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Anionic Hydrogels for Controlled Release of Transdermal Drug

Bashir Ahmad, Shumaila Bashir, Muhammad Nisar and [1]M.B.Huglin
Department of Pharmacy, University of Peshawar, 25120, NWFP. Pakistan
[1]Institute of Material Research and Chemistry,
Cockcroft Building, Salford University, M5 4WT England

Abstract: Anionic hydrogels, using Azo-iso butyronitrile as cross linker, with varying ionic moieties were prepared from N vinyl-2-Pyrrolidone/Methylene Succinic acid/water by heating them at different temperatures for different interval of times. Swelling/drug loading sensitivity with pH and ionic strength of the medium for these hydrogels were investigated. The results anticipate that hydrogels in the ratio of VP/IA 90:10 can be used for local therapeutic Transdermal drug delivery application of cationic, antifungal terbinafine hydrochloride (TER-HCl) in the concentration range of <100 mg ml^{-1}. ***In vitro*** studies in different buffer solutions indicated that pH and IA contents are two basic parameters which affect the release behaviour of the hydrogels.

Key words: VP/IA hydrogel, pH sensitive, antifungal drug, controlled release

Introduction

In the second half of the twentieth century, efforts were started to prepared smart hydrogel for biomedical and biotechnological applications and as a result of these studies, now environmental sensitive material are very common in medical field (Peppas and Nicos, 1986; Brondsted and Kopecek, 1992; Sen ***et al.***, 2000; Karadeg ***et al.***,1994; Seigel, 1993; Bae ***et al.***, 1990; Kaetsu and Naka, 1990). Hydrogel of PVP and acryl amide were showed as biocompatible and potential adsorbents for biological agents and dyes, metal ion and cationic drugs from aqueous solutions (Li and Tanaka, 1990; Karadag ***et al.***, 1996; Ahmad ***et al.***, 2002). Even polyelectrolytes, which contain relatively high concentrations of ionisable groups along the backbone chain, led to their application in biomedical systems. These cationic polyelectrolytes bind or associate to form complexes with oppositely charged polymers, which find applications in silicosis therapy and Immunochemistry (Yau ***et al.***, 1994; Hariharan and Peppas, 1996; Seigel and Firestone, 1996).

Terbinafine Hydrochloride (TER-HCl) solution is topically and orally active allylamine antifungal agent, which appears to act by preventing fungal ergesterol biosynthesis via specific and selective inhibition of fungal squale oxidase (Balfour and Faulds, 1992). In standard ***in vitro*** susceptibility test, TER-HCl has demonstrated activity against a wide range of dermotostrated filamentous, dimorphic and dematiaceous fungi and yeast. The higher affectivity than other antifungal drugs for fungal and yeast skin infections and lower drug requirements are the main advantages of this drug for using in transdermal drug delivery system. Instead of repeated and frequent applications of topical creams, it is anticipated that TER-HCl loaded hydrogels would

be more efficiently used for the comfort of the patient. So an ionic polymer prepared from VP and Itoconic acid (IA) has been examined for controlled release of TER-HCl, influence of IA contents and pH of the medium on the release properties.

Materials and Methods

N-Vinyl Pyrrolidone VP, Aldrich Chemical Co., was distilled under reduced pressure (68°C/2 mm Hg), Methylene succinic acid (Itaconic acid) from Sigma Chemical Co. USA, Azo isobutyronitrile (AIBN), the crosslinker, recrystallized, from Fluka Chemical Co. and Terbinafine hydrochloride were used as received.

Aqueous solutions of monomers of 4 ml VP and 120, 240 and 360 mg of IA were prepared in 2 ml of deionised water in different composition (VP/IA 97.5/2.5, 95/5, 92.5/7.5 and 90/10) degassed, 0.35 wt % of initiator was added, medium size Pyrex test tube were filled, tightly sealed and co-polymerised for 4 hours at 50°C overnight at 70°C and for 2 h at 80°C on water bath. The four composition of gels were designated as P(VP/IA) 2.5, P(VP/IA)5.0, P(VP/IA)7.5 and P (VP/IA) 10.0. Gels thus obtained were cut in to 2-3 mm disc and were equilibrated in water to remove linear PVP if any. The conversion was more than 94% showing the suitability of the polymerization process.

Dried Xerogel were left in deionised water at 15°C for 72 h to attain the equilibrium swelling. Preliminary investigations showed that 36 h are sufficient for complete swelling of gel and maximum loading of drug. The mass percentage swelling and % water in the gel during deswelling were calculated as:

$$\% \text{ Swelling} = [(m_2 - m_1)/ m_1] \times 100$$
$$\% \text{ Water} = [(m_2 - m_1) / m_w] \times 100$$

Where m_1, m_2 and m_w are the weights of the xerogel, swollen gel at time t and water in equilibrium-swollen hydrogel respectively. For the equilibrium degree of swelling (EDS = $1/v_{2m}$) we used the Tong and Liu (1994) equation:

$$v_{2m} = [1 + \rho/\rho_w (w^{-1} - 1)]^{-1}$$

Where ρ and ρ_w are the densities of dry gel and water and w is the weight fraction of polymer in the swollen gel.

Loading/release of drug

The TER-HCl was dissolved in water with a concentration of 1-5 mg/ml and preweighed xerogel discs were immersed in it for 48 h at 15°C. The amount of loaded drug was determined spectrophotometrically at 222 nm with the help of calibration curve of TER-HCl standard solution. The drug-loaded gel was placed in 50 ml of phosphate buffer solution (0.1 mol l^{-1}) for release study and small aliquots withdraw from the medium for spectrophotometric determination of TER-HCl from the gel. pH 3 value was used for the controlled release of terbinafine hydrochloride

from hydrogels and subsequently in pH 2 buffer solution to remove any remaining TER-HCl in the gel.

Results and Discussion

Above 94% conversion of monomers in to polymer gel in the presence of cross linker Azo-isobutyronitrile (AIBN), shows the completeness and suitability of the copolymerization of VP-IA by heating on water bath at 50, 70 and 80 °C for different interval of times. In the near past, (Murat and Olgun, 2002), the same copolymer was prepared with glycol dimethacrylate as cross linker, by γ - rays irradiation at ambient temperature and % conversion was 77%. The selections of feed compositions were made keeping in view the solubility of IA in aqueous solution of VP and shape stability of fully swollen hydrogels. The solubility of IA at 15°C is 850 mg in 4 ml of VP per 2 ml of water mixture. In the literature (Murat and Arzu, 2001) the solubility was shown as 480 mg in 4 ml of VP per 2 ml of water at 4°C. This solubility difference is due to temperature variation among the systems studied.

Percent conversion of different feed compositions of VP/IA.

	Mole % of IA		
Sample	In feed	In gel	%Conversion
P(VP/IA) 2.5	2.5	2.6	94.4
P(VP/IA) 5.0	5.0	5.4	92.6
P(VP/IA)7.5	7.5	8.8	88.5
P(VP/IA)10.0	10.0	12.6	84.7

Those polymers, which are thermo responsive or pH sensitive, can only be used for controlled drug delivery systems. Fig. 1 shows the degree of swelling of P (VP/IA) hydrogels at 15°C in phosphate buffer from pH 2 to 10. For all the four compositions, the degree of swelling from pH 2 to 4.5 is constant, then increases up to pH 7 and between pH 7 and 8 it reached its maximum and then again become constant showing that acidic group dissociation of IA is completed some where between pH 7 and 8.The literature shows (Weast, 1972) that the pKa values of the two acids of the IA are close to one another i.e. 3.85 and 5.44 and due to their probable overlapping sharp swelling point is not possible. Moreover the degree of swelling depends on the concentration of the ionisable groups in the network and this dependence is very clear especially in P (VP/IA) 7.5 and P (VP/IA) 10.0, Where the swelling is much high from pH 4.5 onward.

Fig. 2, 3 shows the effect of drug loading in 2.0 and 4.0 mg/ml TER-HCl solution for different P (VP/ IA) compositions on % swelling (pH 7.5 and at 15°C) at different interval of times. In both cases the equilibrium swelling reached after 36 hours. When drug concentration in the swelling medium increased from 2-4 mg ml^{-1}, decreased in swelling of the gel occurred due to lesser

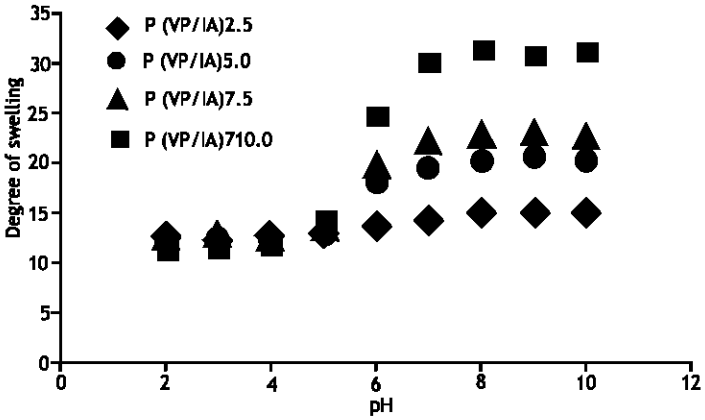

Fig. 1: Effect of pH on the degree of swelling of P (VP/IA) hydrogels

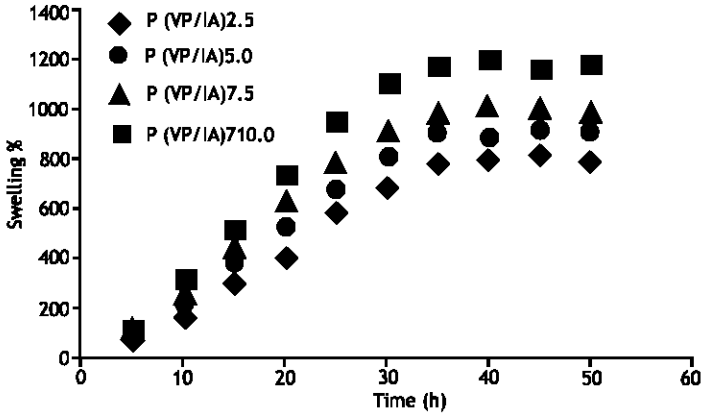

Fig. 2: Swelling variation (drug loading) with time for different compositions of P (VP/IA) at pH 7.5 in 2 mg ml^{-1} TER-HCl solution at 15°C

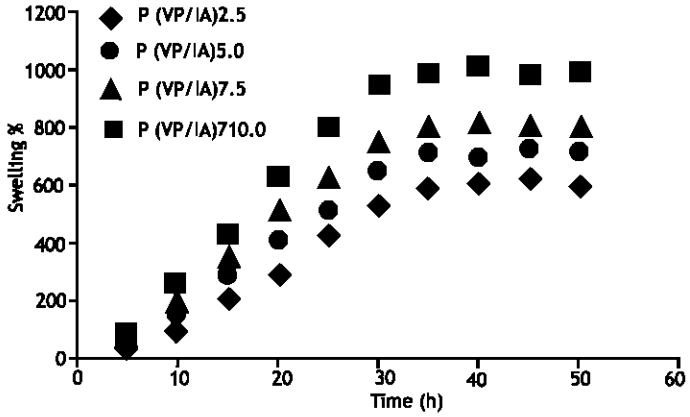

Fig. 3: Swelling variation (drug loading) with time for different compositions of P (VP/IA) at pH 7.5 in 4 mg ml^{-1} TER-HCl solution at 15°C

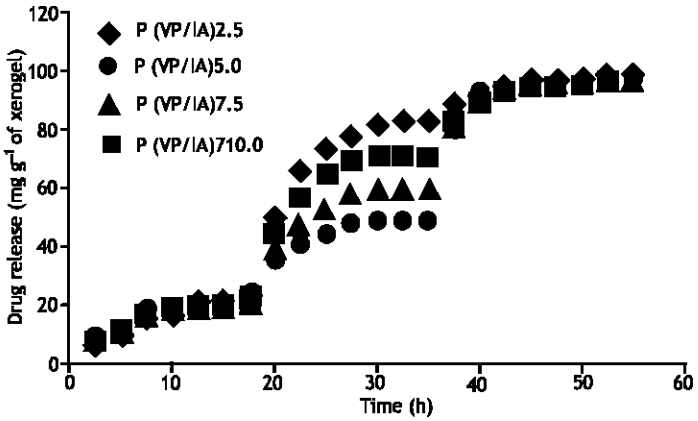

Fig. 4: Drug release profile of TER-HCl from P(VP/IA) hydrogels at different pH

difference in concentration of the mobile ions in gels and solution causing a decrease in the osmotic swelling pressure of the mobile ions inside the gel resulting a decrease in swelling. The gel was also swollen in the same concentration of TER-HCl solution at pH 3 (lowest swelling pH) to see the adsorption of cationic TER-HCl drug on anionic gel surface. The total amount of drug adsorbed (5.2%) into xerogel showed an increase with increasing IA concentration due to increase of free volume available for diffusion and bonding of positively charged drug to partially ionised hydrogel. The same trend with varied adsorption values was observed (Saraydin and Olgun, 1995; Akkas ***et al.***, 1999; Shumaila ***et al.***, 2002) for different adsorption systems like Poly (acryl amide/Maleic acid), PVP-HEMA, P (NIPA-co-AA) etc.

Different (VP/IA) compositions of xerogels were swollen in to equilibrium at pH 7.5 in 3 mg/ml TER-HCl solution for 36 h to load the drug and then they were immersed in pH 6.5, 5.5 and 3 buffered solutions to investigate its release properties. The percentage release values of drug (calculated with equation given below) with time are shown in Fig. 4.

$$\% \text{ Release of Adsorbed TER-HCl} = (W_{pH} / W_{sp}) \times 100$$

Where W_{pH} is the weight of released drug at any pH value and W_{sp}, total weight of specific adsorbed drug in the gel.

At pH 6.5 the percentage release for each hydrogel is more or less constant showing same extent of protonization at this pH while at pH 5.5 (Skin pH) and 3, this protonization is different for different gels i.e. decreased release rate for high IA content in the gel.

At pH 5.5, 53, 61, 78 and 88% drug release were observed for P (VP/IA) 10.0, P(VP/IA)7.5, P(VP/IA)5.0 and P(VP/IA)2.5 hydrogels, respectively. The novel (opposite) trend of TER-HCl release at skin pH gave significant importance to high IA content VP hydrogel (having more capability to absorb maximum TER-HCl quantity) and make it useful for transdermal drug delivery. With the collaboration of Life Sciences department, work has already been started to study the drug release kinetics / diffusion phenomena on human skin.

P(VP/IA) hydrogels with different VP / IA ratios were prepared and used for release study of cationic drug TER-HCl in different concentration range. pH and IA contents determined the feasibility of hydrogel for control release in the present case. We are optimistic that in very near future, these hydrogels can be used for local therapeutic transdermal delivery application of cationic drugs.

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