RESEARCH PAPER

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Evaluation of Polyacrylate film formers for Sustained Release of Drugs

S.P. PUTHLI AND R. SHRIVASTAVA*
The Bombay College of Pharmacy, Kalina, Santacruz (East), Bombay - 400 098

Evaluation of polyacrylate polymers synthesized from acrylic acid, methacrylic acid, ethylhexyl acrylate and methyl methacrylate using solubility evaluation, IR-spectroscopy, intrinsic viscosity determination, differential scanning calorimetry, free film studies as well as release of the drug from coated pellets are presented. Highly flexible internally plasticized films were obtained from two of the three polymers.

RECENTLY three polyacrylate film formers were synthesized in our laboratory.[1,2] Some polyacrylate polymers are now officially recognized in U.S.P. Even though new monomers such as ethylhexyl acrylate have been used by us it is hoped that these new polyacrylate copolymers would have a good probability of being safe for pharmaceutical use. With this view, the physiochemical characters of the film formers and films formed by them were studied and are presented in this paper.

EXPERIMENTAL

METHODS

Polyacrylate film former were synthesized earlier in our laboratory[1,2] by the solution polymerization technique according to the formulae given in Table 1. The codes FF1, FF11 and FF111 are used to designate the three polymers synthesized.

Free films were prepared by solvent casting on a release liner (3M Co.). **Thickness** of the free films was measured with vernier callipers. A qualitative study for the **solubility** of the film formers was conducted in methanol, ethanol, isopropanol (IPA), ethyl acetate and acetonitrile. **The pH - solubility relation** for the film formers were evaluated in buffers of pH 3 to 10, prepared as per I.P.1985.

Colloidal coating formulations was developed on the basis of the following study. 50 mg of each film former was dissolved in IPA; and water was added with intermittent vortexing such that final volume was 1 ml. The ratios of IPA and water used were 1.0, 4:1, 13:7 and 1:1. As the water was added, the turbidity of the system increased and the viscosity decreased. The **intrinsic viscosities** of the copolymers were obtained by measuring the viscosites of 0.4, 0.8, 1.6, 2 and 4% w/v solutions of polymers FFI, FFII and FFIII in IPA using a Contraves low shear 30 viscometer. The **tensile strength, folding endurance and elongation** of the polymer films were determined by standard procedures as detailed elsewhere.[2] The ability of the film formers to **pick-up moisture** from the environment was determined by equilibrating preweighed film at 52, 66, 76 and 93% R.H. at room temperature for 48 h. In **swelling** studies, the free films cut to a definite size were mounted on the stage of a dissecting microscope (magnification 20 X), to which a biprismatic camera lucida was attached. The free films were equlibrated in water at R.T. for 24 h and the size measured again as above. For the **infrared spectra**, KBr pellets were prepared with the help of a die. Film former solution was spread evenly on the KBr pellet so as to form a thin film. The films were allowed to dry and IR - spectrum was then taken on a Jasco FT/IR 5300 instrument. **Differential scanning calorimetric**

*** For correspondence**

Table 1: Formulae for the Synthesis of Film Formers

Ingredients	Quantity taken (g)		
	FFI	FFII	FIII
Acrylic acid	7.0	3.5	—
Methacrylic acid	7.0	3.5	5.83
2-ethylhexyl acrylate	21.0	21.0	29.17
Methyl acrylate	—	3.5	—
Methyl methacrylate	—	3.5	—
Methanol	18.9	18.9	18.9
Benzoyl peroxide	0.35	0.35	0.35

(DSC) scans of the three film formers were taken on Shimadzu Thermal Analyser DT-40 apparatus at a heating rate of 10° per min in a nitrogen atmosphere. **Film permeation studies** involved the use of an Erweka skin permeation system. Salbutamol sulphate (1.5% w/w) incorporated in a 3% w/w Methocel K-100 (hydroxy propyl methyl cellulose) gel was poured on the films placed on the mouth of the receptor compartment. A freshly prepared buffer pf pH 7.4 maintained at 37° was used as the sink solution. **Salbutamol sulphate pellets** (# 14/20 fraction) were prepared by extrusion-spheronization using microcrystalline cellulose (Avicel pH 101) and Lactose I.P., 1:1 mixture as a spheronizable diluent; and water as binder. Their particle size was determined by microscopy. Sphericity was calculated according to the method of Lovgren and Lundberg.[5] 100g of the pellets were taken in a 8" coating pan and a 5% w/v polymer in IPA and Water (6:4) mixture sprayed onto the pellet bed with the help of a pneumatic spray gun. The pellets were intermittently subjected to hot air (60-70°) drying. The percent w/w coat applied on the pellets were 8.579, 8.559 and 8.557 for film formers FFI, FFII and FFIII, respectively. **Drug content** was determined by spectrophotometric analysis at 225 nm. **In vitro release** of salbutamol sulphate from coated pellets was evaluated using USP dissolution apparatus (basket type). The dissolution medium used were 1000 ml buffer of pH 1.25 (0-2 h), 4.5 (2-4 h) and 7.4 (4-12 h). The temperature was maintained at 37 ± 0.5°. The rotation speed was 50 rpm.

RESULTS AND DISCUSSION

Polymer FFIII with the lowest content of acid monomers used for its synthesis was insoluble in methanol and ethanol. FFI and FFII at a concentration of 30% w/v in ethanol and methanol formed opaque colloidal gels. At a concentration of 30% w/v, translucent colloidal gels were formed by FFI and FFII in IPA, while opaque gel was formed by FFIII in IPA. FFI was insoluble in ethyl acetate and FFIII was soluble, while FFII was only slowly soluble in ethyl acetate. All the three polymers were insoluble in acetonitrile, however on overnight standing, FFI and FFII swelled when kept in acetonitrile. The three polymers were insoluble in water. The polymers had poor water solubility which was independent of pH. Only FFI with the largest content of free acid groups showed a marginal increase at alkaline pH.

At a concentration of 5% w/v translucent colloidal solutions were obtained with the three film formers in IPA-water mixtures with IPA water ratio of 4:1. With the ratio reaching 13:7, white translucent dis-

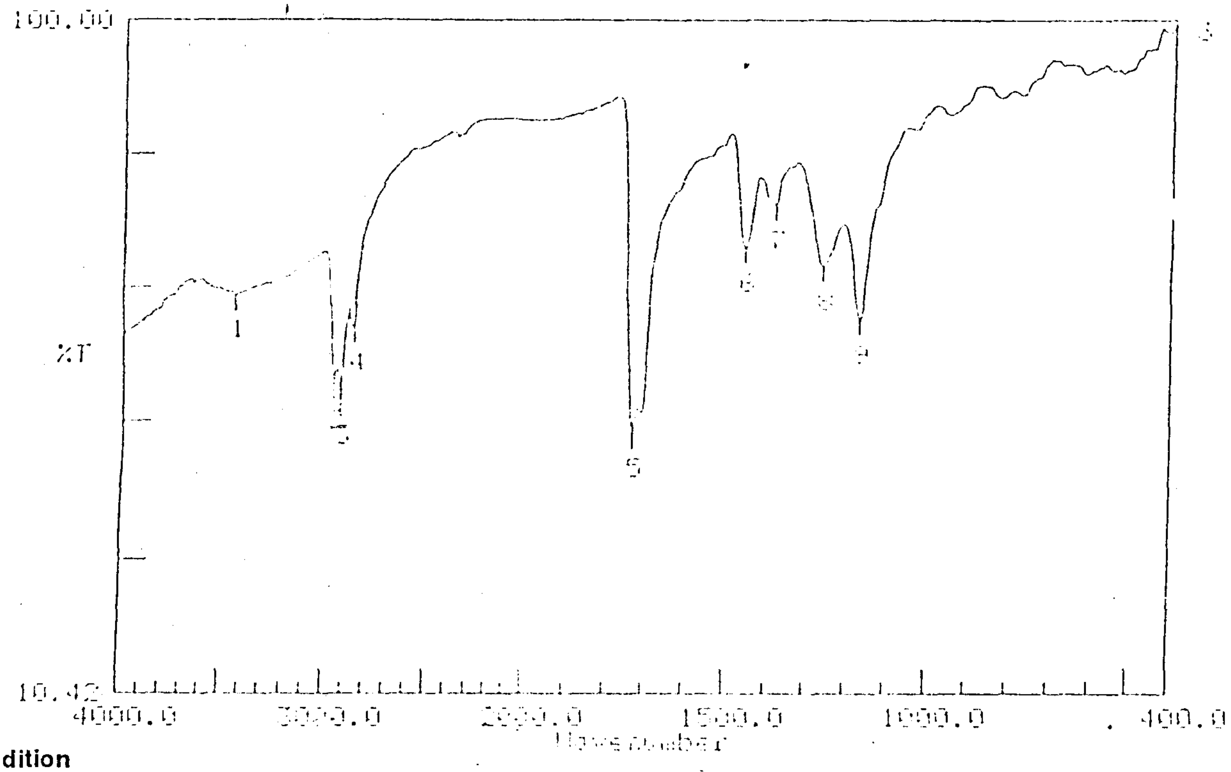
Table 2: Physical Evaluation of free Films

	Test	FFI	FFII	FFIII	FFI (10% triacetin)
1)	Thickness (mm)	0.1416 (0.0008)	0.1352 (0.00714)	0.1324 (0.00158)	0.132 (0.00359)
2)	Tensile strength (dynes/sq.cm)	2118938 (296695)	1811997 (92726)	892557 (87727)	1039715 (30414)
3)	Elongation (%) Dry state	Brittle	342.06 (1.887)	21.83 (1.154)	10.08 (1.712)
	Wet state	—	341.57 (4.79)	45.17 (1.89)	—
4)	Folding endurance (folds)	10.2 (1.92)	2942.8 (57.89)	2678 (69.79)	—
5)	Swelling (percent)	6.28	3.28	7.4	—
6)	Moisture pick-up RH (%)				
	52	—	0.185	0.152	—
	66	0.175	0.138	0.309	6.25
	76	1.365	0.277	0.318	4.0
	93	5.355	9.625	1.285	8.57

Figures in bracket indicate standard deviation

persions were obtained. Dispersions formed with FFI had higher turbidity than FFII and FFIII. At a ratio 1:1, the systems became white opaque colloidal dispersions. No phase separation was observed in all these mixtures on overnight standing. However, when the water to IPA ratio was greater than 1:1, the polymer precipitated and settled on standing. At lower water to IPA ratio than 1:1 the polymer was soluble in the solvent system giving a "colloidal solution" unlike commercial aqueous pseudolatex systems such as Aquacoat which are "colloidal suspensions". Colloidal solutions are thermodynamically stable in contrast to colloidal suspensions which are thermodynamically unstable. Therefore no long term stability problems may be anticipated from the above systems. Upon addition of water, the viscosity of the polymer solution and its flow rate decreased. In order to obtain a more easily sprayable coating dispersion a ratio of IPA: water, 6:4 was chosen.

The y-intercept from the plots of reduced viscosity vs concentration FFI, FFII and FIII gave the value of intrinsic viscosity (n) as 0.3019, 0.1826 and 0.05295 for FFI, FFII and FIII, respectively. The values of K and α for the homopolymer polymethyl methacrylate are 9.4×10^{-5} and 0.76, respectively[4]. Assuming these values for the copolymers the viscosity average molecular weights may be calculated as 41110, 21200 and 4160, respectively. The lower molecular weight of FFIII may be attributed to the shorter polymerization time and its insolubility in methanol, the solvent used for polymerization.



Condition
upper 100.00 **lower 10.41** **depth 2.00**
Peak table
1: 3445.18 (63.1) **2: 2959.07 (50.8)** **3: 2928.21 (48.9)** **4: 2858 .76 (58.5)** **5: 1732.23 (44.6)**
6: 1454.46 (69.4) **7: 1381.16 (75.1)** **8: 1257.70 (67.0)** **9: 1165.11 (59.7)**

Fig. 1 Infra red spectum of FFI film on KBr pellet

The physical properties of the films are given in Table 2. FFI films had high tensile strength, were brittle and showed no elongation. This was perhaps due to the formation of more crystalline films by close packing of the polymer chains resulting from hydrogen bonding between carboxylic acid groups on neighbouring chains. When FFI films were plasticized with 10% by weight of triacetin, flexible films were formed. However, FFII and FFIII films had a high degree of flexibility even in the absence of any plasticizer and thus were internally plasticized. Thus, it may be concluded that the use of a large proportion of a longer chain monomer, ethylhexyl acrylate particularly in combination with acrylate ester monomers and limited quantity of acid monomers as in FFII and FFIII results in highly flexible internally plasticized films. Table 2 shows that FFI films did not show any elongation; being brittle they broke after 8 minutes of stress application whereas FFII films showed a very large elongation. The data in Table 2 also shows that Polymer FFIII with the least amount of acid groups did not show any significant moisture pick-up at all humidity values. FFII and FFI did not show any significant moisture pick-up upto an environmental R.H. of 76% but picked up significant moisture at 93% R.H. The percent swelling in water for the three polymer free films was small.

The infrared spectrum of FFI is given in Figure I. The peak at 2959.07 cm^{-1} may be assigned to the asymmetric C-H Stretching of CH_3 group. Peaks at wave number 2928 $cm^{-\ 1}$ was due to asymmetric C-H stretching of CH_2 and peaks at 2858 cm^2 due to symmetric C-H stretching of CH_3 and CH_2 groups.

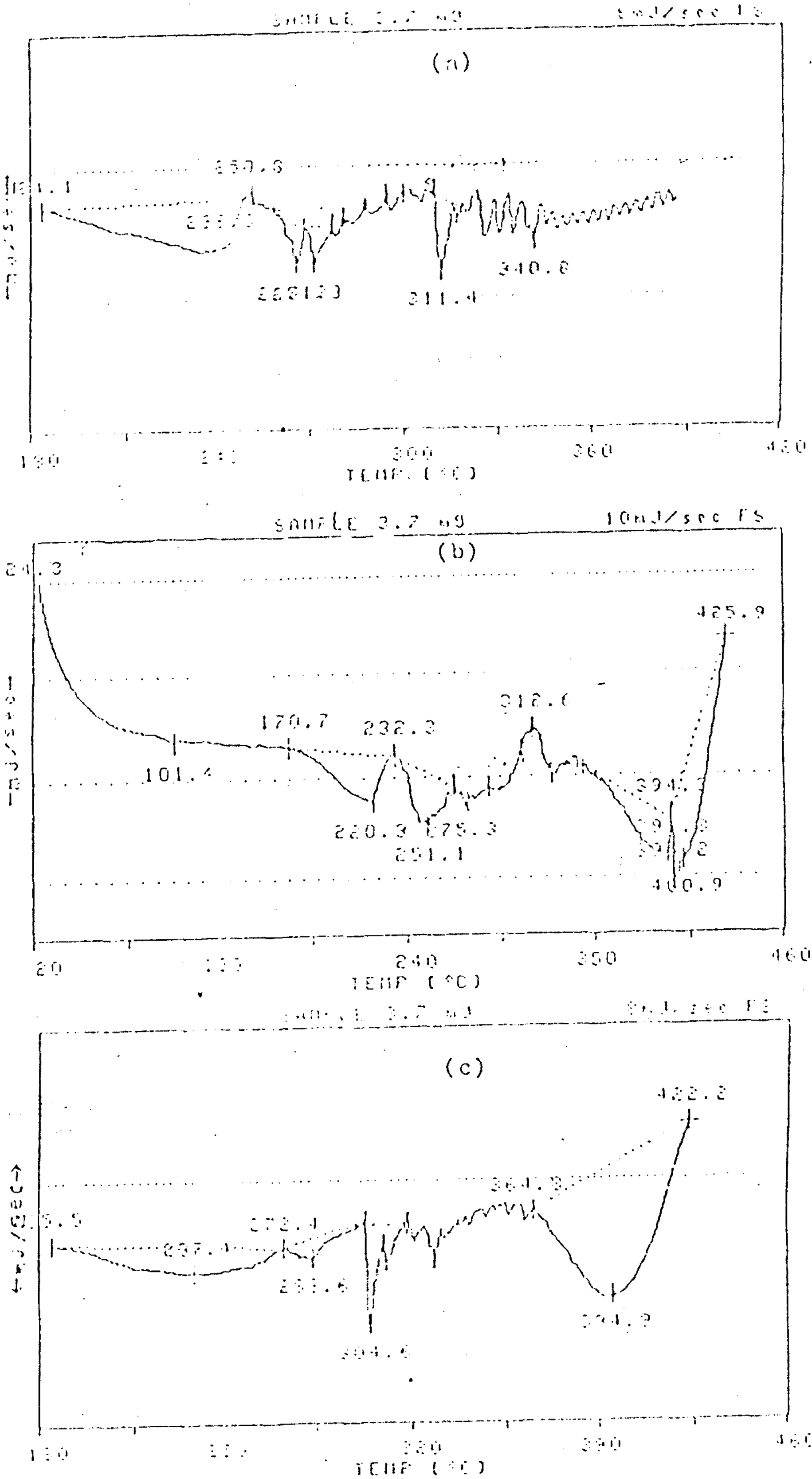


Fig.2: Differential scanning calorimetry thermogram of (a) polymer FFI, (b) polymer FFII and (c) polymer FFIII

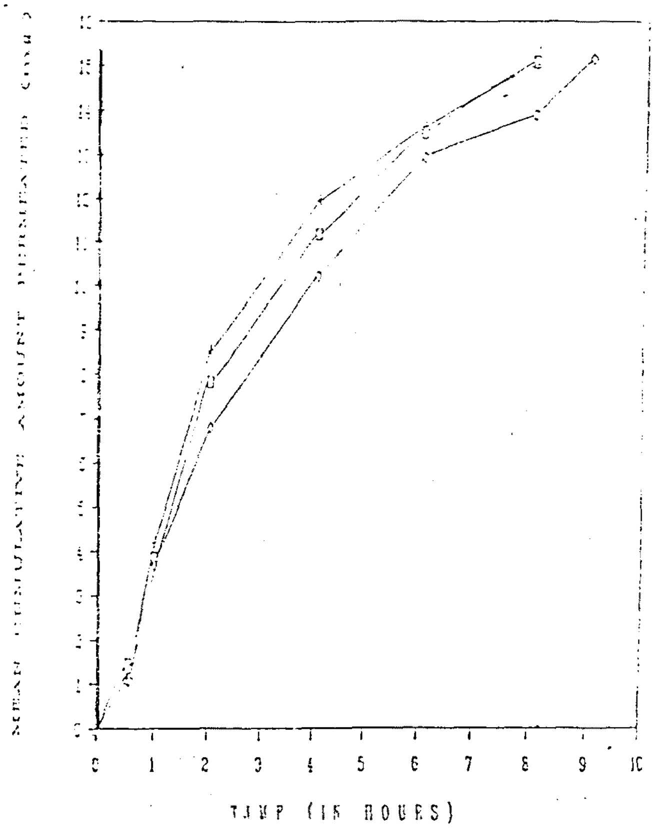


Fig. 3: Mean cumulative amount permeated vs time profiles for permeation of salbutamol sulphate through polymer free films.
Key : ☐ FFI; + FFII; ◊ FFIII.

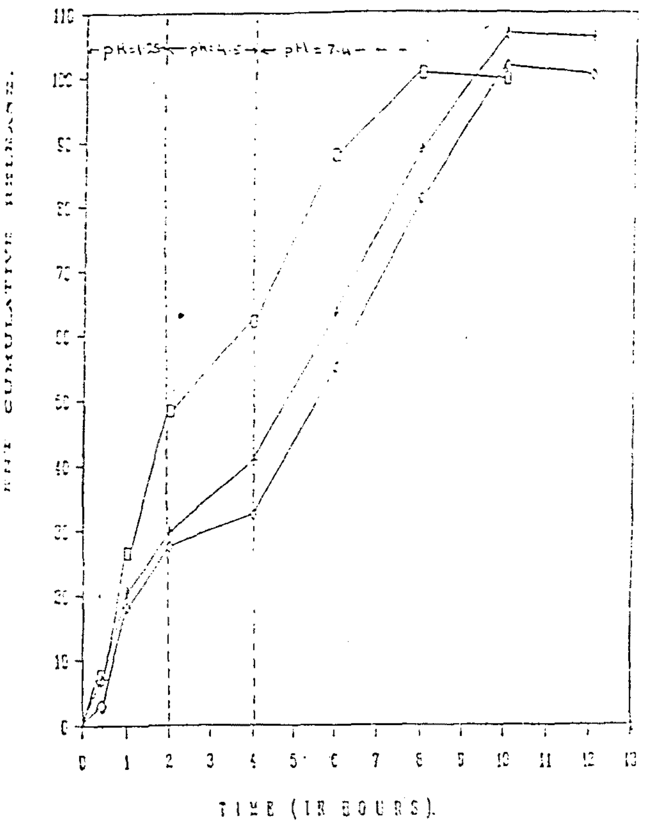


Fig. 4: In-vitro release of salbutamol sulphate from 14/20 mesh pellets coated with polyacrylate film forms.
Key : ☐ FFI; + FFII; ◊ FFIII.

The peaks for the C-H group stretching of acid and the ester can be seen in the spectrum. Similar spectra were obtained for FFII and FFIII.

The DSC scans of FFI, FFII and FFIII are given in Figure 2. The glass transition temperature (T_9) were 184.1°, 170.7° and 185.5° for FFI, FFII and FFIII, respectively. It may be proposed that FFI has a higher glass transition temperature than FFII because of closer packing of the polymer chains resulting from a greater number of carboxylic acid functional groups. Film former FFIII had a higher glass transition temperature than FFII. This could perhaps be due to the lower molecular weight polymer FFIII remaining in an uncoiled state during the process of film formation by solvent evaporation. The extent of interaction between the polymers and the solvent would also be an important factor affecting the crystallinity of the films and the glass transition temperature.

Plots of mean cumulative amount permeated vs time for FFI, FFII and FFIII films are given in Figure 3. The plots of ln (amount remaining to be permeated) vs time for FFI, FFII and FFIII films gave linear plots conforming to the equation.

$$\ln A = 1n\, A_o - k't$$

$$\text{where } k' = \frac{DKS}{hV} = \frac{P'S}{hV}$$

D is the diffusion coefficient of drug through the polymer film, K the water/membrane partition coefficient, S is the area of the membrane, h is the thickness of the polymer film and V is the volume of the solution in the donor compartment. The values of the constant P', were found to be 0.001338 ± 0.00004 $cm^2 hr^{-1}$, 0.0013875 ± 0.000152 $cm^2 hr^{-1}$ and 0.001172 ± 0.000052 $cm^2 hr^{-1}$ for FFI, FFII and FFIII films, respectively. The constant P' would be dependent on both the diffusibility of the drug through the films as well as the partitioning characters of the drug into the polymer films if the mechanism of release involved partitioning of the drug into the polymer matrix followed by diffusion through the polymer metrix. If the release occured by diffusion of the drug through dissolution medium filled channels then the constant P' would be dependent only on the diffusibility of the drug which in turn would depend on the tortuosity and porosity of the polymer film. Whereas the partitioning of weak base salbutamol may be expected to increase with increasing acid functionality of the polymer (FFI > FFII > FFIII), the diffusibility would depend on the density of packing of the polymer chains. Free films of polymer FFII with the lowest glass transition temperature had the highest permeability whereas free films of polymer FFIII with the highest glass transition temperature had the lowest permeability.

The sphericity of salbutamol sulphate core pellets was found to be 94.07%. The volume surface mean diameter was 1.582 mm and the specific surface was found to be 37.92 cm^2/cm^3. The angle of repose for # 8/16 pellets coated with FFI, FFII and FIII were 22.69°, 27.07° and 24.7°; and the mean flow rates were found to be 220, 180 and 200 g/min. respectively. The mean salbutamol sulphate content per gram of the pellets coated with FFI, FFII and FFIII were 18.411 ± 0.0357 mg. 18.433 ± 0 mg and 18.4325 ± 0.625 mg. respectively. Figures 4 gives the release profiles of salbutamol sulphate from pellets coated with FFI, FFII and FFIII. The difference in the release of salbutamol sulphate in 2 hour was statistically significant ($\propto$ = 0.05) with FFI coated pellets releasing faster than FFII coated pellets which released faster than FFIII coated pellets. The slow release from polymers FFIII coated pellets correlates with it's low permeability coefficient determined from **in-vitro** studies. However, faster release was obtained from polymer FFI coated pellets as compared to polymer FFII coated pellets. In this case there was a disagreement between prediction from the free film permeability study and release from coated pellets. This may be because the free films were relatively thick and planar whereas the pellets provided a curved and a microscophically rough surface over which a relatively thinner film was formed. The higher permeability of polymer FFI coated pellets could thus be because unplasticized more brittle polymer FFI could not form a perfect film over the pellet surface.

In conclusion it may be stated that highly flexible internally plasticized films can be obtained from polyacrylate polymers synthesized using a relatively large proportion of a longer chain monomer, ethylhexylacrylate and limited quantity (15 to 20% by weight) of acid monomers. These polymers (FFII and FFIII) provided slow release of a water soluble drug salbutamol sulphate. Their high flexibility, tensile strength and elongation suggest that films formed from them are not likely to burst/fail inspite of swelling of the core making them suitable for sustained release applications. Finally, these polymers avoid the use of plasticizers and thus would reduce the risk of adverse reaction in parenteral applications.

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