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SWELLING BEHAVIOUR OF pH-SENSITIVE CROSSLINKED POLY(VINYL ACETATE CO-ACRYLIC ACID) HYDROGELS FOR SITE SPECIFIC DRUG DELIVERY

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ABSTRACT:

The present work was undertaken to combine nonionic vinyl acetate (VAC) with anionic acrylic acid (AA) or methacrylic acid (MAA) monomers in the presence of ethylen glycol dimethacrylate (EGDMA) as crosslinking agent through radical polymerization. Poly (vinyl acetate-co-acrylic acid) VAC/AA 50:50 to 100:0 six samples and Poly(vinvl acetatecomethacrylic acid) VAC/MAA one sample were prepared. All the samples were used for swelling studies. High swelling occurred at above pH 5.5 through chain relaxation. It was observed that swelling to VAC/MAA was lower than VAC/AA copolymers. The lower swelling in VAC/MAA copolymer is due to the presence of hydrophobic methyl group and higher pKa value of this copolymer.

INTRODUCTION

Delivery of orally administered drugs targeted to the colon is desirable for the treatment of the diseases which developed at colonic site. There are many strategies far delivering drugs to the colon. Among them the two approaches based respectively on pH (Ashford et al., 1993; Peelers and Ringo), 1993; Ranjha and Doclker, 1999a. 1999b, 1999c) and enzymes are the most important (Garretto et al., 1983: Yamaguchi et al., 1994, Rao and Ritschel, 1995). In first case, various pH-sensitive copolymers have been used for obtaining the required effects, either in the form of coating agents or in the form of hydrogels. In case of coatings, drug delivery is affected by the nature of the polymer and the thickness of the film, while in the case of monoliths, drug delivery is controlled by the degree of crosslinking and by the monomeric composition of the network. In the second approach, prodrugs, polymeric prodrugs and biodegradable polymers that the degraded mostly by the unique enzymes of the colon are used.

In fact, the drug delivery to the colon can be achieved by the use of pl l-sensitive Ity-drogels, although the pit *of* the large intestine is rather lower than that of small intestine (6.6 vs 7.3) (Pye et al., 1990), because the high residence time (22-36) (Mrsny, 1992) in large intestine results in most of the drug being delivered in that organ.

We were interested in synthesizing new pH-sensitive copolymers which show no

swelling at lower pH values but a maximum swelling at higher pH values. In this paper VAC monomer was polymerised with AA and MAA monomers. Their dynamic and equilibrium swelling were studied in solution of different, pH. Both components of the gels are hydrophobic in acidic media. On arrival in a basic or a neutral environment, the carboxyl containing component from hydrophobic to hydrophilic and drug is released due to swelling of the hydrogels.

MATERIALS AND METHODS

Materials:

The comonomer used were VAC, AA, MAA. (Fluka, Buchs, Switzerland). All the liquid monomers were distilled tinder reduced pressure before use. Ethylene glycol dimethacrylate (EGDMA, Merck) as crossl inking agent, hemoyl peroxide (Merck) as catalyst were used.

Preparation of the Copolymers:

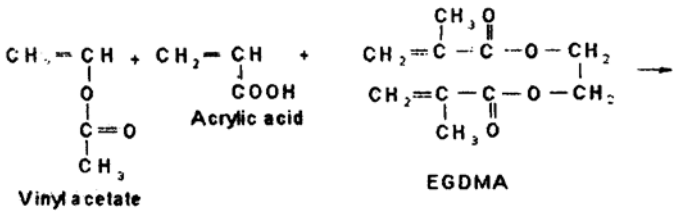
(Khare and Peppas 1995, Ranjah and Doelker 1999a, 1999b). Six samples of VAC/AA 50:50 to 100.0 were prepared but in case of VAC/MAA 70:30 molar ratio was prepared. The amount of catalyst was I% w/v to the total monomers. The mixture of monomers, crosslinking agent and catalyst was diluted using ethanol. The ratio of ethanol and monomers was I: I by volume. Solution polymerization was carried out after adding the solution into polyethylene tubes. The reaction condition for obtaining VAC/AA copolymers were 45°C for 1 h, 50°C for 2 h, 55°C for 3 h, 60°C for 4 h, 65°C for 24 h. In case of VAC/MAA copolymers, the temperature was gradually increased only up to 60°C, because cylinders started to break at higher temperature. After this period, tubes were cooled to room temperature, the cylinders were removed from the tubes. In all trials, cylinders *were* cut into small disks (11.5 x 1.7 mm) and were dried, at first at room temperature and then in a vacuum oven at 40-45°C for one week. The crosslinking ratio of EGDMA was calculated as:

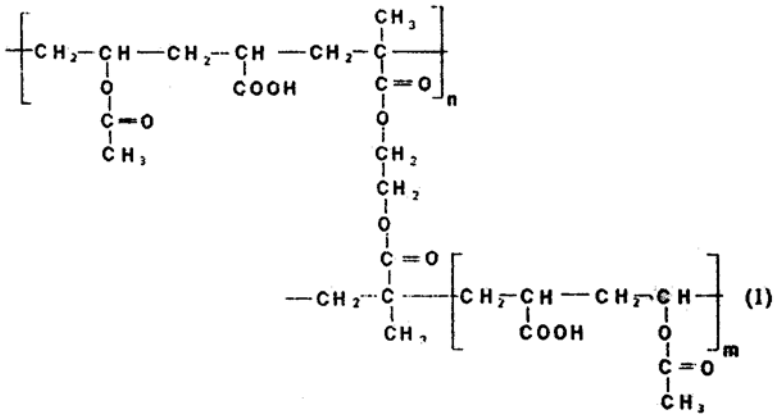
$$\text{Crosslinking} = \frac{\text{Mole of EGDMA 100}}{\text{Mole of bifunctional monomers}}$$

Copolymerization and crosslinking reactions occur simultaneously. An example of crosslinked hydrogel structure of vinyl acetate/acrylic acid in the presence of EGDMA is illustrated by scheme 1.

Swelling behaviour of the polymers:

The dynamic and equilibrium swelling experiments were carried out in 100 ml of solution at 37°C. To eliminate the resistance associated with the stagnant film layer on the surface of the disks, flasks were shaken at a speed of 120 rpm in a shaker (type 3022, Ge-





sellschaft fur Labortechnik. Burgwedel, Germany). Two types of solutions were used for the swelling experiments, 0.1 M HCl as simulated gastric fluid (pH 1.2) and USP phosphate buffer solutions (0.05 M pH 1.2, 4.5,5.5.6.5. and 7.0). The pH of these solutions was adjusted by adding HCI or NaOH solution. After specified times the disks were taken out from the flasks, and weighed after removing the excess surface water by blotting with laboratory tissue. For equilibrium swelling experiments these disks were weighed until they attained a constant weight. The equilibrium swelling was attained after 3-4 weeks in solutions of lower pH values and after 2-3 weeks at higher pH values. The swelling coefficient q was calculated as (Pappas and Barr-Howel, 1987).

$$q = w_h/wd \quad (2)$$

where w_h and w_d are the weights of the hydrated and of the dry gel, respectively.

RESULTS AND DISCUSSION

Owing to different pH in the segments of GIT, various types of ionic hydrogels are

used for site specific drug delivery. The pH of the medium affects the chain relaxation that leads to swelling and modifies the drug release behaviour. Swelling and water content are the important properties of the ionic hydrogels and they depend upon the fraction of ionizable groups, degree of crosslinking and composition of the medium in which the hydrogels are placed. In anionic hydrogels, swelling increases as the external solution pH in-creases. The pKa of the buffer components and the pKa of the gels play a key role in the ionization of the ionic gels. In these gels the pKa of the buffer components should he above the pKa of the gel carboxylic acid. At this pKa, the buffer will accept protons and ionizes the gels. Lownan et al (1999) prepared microparticles consisting of corsslinked co-polymers of poly (methacrylic acid-grafted-ethylene glycol). The structure of the copolymers exhibits pH sensitive swelling behaviour due to reversible formation of interpolymer complexes stabilized by hydrogen bonding between carboxylic acid proton and the etheric groups on the grafted chain. They claimed that in the acidic environment the gels do not show swelling due to being in the complexed state. As the pH increases above transition pH of the gel, the complexes immediately dissociated and the network pore size rapidly increases and copolymers show swelling in basic environment. Pillay and Fassihi (Pillay and Fassihi 1999) investigated that electrolytes and hydrophilic polymers establish a heterogeneous gel structure referred as "metamorphic scuffled" in the matrix containing electrolytes and hydrophilic polymers on contacting with dissolution medium. This structure enables to influence on swelling control release of the drug in a zero order manner in a different pH environment over a 24 h period. Concerning to the swelling behaviour of VAC/AA or VAC/MAA hydrogels, in acidic pH values the hydrogels do not show swelling due to being nonionized of the carboxylic groups in this medium. At higher pH values the acidic fraction is fully ionized and the repulsive forces of the ions tend to swell the gels considerably. Table I shows the equilibrium swelling coefficient of VAC/AA and VAC/MAA gels. In both polymers swelling increased by increasing the pH of the medium and it was very abrupt in VAC/AA polymers. The samples containing 10 and 20 mol % AA disintegrated at higher pH values, which may be due to very low molecular weight of the polymer and this is the influence of high fraction of VAC monomer in the monomeric solution (Lindsjo et al., 1996), while the samples containing 30,40 and 50 mol % AA broke before attaining the equilibrium values due to excessive swelling.

The knowledge, of the maximum swelling capacity of the hydrogels is useful for evaluating the sensitivity to pH, but to have the impact on drug release, it is important to know the kinetics of swelling. Because of their monomeric composition and degree of crosslinking the swelling coefficient of VAC/AA 7030 and VAC/MAA 70,30 en be compared. The swelling coefficients of VAC/AA polymer are generally higher than those of VAC/MAA, as expected because the methyl groups of MAA make the polymer more hydrophobic and pKa of poly(methacrylic acid) (PMAA) is higher than that of poly(acrylic acid) (PAA). The pKa of PMAA is 5.65, while that of PAA is 4.75 (Greenwald and Luskin, 1980), which also affects the swelling coefficient of the polymers at pH values close to the pKa. It is suitable to be mentioned that all the VAC/AA samples were elastic

in nature. It is a fact that the solvent front takes more time to progress in hard glassy polymers than in rubbery polymers, because the solvent has to convert the glassy form to a rubbery form for advancing further. There is big difference in the penetrant diffusion coefficient of glassy and of rubbery polymers. The diffusion coefficient of a penetrant in a glassy polymer is 10^{-11} to 10^{-13} cm2/s, while in rubbery polymer, it is about 10^{-5} to 10^{-6} cm2/s (Baker and Londsdale, 1976). Recently it is reported (Sipmann et al 1999) that the diffusion coefficient of water and propranolol hydrochloride within the fully swollen tablets of hydroxypropyl methylcellulose was $5.6x10^{-6}$ cm2/s and $6.3x\ 10^{-7}$ cm 2/s respectively. It is observed that the surface area increased in axial direction is more than radial direction. Increasing dimension of the tablets lead to increasing diffusion pathway and thus decreasing diffusion rates. The size of the diffusing molecules significantly affects the transfer rate. In diffusion the molecule jumps from one cavity (free volume or hole) to another for a given cavity size distribution is easier for smaller than for larger molecules. For small diffusing molecules diffusion occurs by localized activated jumps from the preexisting cavity to another, only a few monomer segments are involved. With larger diffusing species preexisting cavities may be unable to accommodate the diffusing molecules: Therefore, larger number of monomer segments must be rearranged to allow the molecule to diffuse. Hence the diffusion coefficient of water in the fully swollen tablets is higher than the respective diffusion coefficient of propranolol hydrochloride. In samples of VAC/AA, the solvent front moved fast without any hindrance but in case of VAC/MAA, the solvent front faces two types of hindrances; fusty, the samples are very hard and glassy and secondly, the presence of methyl groups that are hydrophobic and hinder the advancing solvent (Khare and Peppas 1995; Ranjha and Doelker 1999a, 1996).

The diffusion of the penetrant into the polymer and the relaxation of the polymer chains in response to the presence *of* the penetrant are important in swelling controlled release systems. In particular, it is important to analyze the kinetics of the hydrogel swelling. The mechanism of the penetrant can he determined by the general equation (Frisch 1980):

$$M_t/M_a=kt^n \qquad (3)$$

where M_t is the mass of penetrant absorbed at specified time t, M_a is the amount absorbed at equilibrium, k is kinetic constant, n is the diffusional exponent and indicates the mechanism of absorption. For slabs, in the case of Fickian kinetics, the value of n is 0.05; a value of n lying between 0.50 and 1.0 indicates a non-Fickian process, i.e., diffusional polymer relation, and n= I for case II transport (zero order kinetics).

Exponent n of two samples was calculated by putting the results of dynamic swelling coefficient of figures 1 and 2 in equation 3. The n values are given in Table 2. When no swelling was observed, no n values were calculated. In VAC/AA polymer, all the values in different solutions were around 1 (actually more). Fast advancing of the solvents front and rapid chain relaxation seem parallel because this polymer was very elastic in nature.

In this polymer, the n values did not increase uniformly by increasing the pH of the medium and it might be due to the elasticity of these polymers. The case II transport could be suggested due to fast advancing and rapid ionization *of* the gels, although this needs further confirmation. For VAC/MAA polymers, it is observed that by increasing the pH of the medium, n values increased i.e. shifted from Fickian to non-Fickian. Ranjha and Doelker (Ranjha and Doelker 1999a, 1999b) also observed similar results in crosslinked methyl acrylate/methacrylic acid and ethyl acrylate/methacrylic acid hydrogels.

Table 1
Equilibrium swelling coefficient of crosslinked VAC/AA VAC/MAA gels using EGDMA with degree of crosslinking 0.45 mol % as a function of monomer ratio and pH

PH of solution	Acylic acid content						Methacrylic acid content
	0	10 mol%	20 mol%	30 mol%	40 mol %	50 mol%	30 mol%
1.2	1.2	1.2	1.1	1.1	1.3	1.3	1.3
4.5	1.2	1.1	1.4	2.0	2.9	1.9	1.5
5.5	1.3	a	a	8.2	6.5	12.2	7.7
6.5	1.3	a	a	16.4[b]	28.3[b]	17.2[b]	16.8
7.0	1.2	a	a	22.7[b]	36.3[b]	26.1[b]	21.2

a. the samples disintegrated b. the samples broke.

Table 2
Analysis of dynamic swelling of VAC/AA and VAC/MAA gels with a degree of crosslinking 0.45, swollen in various solutions of different pH at 37°C

pH of solution	VAC/AA (70:30) n	VAC/MAA (70:30) n
1.2	-	-
4.5	1.29	-
5.5	1.37	0.64
6.5	1.00	0.70
7.0	1.18	0.76

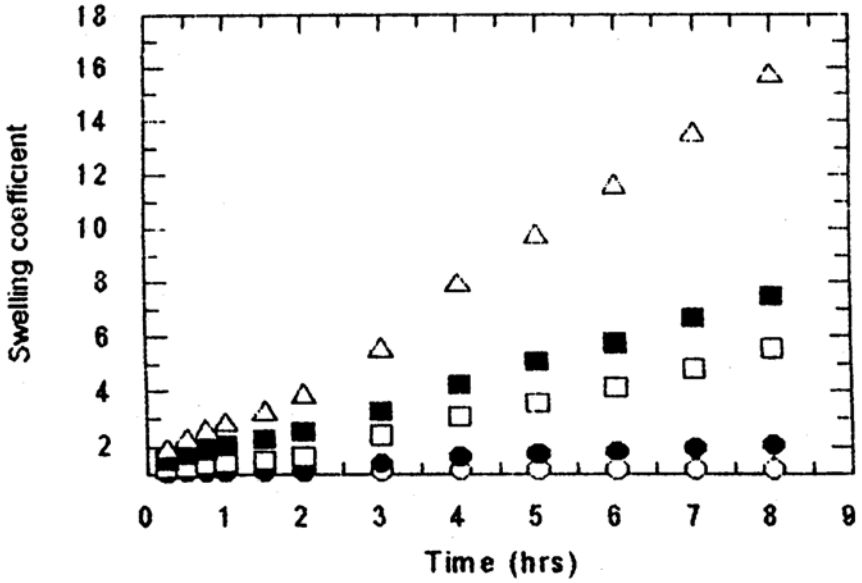


Fig. 1: Dynamic swelling behaviour of VAC/AA (70/30)x = 0.45 copolmer in various pH solutions at 37°C. The pH values are: pH 1.2 (O), pH 4.5 (•).pH 5.5 (□), pH (■), pH 7.0 (Δ)

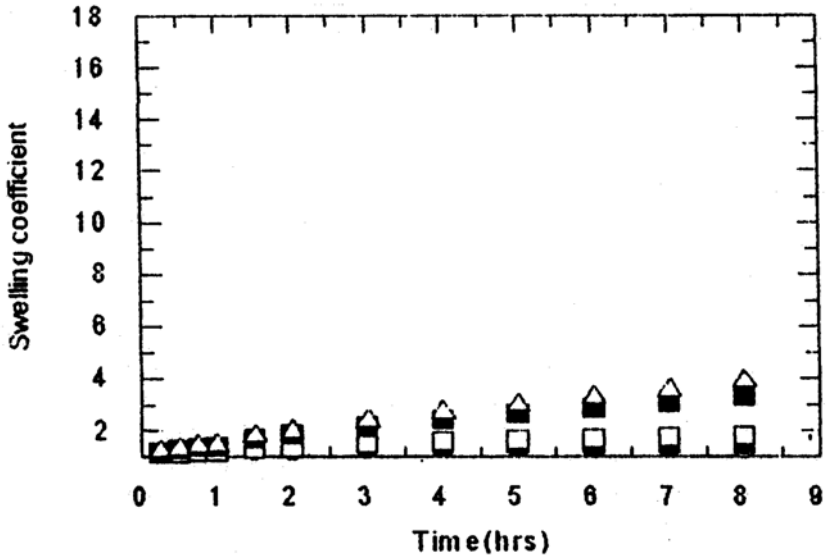


Fig. 2: Dynamic swelling behaviour of VAC/MAA (70/30) x = 0.45 copolmer in various pH solutions at 37°C. The pH values are: pH 1.2 (O), pH 4.5 (●), pH 5.5 (□), pH 7.0 (Δ).

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REFERENCES

Ashford M., Fell J.T. Attwood D., Sharma Woodhead P. (1993). An in vitro investigation into the suitability of pH-dependent polymers for colonic targeting. *Int. J. Pharm.* **91**: 241-245.

Baker R.W. and Lansdale H.K. (1976). Controlled release mechanism and rates. *In*: Controlled release of biologically active agents. (Tanquary, A. C. and Lacey, R.E. ED.), Plenum Press, New York and London, pp.15-71.

Frisch H.L. (I 980). Sorption and transport in glassy polymers-A review. *Polym Eng.. Sci.* **20**: 2-13.

Garrett() M., Kiddel RH and Winans CS. (1983). Treatment of chronic ulcerative colitis with poly-ASA: A new nonabsorbable carrier for release of 5-aminosalicylate in the colon. *Gastrogenterology,* **84**: 1162.

Greenwald H.L. and Luskin L.S. (1980). In: Handbook of water-soluble gums and resins. (Davidson, R.L. Ed.), McGraw-1E11, New York, pp.17.1-17.19.

Khare A.R. and Peppas N.A. (1995). Swelling/deswelling of anionic copolymer gels. *Biomaterial.* **16**: 559-567.

Lindsjo M.C., Lkman K.B. and Nasman 1.H. (1996). Glass-Ionomer cements based on *poly* (acylic acid-co-viny lalcohop in drug release model lornudat ions. *Biomateriais.* **17**: 913-919.

Lowman A.M., Morishita M., Kajita M., Nagai T. and Peppas N.A. (1990). Oral delivery of insulin using pH responsive complexation gels. *J. Pharm. Sci.* **88**: 933-936.

Mrsny R.J. (1992). The colon as a site for drug delivery. *J. Control. Rel.* **22**: 15-34.

Peeters R. and Kinget R. (1993). Film-forming polymers for colonic drug delivery: Synthesis, physical and chemical properties of methyl derivatives of Eurdragit S. *Int. J. Pharm.* **94**: 125-134.

Peppas N.A. and Barr-Howel B.D. (1987). Characterization of the cross-linked structure of hydrogels. In: Hydrogels in Medicine and Pharmacy Vol. I Fundamentals. (Peppas, N.A., Ed). CRC Press, Boca Raton, Florida, pp.27-56.

Pillay V. and Fassihi R. (1999). Electrolyte-induced compositional heterogeneity. A novel approach for the controlled oral drug delivery. *J Pharm. Sci.* **88***:* 1140-1148.

Pye G., Evans D.F., Ledingham S. and Hardeastle J.D. (1990). Gastrointestinal intraluminal pH in normal subjects and those with colorectal adenoma or carcinoma. Gut 31: 1355-1357.

Ranjha N.M. and Doelker E. (1999a). pH-Sensitive hydrogels for site specific drug delivery. I. Swelling behaviour ofcrosslinked copolymers of acrylic and methacrylic acid. *S.T.P. Pharma. Sci.* **9**: 335-340.

Ranjha N.M. and Doelker E. (1999b). pH-Sensitive hydrogels for site specific drug delivery. II. Drug release behaviour from crossliked alkyl acrylates-methacrylic acid co-

polymers. *S T. P. Pharma Sci.* **9**: 341-349.

Ranjha N.M. and Doelker E. (1999) pH sensitive noncrosslinked poly (vinyl alcohol-co-acrylic acid) hydrogels for site specific drug delivery. *Saudi Pharmaceutical Journal,* **7***:* 137-143.

Rao S. and Ritschel W.A. (1995). Colonic drug delivery of small peptides. *S.T.P. Pharma. SM.* 5. 19-29.

Siepmann J., Podual K., Sriwonganya M., Pappas N .A. and 13odmcier R. (1999). A new model describing the swelling and drug release kinetics Mom hydroxypropyl methyl-cellulose tablets. *J Pharm. Sci.,* **88**: 65-72.

Yamaguchi T., Sasaki K., Kurosaki Y., Nakayama T. and Kimura T. (1994). Biopharmaceutical evaluation of salicylazosulfanilic acid as a novel colon-targeted prodrug of 5-aminosalicylic acid. *J Drug Targeting,* **2**: 123-131.