PP and SA have smaller volumes compared with the co-polymer NIPAM/BA/MAA, over the temperature range studied (283–333 K). This reduction in volume could be explained on the basis of shielding of the charged groups within the microgel, but as the pH is increased, the reductions in volume are more significant. With increasing pH, the absolute volume of the microgel particles increases, allowing more drug to go into the particles. Therefore there is a higher shielding effect between charged groups and bigger reduction in volume.

3.2. Solubility studies

The solubility of MP, PP and SA increased slightly from pH 3 to 7, remaining almost constant taking into consideration the error value (Table 1). In this case, the small increment in the solubility over the range of pH studied is because the pK_a value of MP, PP and SA are 8.31, 8.23 and 8.4, respectively. The pH effect is important for swelling of the microgel particles but insignificant in terms of solubility.

3.3. Diffusion studies

Diffusion studies for the saturated solutions of MP, PP, and SA and microgel particles incorporating the three substances were performed at constant temperature for all the samples, at 305 K (32 °C) in the range of pH 3–7 (Tables 2–4). Different pH values were chosen with the view to examine the pH sensitive behaviour of the co-polymer NIPAAM/BA/MAA on the permeation of the drugs through human skin. Flux values for all the samples were calculated using Fick's first law (Eq. (1)) in the same way as a previous publication (Lopez et al., 2004).

Figs. 2–4 show steady state flux values for MP, PP and SA, respectively, at 305 K (32 °C) in the range of pH 3–7, through human skin. As pH increases, steady state flux for each of these saturated solutions is maintained constant, within the error value. These results are not surprising because they correspond to pH values below the pK_a values of the compounds, and therefore only unionised species will be present. The aim of working at pH values below the pK_a values was based on that for a more efficient permeation, compounds should be unionised for delivery across the stratum corneum (Leveque et al., 2004).

Flux values for the saturated colloidal dispersions (swollen microgels in the correspondent filtered saturated solution) are constant over the pH range studied, however, the fluxes are reduced compared to the flux corresponding to the saturated solutions (Tables 2–4; Figs. 3–5). As it can be seen in Figs. 3–5 the transport rate for these microgels incorporating MP was reduced by 2/3-fold compared to the saturated solution ($P < 0.05$, unpaired test), by one order of magni-

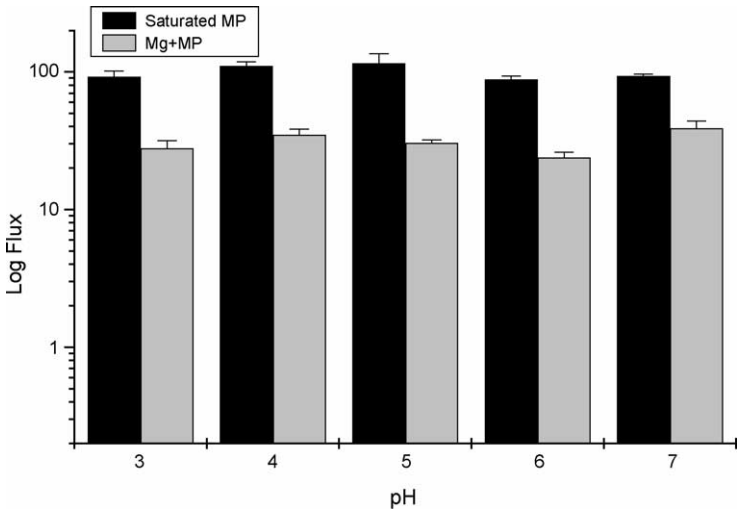

Fig. 3. Flux of MP from co-polymer NIPAAM/BA/MAA microgels and saturated solutions at 305 K (32 °C), as a function of pH using human skin.

tude for PP ($P < 0.05$, unpaired test), approximately, compared to the transport rate from saturated solution of PP, meanwhile the transport rate for these microgels incorporating SA is the same order of magnitude than that for the corresponding saturated solutions ($P > 0.05$, unpaired test). These flux reductions seem to be linked to the hydrophobicity of the compounds and hence their affinity to the interior of the microgel particles.

As it was described in a previous publication (Lopez et al., 2004), it is reasonable to consider the free solution concentration for each of these substances in the colloidal microgel systems, depending on the pH, in an attempt to determine the explanation for the decrease in flux values. Considering Fick's first law (Eq. (1)), the free concentration of the drugs of these microgels can be calculated assuming that K and D are constant. Therefore:

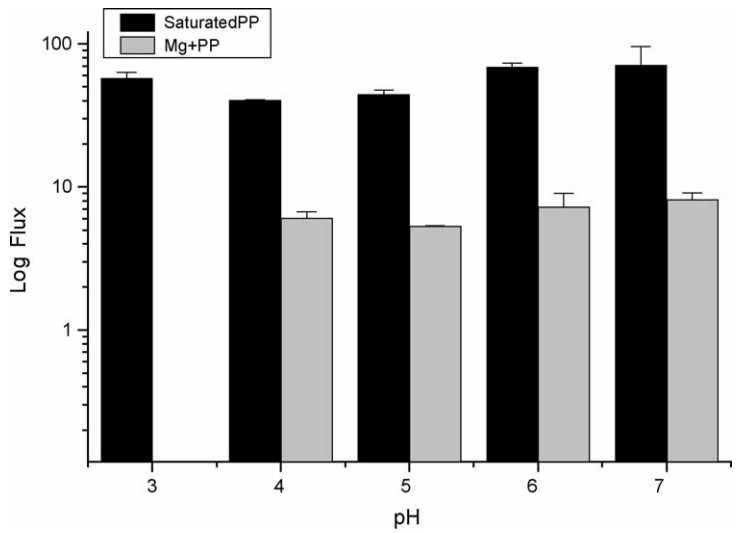

Fig. 4. Flux of PP from co-polymer NIPAAM/BA/MAA microgels and saturated solutions at 305 K (32 °C), as a function of pH using human skin.

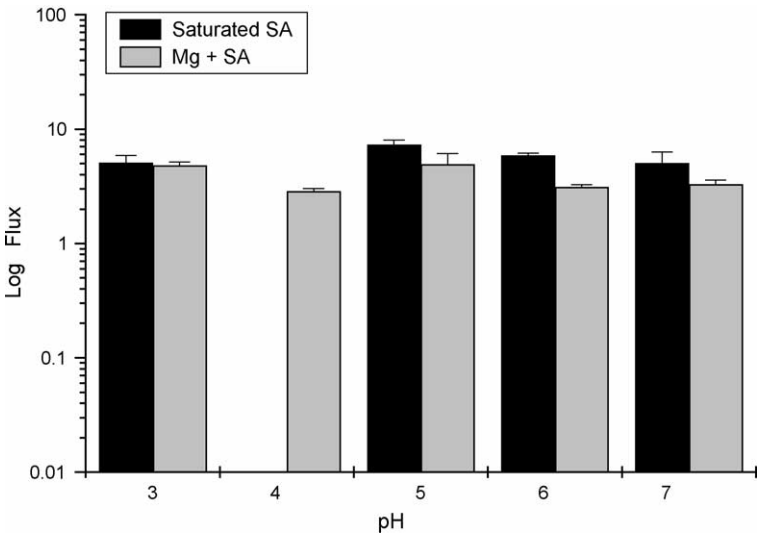

Fig. 5. Flux of SA from co-polymer NIPAAM/BA/MAA microgels and saturated solutions at 305 K (32 °C), as a function of pH using human skin.

$$C_{\text{freegel}} = \frac{C_{\text{sat}} J_{\text{freegel}}}{I_{\text{sat}}} \quad (2)$$

where C_{sat} is the solubility of each drug depending on the pH value, J_{freegel} the flux corresponding to the free concentration of the substances in the presence of the microgels and J_{sat} the flux corresponding to the saturated solutions. Therefore, applying Eq. (2) to the experimental flux values, as the pH increases, the free concentration of the drug in the presence of the microgels remains reasonably constant (Table 5). For MP the values are constant within experimental error for the pH range 3–6. For PP they are constant for the range of pH 4–7 and for SA for pH range 5–7. The high value for SA at pH 3 could be artifactual and requires further examination. There is no significant change in the free concentration of these compounds with a change in the size of the microgel. The skin permeation studies for the saturated colloidal dispersions indicated that pH had little effect (see Tables 2–4). Results similar to these were found in a previous study (Lopez et al., 2004), considering only thermo-responsive properties of the poly(NIPAM). A similar study was carried out by Brazel and Peppas (1996). Antithrombotic agents were loaded into the hydrogels by partitioning, and released into buffered solutions as a function of pulsatile changes in pH, temperature and a combination of temperature and pH. pH and temperature on their own had no significant effect on release. A combination of both was able to effect different release characteristics.

Table 5
Calculation of the free available drug concentration in the microgel solution

pH	MP	PP	SA
3	30		94
4	31	15	
5	26	11	67
6	27	10	53
7	41	11	65

It could be said that the incorporation of drugs into the co-polymer NIPAM/BA/MAA (85/10/5), being pH–temperature sensitive poly(NIPAM) microgels, and the subsequent release, depends on the octanol/water partition coefficient and solubility of the compounds. The drug release studies of the saturated colloidal dispersions, across human skin, indicated that pH-control of the drug release was marginal.

4. Conclusions

The microgels have potential in drug release to the skin. They may be of particular importance

where the skin barrier is compromised, as in disease state, or in wound management. In this situation controlled delivery to the skin of actives can provide therapeutic levels where required and minimize systemic uptake. The microgels could be used at higher temperatures and release more material as may be anticipated within wound tissue. They appear to be pH insensitive in the release of the compounds and therefore any pH effects in the wound would be negligible.

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