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BIOADHESIVE POLYMERS - SYNTHESIS, EVALUATION AND APPLICATION IN CONTROLLED RELEASE TABLETS

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ABSTRACT

Synthesis of series of cross linked polymers of methacrylic acid (PMAs) and acrylic acid (PAAs) is reported. Polymers of both the types have been investigated for physiochemical properties like solubility, density, swelling index and equilibrium swelling. A suitable method was devised for study of bioadhesion. Floating tablets were prepared and coated with some of the synthesized polymers. The tablets were then evaluated for physical properties (including bioadhesion) as well as for drug content and in vitro drug release. The results were compared with those obtained with Carbopol 934P. Some polymers showed better bioadhesion and drug release pattern as compared to Carbopol 934P.

INTRODUCTION

Successful development of a solid oral controlled release delivery system is hampered by the wide fluctuations in its gi tract residence time. Different approaches for prolonging the gastro-intestinal residence time include (1-5) the use of

a. Multiunit dosage forms
b. Intragastric Floating Drug Delivery systems (IGFT)

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c. Sandwich -type polymeric delivery systems and
d. Use of bioadhesive polymers.

The otherwise excellent concept of floating system suffers from a disadvantage that it is effective only when the fluid level in the stomach is sufficiently high. This serious limitation can be overcome by coating the IGFT with bioadhesive polymer to enable it to adhere to the mucous lining of the stomach wall.

With this background, an attempt has been made to synthesise and evaluate in vitro, some bioadhesive polymers and their coating on IGFTs.

Various methods have been employed for the synthesis of polymers of methacrylic acid and acrylic acid and their copolymers. The method reported by Ch'ng et al (6) has been employed in this work.

EXPERIMENTAL AND RESULTS

Materials :

The following materials were used as supplied and without further purification.

Methyl acrylate, azobis (diisobutyronitrile) (AZDN) (Fluka Chemicals); methacrylic acid and divinyl benzene (DVB) (Polychem Ltd, India); acrylonitrile (E. Merck), poly vinyl pyrrolidone (PVP K-30) (BASF); Sodium CMC(HV) (Cellulose Products of India); Isosorbide mononitrate (Boehringer-Knoll Ltd); Carbopol 934 P (B.H. Goodrich), Methocel F4M (Colorcon Ltd); Avicel PH 101 (FMC Corporation), Crude procin mucin (Sigma Chemicals). Other chemicals, solvents and reagents were of highest purity grades.

METHODS

Synthesis of Polymers :

After conducting several experiments with varying processing conditions, the final conditions were arrived at as follows :-

Synthesis of Poly (Methacrylic acids) (PMAs) :

About 23 gm sodium chloride and 1 gm CMC (HV) were dissolved in 100 ml water. To this solution was added of 0.04 gm AZDN in 20 ml solution of methacrylic acid and 0.04 - 0.2 ml DVB (55.2%) with constant stirring at 70^0 C. Polymerization occured within about 30 minutes, after which the polymer was cured for 8-10 hrs. The polymer was collected by vacuum filtration and dried at 65^0 C.

TABLE - 1

Polymer	% Crosslinking agent	Swelling index at pH of 2	4	6	8
Carbopol 934 P	-	6.0	8.0	-*	-*
Poly (methacrylic acid)	0.10	2.0	2.0	2.0	1.5
"	0.13	2.3	2.5	2.3	2.6
"	0.15	2.5	2.0	2.5	2.0
"	0.17	3.0	2.3	2.5	2.3
"	0.20	2.5	2.5	2.5	3.0
Poly (acrylic acid)	0.33	5.7	17.0	20.0	12.5
"	0.50	5.5	5.6	6.0	5.5
"	1.00	2.5	3.3	2.5	2.5
"	2.00	3.0	3.3	3.3	2.6
"	3.00	2.6	3.3	3.3	2.3

* As the polymer dissolved, swelling index could not be measured.

Synthesis of Poly (acrylic acid) (PAAs) :

The aqueous phase was prepared by dissolving 2.5 gm sodium chloride and 0.2 gm CMC (HV) in 100 ml water. To this was added a solution of 0.3 gm AZDN and 0.33-3.0 gm DVB in a mixture of methyl acrylate and acrylonitrile (3:1) at 60-65^0 C . After curing for 12-15 hours, the polymer was collected and hydrolysed with 20% sodium hydroxide at 85-90^0 C. The hydrolysed polymer was collected, washed and neutralized with conc. HCl. The product was then washed free of acid and dried in air.

Physicochemical properties of Polymers :

Solubility : Solubility of polymers was determined in aqueous and organic solvents. About 0.5 gm polymer was kept in contact with 10 ml of solvent, at 30 $\pm$ 1^0 C for 24 hrs with occasional shaking. The solubility was determined by visual observation as well as by weighing the residue left after evaporating the filtrate obtained.

Both the PMAs and PAAs were found to be insoluble in any of the aqueous or organic solvents tried. However, they swelled to variable extent when placed in water, methanol, absolute alcohol and dioxane:water (80:20) system.

Density : The granular density of the polymers was measured by liquid displacement method in triplicate . The average densities of PMAs varied between 1.357gm/cm for 0.15% crosslinking and 1.665 gm/cm for 0.1% crosslinking while for PAAs, the variation was between 1.676 gm/cm for 3% crosslinking and 3.142 for 0.33% crosslinking.

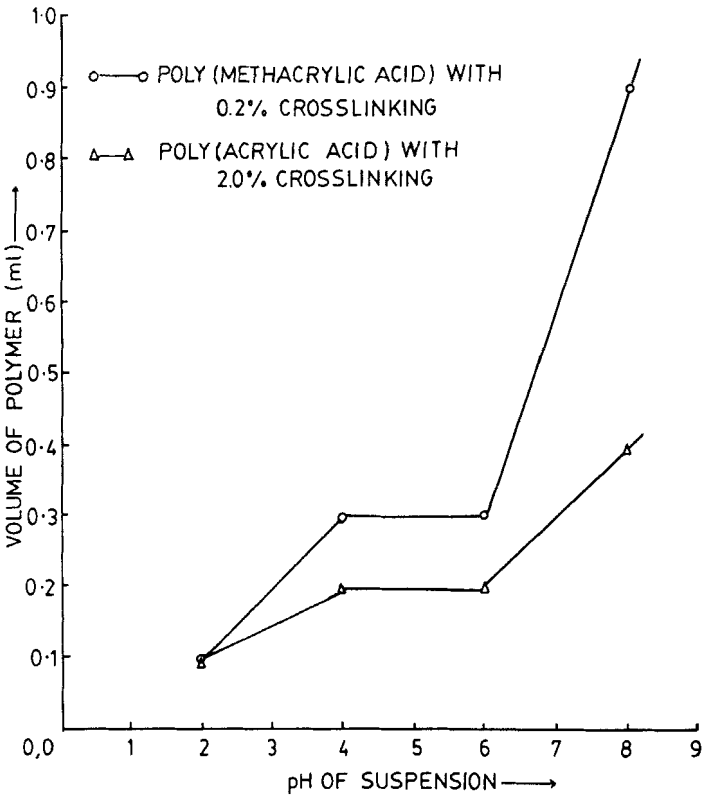

FIG. 1: EFFECT OF pH ON EQUILIBRIUM SWELLING OF POLYMERS

Effect of pH on Swelling Index : Deionised water, adjusted to pH 2, 4, 6 and 8(±0.1) with dil. HCl or NaOH was taken in a cylinder and 1 gm polymer was added to it. The suspension was allowed to stand and the level of hydrated polymer was read at regular intervals till no further hydration could be seen. The swelling index was calculated as the ratio of maximum height of the polymer after swelling to its initial height. The swelling indices of different polymers at different pH levels are included in Table 1.

pH of Suspension : The pH of a 0.5% suspension of polymer in deionised water and in 0.5% carbopol 934 P gel was read. The aqueous supensions gave pH in the range of 4.15 to 4.55. Addition of the polymer to carbopol further reduced pH of suspension to between 3.7 and 3.8.

Effect of pH on Equilibrium Swelling of Polymers : A 0.1% suspension of the polymer was prepared in deionised water,

TABLE - 2

Solution	Vi for poly(meth acrylic acid) with 0.2% crosslinking / Vw	Vi for poly (acrylic acid) with 2% crosslinking / Vw
0.6 M NaCl	0.286	0.667
0.1 M Sodium Citrate	0.714	1.333
0.2 M Na HPO .2H O	0.571	1.333
0.2 M sodium tartarate	0.714	0.667
0.6 M KCl	0.286	0.667
0.2 M CaCl	0.143	0.667
0.2 M MgCl	0.286	1.000

adjusted to pH 2, 4, 6, 7 and 8 (±0.1). The suspension was stirred frequently during 24 hours. The pH was readjusted to the original value, if necessary. The hydrated polymer was transferred to a measuring cylinder and its volume was read after a few hours. The finding of these experiments are shown in Fig 1.

Effect of Ions on Equilibrium Swelling of Polymers : The following solutions of ionic strength of 0.6 millimoles were selected for this study - 0.6M sodium chloride, 0.2M disodium hydrogen phosphate, 0.1M sodium citrate, 0.2M sodium tartarate, 0.6M potassium chloride, 0.2M magnesium chloride and 0.2M calcium chloride.

The Equilibrium Swelling of the polymers in these solutions was studied by the method described above; pH of all the suspensions was adjusted to 7 (±0.1) and the volume of the hydrated polymer in the ionic solutions (Vi) was compared with the volume of the hydrated polymer in deionised water (Vw). The results are given in Table 2.

Bioadhesion : After conducting various experiments, a simple equipment was devised for the study of adhesion of the polymers to an artificial biological medium viz. mucin solution. The method is based on Wilhelmy plate principle. A 0.5% w/v suspension of the polymer was prepared in 0.5% carbopol gel. This was then spread evenly on a rexin sheet of 1.5 cm x 1.5 cm and dried at 60^0 C. This rexin supported material was then suspended from the hook of a small crane

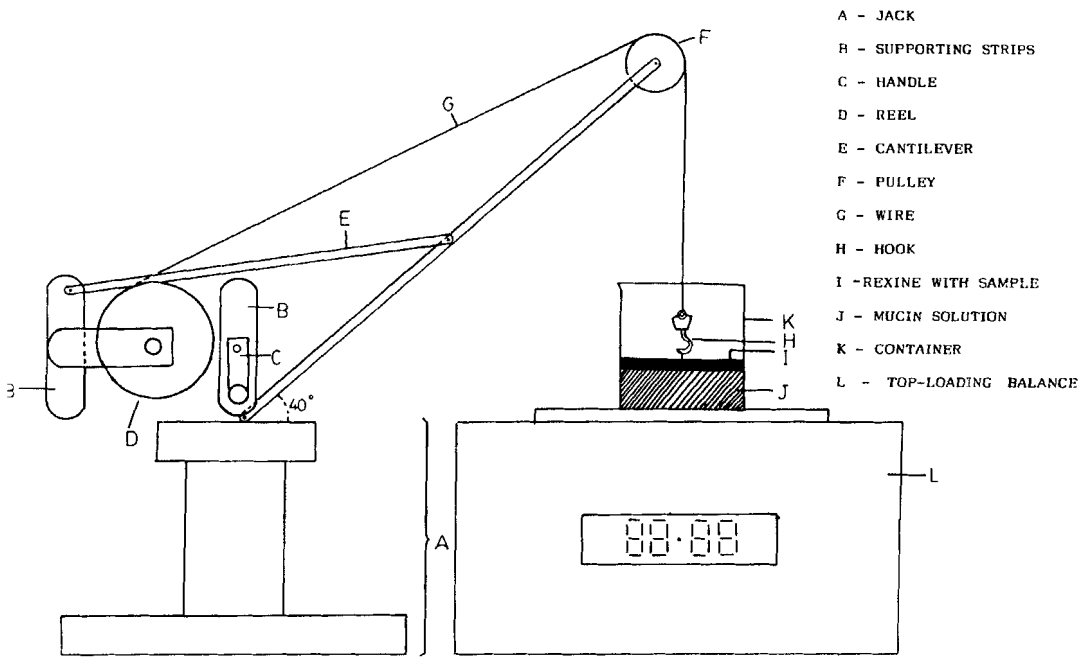

FIG.2. DIAGRAMMATIC REPRESENTATION OF ASSEMBLY EMPLOYED FOR DETERMINING BIOADHESION

(Fig. 2) and brought in contact with 5% mucin solution contained in a beaker, kept on a top loading balance. The polymer was allowed to hydrate for 5 min. and then the sheet was slowly pulled away from the mucin recording the minimum weight displayed. The per cent force/unit area (%F/A) required for the separation of the polymer from the solution was calculated as -

$$\frac{\%F}{A} = \frac{\text{Force/area required for polymer + Carbopol 934 P}}{\text{Force/area required for carbopol 934 P}} \times 100$$

The results of these studies are given in Table 3.

Effect of Contact Time on Bioadhesion : The rexin sheets were coated with 0.5% polymer suspension in 0.5% carbopol gel as described above. The polymer was kept in contact with the mucin solution for a period of 2 min. to 120 min. after which the force required for separation was measured. The plot of the findings is given in Fig. 3.

Infrared Spectra : The IR spectra of the polymer in KBr discs was recorded. The IR of the films of polymer suspension in carbopol was also recorded by attenuated total reflectance (ATR) technique (Fig.4)

TABLE - 3

Polymer (% C.L.A.)	Avg. force ± S.D. required for separation (mg)*						Combined F/A for Polymer and Carbopol (mg/cm)			% F/A for polymer	
	pH 1		pH 3		pH 5					pH 1	pH 3
	Thick-ness (u)	Force	Thick-ness (u)	Force	Thick-ness (u)	Force	pH 1	pH 3	pH5		
Carbopol 934	20± 13	785± 88	11± 7	870± 71	-	- a	348.89	386.67	-	100	100
PMA											
(0.1)	28± 13	731± 105	27± 6	855± 131	-	- a	325.07	379.82	-	93.17	98.23
(0.13)	26± 9	874± 139	20± 6	809± 98	-	- a	388.62	359.73	-	111.39	93.03
(0.15)	22± 11	851± 75	37± 10	741± 131	-	- a	378.18	329.42	-	108.4	85.2
(0.17)	29± 9	728± 38	32± 7	879± 91	-	- a	323.73	390.6	-	92.8	101.01
(0.20)	36± 6	885± 119	27± 4	848± 46	-	- a	393.24	376.8	-	112.71	97.45
PAA											
(0.33)	46± 14	735± 126	38± 4	845± 78	40± 11	895± 116	326.6	375.6	398.04	93.61	97.13
(0.5)	34± 10	892± 74	32± 8	831± 118	40± 6	856± 114	396.36	369.33	380.62	113.61	95.52
(1.0)	98± 34	838± 136	117± 30	818± 114	-	- a	372.33	363.47	-	106.7	94.00
(2.0)	48± 12	806± 81	38± 8	826± 85	40± 6	873± 53	358.5	367.02	387.91	102.75	94.92
(3.0)	42± 16	790± 61	32± 10	775± 46	32± 12	893± 88	351.02	344.36	397.00	100.6	89.06

* Average of 5 readings per sheet and 5 sheets per polymer (total 25 readings)
a Readings could not be taken because the polymer was pulled away from the sheet by the mucin

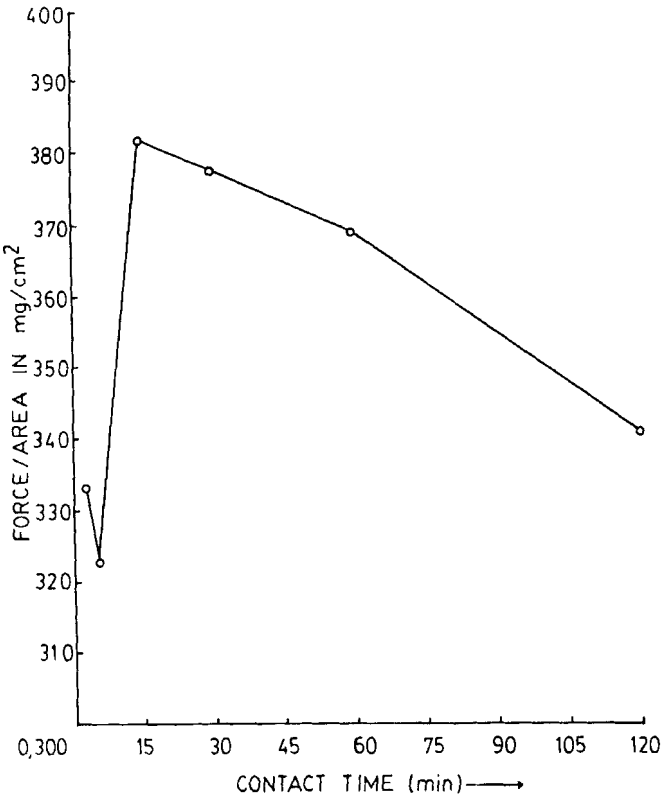

FIG. 3: EFFECT OF CONTACT TIME ON BIOADHESION

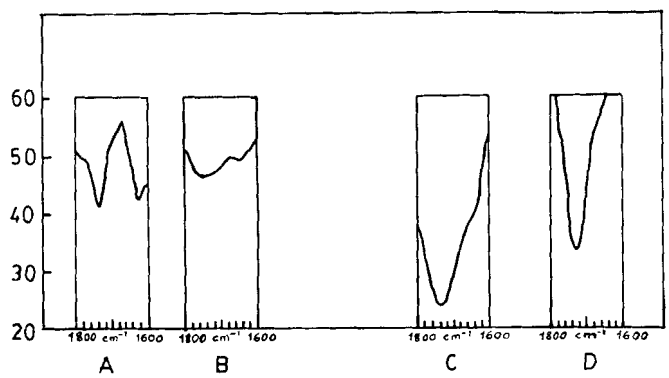

FIG.: 4 IR SPECTRA IN THE REGION OF 1800 cm^{-1} TO 1600 cm^{-1}

A: PAA WITH 0.5% CROSSLINKING

B: PAA WITH 2.0% CROSSLINKING

C: PMA WITH 0.13% CROSSLINKING

D: PMA WITH 0.20% CROSSLINKING

TABLE 4 : PHYSICAL PROPERTIES OF TABLETS

Set No.	Coating Polymer	Average Weight (mg) (± SD)	Density (gm/cm)
1	Uncoated	444.3 ± 14	0.946
2	Carbopol 934 P	458.8 ± 11	0.903
3	Carbopol + PMA with 0.13% crosslinking	461.6 ± 8	0.821
4	Carbopol + PMA with 0.2% crosslinking	439.1 ± 15	0.821
5	Carbopol + PAA with 0.5% Crosslinking	453.3 ± 17	0.806
6	Carbopol + PAA with 2% crosslinking	445.4 ± 19.6	0.798

TABLE - 5

Sr. No.	Coating polymer	Percent F/A
1	Carbopol 934	127.72
2	Poly(methacrylic acid) with 0.13% cross linking	104.26
3	Poly(methacrylic acid) with 0.2% cross linking	106.93
4	Poly(acrylic acid) with 0.5% cross linking	107.63
5	Poly(acrylic acid) with 2% cross linking	106.17

Preparation of bioadhesive tablets of isosorbide mononitrate (ISMN) : Hydrodynamically balanced intragastric floating tablets of ISMN were prepared based on the formula reported by Maru et al (9) for the tablets of Cimetidine. Their density and floating behaviour were checked. The tablets were then dip-coated with 0.5% suspension of the polymer in 0.5% carbopol gel. They were air-dried and checked for floating chracteristics and density (See Table 4). Different sets were prepared using suspensions of different polymers in carbopol and compared with a set prepared by application of plain carbopol coat and with uncoated tablets.

TABLE 6 : IN VITRO RELEASE FROM TABLETS (Replicate of 3 determinations) (± S.D.)

Time (hr)	% Cumulative release from tablets in					
	Set 1	Set 2	Set 3	Set 4	Set 5	Set 6
1	33.75±5.6	21.02±8.11	28.42±3.7	42.63±1.34	25.76±6.01	35.23±4.0
1.5	-	29.54±6.88	-	-	-	-
2	46.56±7.24	-	33.18±2.07	-	35.18±4.89	45.02±3.21
2.5	-	-	-	46.66+4.18	-	-
3	48.87±2.96	45.86±4.35	40.65±6.18	-	32.66±1.23	48.83±6.17
4	54.71±2.33	49.02±7.56	41.09±4.61	64.93±3.87	68.54±6.44	49.36±3.72
5	54.41±3.82	86.27±6.41	41.54±2.37	69.2±5.66	63.96±8.15	56.11±4.98
6	52.33±4.19	91.35±6.38	48.2±7.56	66.1±2.05	66.42±4.35	59.38±7.11
7	71.54±5.18	88.79±3.73	58.46±8.4	79.54±6.92	88.45±8.93	-
8	-	89.73±7.9	82.77±1.46	85.71±3.62	110.71±8.93	-
9	77.63±1.94	113.77±9.65	78.33±3.72	84.85±5.8	-	68.89±2.31
10	75.78±5.85	-	84.49±6.12	92.84±4.96	104.79±8.06	82.05±5.13
11	-	-	-	-	-	97.13±6.65
12	-	-	-	-	-	-
13	-	-	110.01±11.08	94.15±7.2	-	-
14	103.03±7.46	-	-	93.41±8.78	-	99.47+7.36

Set 1 = Uncoated tablets, Set 2 = Carbopol 934 P, Set 3 = Carbopol + PMA (0.13% crosslinking), Set 4 = Carbopol + PMA (0.2% crosslinking), Set 5 = Carbopol + PAA (0.5% crosslinking), Set 6 = Carbopol + PAA (2% crosslinking)

EVALUATION OF TABLETS :

Physical Characteristics : The average weight, densities and hardness of different sets were compared with uncoated tablets. (Table 4).

Bioadhesion : The tablets were entwined in stainless steel wire and suspended from the hook of the crane shown in Fig. 2. The tablet was kept in contact with the mucin solution for 5 min and the % F/A required for separation was measured. The results are given in Table 5.

Drug Content : The content of ISMN in the tablets was determined using colorimetric estimation procedure described by Bell et al (7). The drug content per tablet was found to be 93.05 mg. (sd ±)

Drug release pattern : The release of drug from the tablets was measured in dissolution rate test apparatus using paddle at 75 rpm. The tablet, entwined in stainless steel wire was placed in dissolution flask containing 450 ml of 0.1N HCl. An aliquote of 10 ml was withdrawn at an hourly interval during 24 hours, replenishing the medium each time. The results of these studies are given in Table 6.

DISCUSSION

The colourless, spherical beads of the acrylic and methacrylic acid polymers were found to be insoluble in any of the aqueous or organic solvents tried. However, they exhibited swelling when placed in water, methanol, absolute alcohol and dioxane:water (80:20) system.

Density : The densities of both the polymers showed an initial decrease, followed by an increase with increase in the degree of crosslinking. However, no definite relationship could be established between the degree of crosslinking and density.

Swelling Index : The swelling index of PMA did not show any significant variations, either with change in pH or with variable degree of crosslinking. In case of PAAs, highest swelling was observed at pH of 6 with 0.33% crosslinking. An increase in the degree of crosslinking caused a drastic fall in the swelling index. Also, at these values of crosslinking, no substantial difference in the swelling indices at different pH levels was observed. This indicates blocking of carboxyl groups at 1% crosslinking and above.

The equilibrium swelling of both the types of polymers in solutions of alkaline salts of monobasic hydrochloric acid (i.e. NaCl and KCl) showed the same value of Vi/Vw for different degrees of crosslinking (See Table - 2). A switch over to sodium salts of diabasic and tribasic acids gave much higher values of Vi/Vw. When instead of alkali salts, alkaline earth metals like calcium was used, Vi/Vw values for PMAs dropped to almost half while that of PAAs remained

unaffected. However, changeover from calcium to magnesium caused rise to 1.5 and two times the Vi/Vw value of calcium for PMAs and PAAs resspectively.

A possible explanation for this is that when the molecules or ions are small, they can penetrate the network of the polymers and inhibit their swelling. This is not possible for bulky molecules like citrates and tartarates and hence, the polymer can swell without any interference. More experiments are neccesary to draw any definite conclusion about relationship between valency of electrolytes, their molecular size and their effect on swelling of polymers.

Bioadhesion : The PMAs with 0.13% and 0.2% crosslinking showed better adhesion properties at pH of 1 as compared to carbopol 934. But at higher pH values, none of the PMAs showed satisfactory results. Since, pH of gastric fluid is expected to be between 1 and 1.5, these polymers could be considered satisfactory. Except for the PAA with 0.33% crosslinking, all the other PAAs gave satisfactory results at pH of 1 whereas all the polymers showed less bioadhesion at higher pH.

Some results show less bioadhesion in case of polymer-carbopol combination as compared to only carbopol suspension. This could be due to heterogeneous nature of the film of polymer-carbopol suspension. The film does not have a uniform, leveled surface and these surface irregularities can result in overall decrease in the effective contact surface available for the adhesion.

In all the experiments, the contact time available was 5 mins. which was the one which showed minimum bioadhesion. Hence, much higher values could be expected in in vivo studies.

IR Spectra : The IR spectra of PMAs show a distinct ester peak at 1720 cm^{-1} , which was unexpected. Further, the carboxylic acid peak at 1650 cm^{-1} is missing. Both of these point to possibility of intramolecular condensation.

In contrast to this, the IR spectra of PAAs show presence of the carboxylic acid peak at 1650 cm^{-1} and absence of ester peak, supporting the expected polyacrylic acid structure.

When the floating tablets of ISMN were coated with suspensions of carbopol or synthesized polymer-carbopol combinations, their densities showed further fall indicating that the polymer coat does not interfere with floating properties.

The higher adhesive force exhibited by tablets coated with carbopol suspension could be attributed to high viscosity and film continuity due to homogeneity of the suspension.

Drug Release: The drug release pattern of all the sets showed some interesting results. The uncoated tablets gave maximum cumulative release of 77.63 ± 1.94% in 9 hours. Application of carbopol coat caused an increase in the bioavailability of the drug, giving release of 86.3 + 6.41% in only 5 hours. In contrast coating of all the synthesized polymers released 82%-88% drug from the coated tablets during 7-10 hours. Thus the PMAs and PAAs seem to have increased the amount of total drug available to the body, during the defined period of time. Maximum retardation of release was seen in the case of PAA with 2% crosslinking which released 82.05 ± 5.13% of the drug during 10 hours and 99.47 ± 7.36% during 14 hours.

This phenomenon could perhaps be explained on the basis of differences in hydrophilicity of the polymers. Carbopol 934 P, due to the predominance of hydrophobic sites, initially offers a barrier for durg penetration. Hence, drug release in first two hours (29.54% ± 6.88%) is less than that from the uncoated tablets (46.56% ± 7.24%). However, once proper wetting is achieved, there is no control over drug release and hence the maximum release is achieved in only 5 hours (86.27% ± 2.41%). In contrast, the tablets coated with combination of carbopol 934P and PMA with 2% crosslinking (Set 4), initial release is high (42.63% ± 1.34%). This can be attributed to improved wetting of the tablet surface due to hydrophilicity of the PMA. However, after the initial release, the polymer controls the diffusion of drug through it to give a steady drug release over the next 13 hours (93.41% ± 8.78% at end of 14 hours). Thus, this combination may be expected to give a hydrodynamically balanced, bioadhesive controlled release drug delivery system.

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