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CONTROLLED RELEASE COPRECIPITATES OF IBUPROFEN AND A CARBOMER: PREPARATION, CHARACTERIZATION AND *IN VITRO* RELEASE STUDIES

GUL MAJID KHAN* AND ZHU JIABI
Zhang Kun Pharmaceutical Research Institute, School of Pharmacy,
China Pharmaceutical University, Nanjing 210009, P. R. China
**Faculty of Pharmacy. Gamal University. Dena Ismail Khan. N.W E P., Pakistan.*

ABSTRACT:

Extended release coprecipitates *of* ibuprofen (IBF) and carbopol 934P-NF, in the form of micro-matrices, were prepared using two different methods. The drug-carbomer interactions in the solid state were investigated employing Infra Red (IR) Spectroscopy, Differential Scanning Calorimetry (DSC), and Scanning Electron Microscopy (SEM) Dissolution experiments were performed using simulated gastric fluid (SGF- pH 1.2), distilled water, and pH 7.2 phosphate buffer solution as dissolution media. No well-defined chemical interaction between the ingredients was found. The methods of preparation of the coprecipitates are simple, practical, minimize the use of toxic organic solvents, and can be used in the production of controlled release tablets.

1. INTRODUCTION

Coprecipitates of drugs and polymers have been studied extensively for enhancing the dissolution of poorly soluble compounds (Simonelli, A.P., 1969, Kawashima.Y., 1989, Goracinova, K., 1995). The use of this technique in sustaining/controlling release of drugs has been recently examined Karachi, A.A., 1995, Khan M.A., 1996.

Carbopol 934P-NF is a polymer of acrylic acid that is cross-linked with polyalkenyl polyether. It is a high molecular weight polymer that readily hydrates, absorbs water, and swells. Its hydrophilic nature and highly cross-linked structure makes it a potential candidate for use in controlled release delivery systems. Zhang and Schwartz (Zhang. X. Y., 1986) reported that the drug release from carbomer tablets appears to follow a zero order release mechanism in most of the cases studied. Moreover, the articles appearing in the literature over the recent few years (Meuey, I., 1987, Huang, L.L., 1995) and the patent formulations of carbomers, especially of the *widely* used carbopol 934P-NF (DeCrosta, M.T., 1987, Ueda, Y., 1987) show that carbomers occupy an important position in the field of controlled release drag delivery systems and needs further investigation and more research work to be done.

The objective of the present study was to investigate the possibility of IBF/Carbopol 934P-NF coprecipitates formation, characterization of the coprecipitates formed, their compression as tablets, and *in vitro* release behavior of IBF from the carbomer matrix tablets.

*For Correspondence

2. MATERIALS AND METHODS

2.1 Materials

Ibuprofen was purchased from Xin Rua Pharmaceutical Factory (Shan Dong, China); Carbopol 934P-NF was obtained as a gratis supply from BF Goodrich Specialty Chemicals (Ohio, USA). All other chemicals used were of analytical grade and were used as received.

2.2 Methods

IBF/Carbopol 934P-NF coprecipitates at different drug to polymer ratio were prepared using the following two methods.

2.2.1 Method A:

Ibuprofen and the required amount of carbopol 934P-NF (Table 1) were dissolved in 7.5 ml of ethanol (USP). To this alcoholic solution, 0.025%(w/v) aqueous solution (200 ml) of sucrose fatty acid ester at room temperature was added while stirring at a rate of 600 rpm for 15 minutes, using a constant velocity electric stirrer (Especial Medical Instruments Factory. Shang Hai, China). The mixtures were instantly coprecipitated giving rise to dispersed fine spherical micro-matrices, which grew in their size while retaining the spherical shape and resulted in to the solidified spherical matrix structures. The resultant coprecipitates were filtered and dried at 60°C for 4 hours and then stored overnight at 40°C. The dried samples were screened through # 18 mesh sieve and store in labelled bottles in a desiccator till further use.

2.2.2 Method B:

In this method IBF was dissolved in 3 ml of ethanol. Aqueous solutions of the carbomer (200 ml) containing 0.025% (w/v) of sucrose fatty acid ester were prepared separately. These aqueous solutions, at room temperature, were added to the ethanolic solutions of IBF while stirring at a rate of 600 rpm for 15 minutes. The instantly coprecipitated spherical micro-matrices were processed similarly as mentioned in “method A”.

2.3 Methods for Characterization and Evaluation of the Coprecipitates

2.3.1 Scanning Electron Microscopy (SEM):

The shape and topography of the ingredients and that of the coprecipitates were studied by SEM (ISI – SX – 40). The samples for SEM were mounted on sample-stubs with double sided adhesive tape, vacuum coaled with gold, and photographed at suitable magnification.

2.3.2 Differential Scanning Calorimetry (DSC):

DSC patterns were determined using a differential scanning calorimeter (DSC–25 Mettler). Each sample was heated between 40°C and 200°C with a scanning rate of 10°C/min. DSC thermogram of the carbomer was also obtained between 40°C and 250°C.

2.3.3 Infra Red (IR) Spectroscopy:

Infra red spectra of all the formulations prepared were scanned using Model 983 Perkin Elmer IR. Spectrophotometer, from the KBr pellets. The scanning range used was 4000 cm^{-1} to 400 cm^{-1}

2.3.4 Compression of the Coprecipitates:

Coprecipitates corresponding to 200 mg of IBF were individually poured in to a die. Tablets were compressed on a single punch machine (Shang Hai Mechanical Equipment Factory) using 9 mm diameter flat surfaced beveled punches. The tablets hardness ranged from 7 to 9 kg.

2.3.5 In Vitro Drug Release studies*:*

Drug release studies *were* carried out using the USP basket method with ZRS – 4 Intellignet Dissolution Tester (Tian Jin University Radio Factory, Tian Jin, China) with a rotation speed of 100 rpm. 900 ml of each i.e., SGF (pH 1.2), distilled water, and pH 7.2 phosphate buffer solution was used as dissolution medium. The dissolution media were maintained at 37 ± 0.1°C. Five ml samples at predetermined time intervals were withdrawn, filtered (0.45 μ m). and analyzed using 752 C Spectrophotometer (The 3rd Analytical Instruments Factory. Shang Hai, China) at 222 nm. After each sampling, equal volume of the respective dissolution medium (maintained at 37± 0.1°C) was added as replacement. From the absorbance values the cumulative percentage of ibuprofen released was calculated. T_{50} and T_{90} were also determined (Table 2). All the experiments were performed in triplicate.

3. RESULTS AND DISCUSSION

3.1 Scanning Electron Microscopy (SEG)

Figure 1 shows the scanning electron photomicrographs of IBF, Carbopol 934P-NF, and their coprecipitates prepared in this study. Analysis of the SEM revealed that the large elongated crystals of BF and the relatively small sized polyhedral particles of the carbomer have been transformed in to spherical matrix structures, demonstrating totally different picture than that of the ingredients.

3.2 Differential Scanning Calorimetry (DSC)

As shown in Figure 2, the thermograms of IBF did not show any major change in the endothermic peak with the carbomer. However, slight shifts at the peak location of IBF towards lower temperatures were demonstrated. Slight changes in the values of heat of fusion (ΔH_f) were also shown by the coprecipitates.

3.3 Infra Red (IR) Spectroscopy

The I R spectra of IBF and its physical mixtures with the carbomer demonstrated the most prominent and the characteristic bands due to C=O stretching vibrations of the esterified carboxylic acid groups at 1730 cm^{-1} and of carboxylic acid groups at 1706 cm^{-1}. In case of the coprecipitates overlapping of the characteristic peaks was observed, indicating that no strong interaction exists between the drug and the carbomer.

3.4 Compression of the coprecipitates

Preliminary investigations were made to determine whether the coprecipitates obtained could be compressed directly or needed some additives. It was then decided to use the direct compression method. The spherical matrix structures provided with a good flow property and their spongy texture helped in better and easy compression. The tablets thus compressed were without any visible defect. They were elegant and had a potential promise for the preparation of 24 hour controlled release tablet formulation.

3.5 In Vitro Drug Release studies

The release profiles of ibuprofen (precipitated from ethanol), IBF/Carbopol 934P-NF physical mixture, and coprecipitates prepared at different drug to polymer ratios, using two different methods, in SGF (pH 1.2), distilled water, and pH 7.2 phosphate buffer solution are shown in Figures 3 to 6. T_{50}, T_{90} and the cumulative percent drug release at the end of 6 hours and 10 hours are given in Table 2.

During the dissolution testing, two general trends were observed: (a) The polymer swelled, the more polymer in the sample, the more the sample swelled, (b) the swelling of the drug/carbomer compressed coprecipitates occurred in all the dissolution media. i.e., SGF (pH1.2), distilled water, and pH 7.2 phosphate buffer solution. However, the degree of swelling in each of the medium was not the same. The peak swelling of the polymer was observed in the pH 7.2 phosphate buffer solution. The reason for this effect is the apparent further ionic repulsion of the polymer, which is manifested on a macro level as swelling, in addition to the hydration effect seen at lower pH levels (Carbopol, 1984).

In case of IBF in our study, there is a shift from an anomalous behavior towards a Case II type release mechanism for the coprecipitates containing carbopol 934-NF. This shift is dependent on the pH of the dissolution media. A pH dependent swelling of this anionic polymer occurs as the pH is increased from 1.2 to 7.2. In SGF (pH 1.2) the polymer is not fully swollen and there are larger regions of low microviscosity. As the pH is increased to 7.2 the ionization of the carboxylic acid groups causes maximum swelling, resulting in fewer and smaller regions of low micmviscosity. In this case drug release is controlled by the degree of swelling of the polymer and therefore the release kinetics profile shifts towards a swelling-controlled, Case II mechanism.

Moreover, increasing the amount of the carbomer in the coprecipitates resulted in a reduction of the drug release rate and a linearization of the drug release curve, leading to a shift towards a swelling-controlled mechanism. This may be due to the closing of the micropores and a reduction in the regions of low microviscosity in the swollen tablet. The swelling of tablet is due to the hydration of the polymer, which results in a rapid decrease in its glass transition temperature (T_g) to the temperature of the dissolution medium Microscopically, there is a relaxation of the polymer chains due to stresses introduced by the presence of the dissolution medium which results in an increase in the radius of gyration and end-to-end distances of the polymer chains (Rangy Rao, K. V., 1988). There is a significant increase in the molecular volume of the hydrated polymer that reduces the free volume due to the presence of the microspores. This effect may manifest itself as a shift in the drug release mechanism. This is in accordance with the results obtained by Durrani et al. (Durrani, M.J., 1992) and several other authors who have studied the impact of concentration on dissolution kinetics (Capan, Y., 1990, Seng, C.H., 1985).

4. CONCLUSION

IBF/Carbopol 934P-NF coprecipitates in the form of micro-matrices were obtained by two different methods. Both the methods are simple, practical, and minimize the use of toxic organic solvents. The coprecipitates thus prepared could successfully controlled the release of IBF and have the potential to be used in the formulation of a 24 hour controlled release tablet formulation.

Drug release from Carbopol 934P-NF can occur both by diffusion through low microviscosity pores (polymer hydrofusion), and by a swelling-controlled mechanism. Factors which reduce the number and size of the microviscosity voids, such as increasing pH. which increases polymer swelling and consequently, decreases drug release, or increasing polymer concentration, tend to shift the drug release profiles of the coprecipitates from diffusion-controlled mechanism towards the swelling-controlled, Case II (Zero Order) type release mechanism.

Table 1

Amounts of IBF and Carbopol 934P-NF used in the preparation of CR coprecipitates

S. No.	IBF: Carb.	Amount of IBF used (g)	Amount of Carb. Used (g)	% of Carb. Used	Drug Loading (%)
1	10:0.5	2	0.1	4.76	95.24
2	10:1	2	0.2	9.09	90.91
3	10:2	2	0.4	16.67	83.33
4	10:3	2	0.6	23.08	76.92

Table 2

Dissolution data of IBF-Carbopol 934P-NF coprecipitates in dissolution media with different pH environments

S. No.	Method of Preparation	Dissolution Medium	Formulation	Cumulative % Released 6 hrs	10 hrs	T_{50} min.	T_{90} min.
1.		PH 7.2 Phosphate Buffer Solution	IBF (precipitated From Ethanol)	100	----	130	270
2.		- do -	Physical Mixture (10:1)	73.5	92.8	170	528
3	*Method A*	- do -	Coprecipitates				
4.	- do -	- do -	10:0.5	58.8	90.0	310	598
5.	- do -	- do -	10:1	55.1	85.5	328	639
6.	- do -	- do -	10:2	52.1	84.1	347	651
7	- do -	- do -	10:3	43.2	76.1	405	708
8.	*Method B*	- do -	10:1	64.1	93.9	292	546
9.	- do -	- do -	10:2	48.8	86.7	366	623
10.	- do -	- do -	10:3	42.6	82.4	406	650
11.	*Method A*	Distilled Water	10:1	75.8	93.3	242	530
12.	- do -	- do -	10:2	63.7	86.1	292	655
13.	- do -	- do -	10:3	56.1	79.6	328	700
14.	*Method B*	- do -	10:1	79.8	95.1	230	488
15.	- do -	- do -	10:2	66.6	89.0	280	620
16.	- do -	- do -	10:3	59.9	83.4	310	680
17.	*Method A*	SGF (pH 1.2)	10:1	86.4	98.4	186	421
18.	- do -	- do -	10:2	76.1	93.0	213	567
19.	- do -	- do -	10:3	64.7	88.7	255	620
20.	*Method B*	- do -	10:1	90.6	99.5	158	360
21.	- do -	- do -	10:2	82.7	95.0	198	513
22.	- do -	- do -	10:3	79.6	90.0	210	600

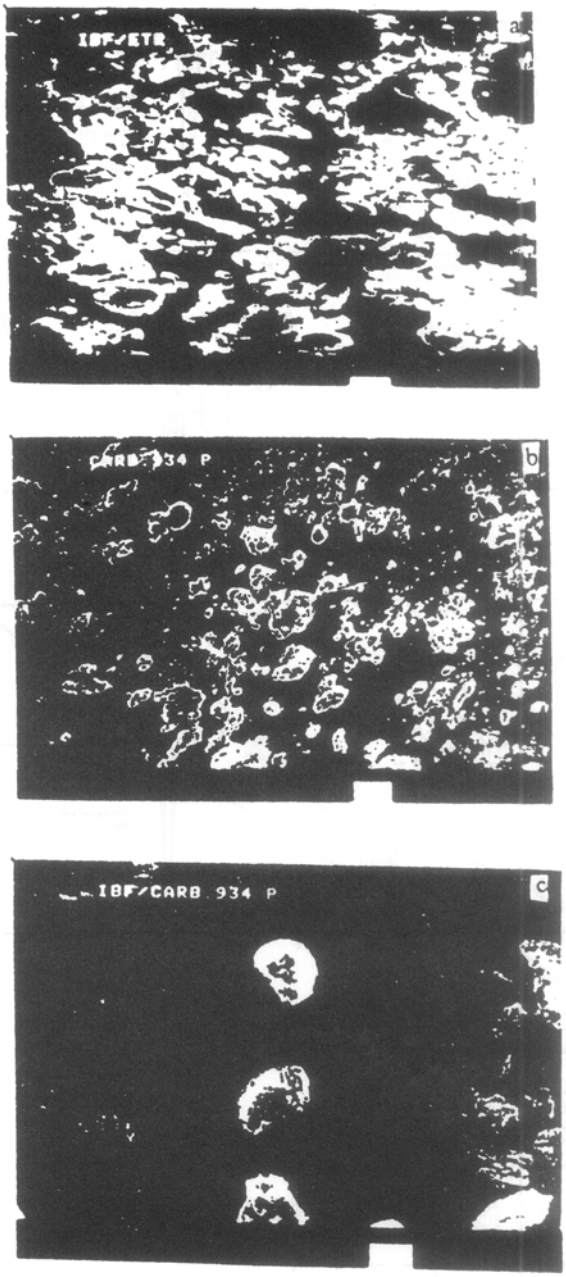

Fig. 1: Scanning Electron Photomicrographs of (a) Ibuprofen (precipitated from ethanol), (b) IBF / carbopol 934P Physical Miture and (c) CR Coprecipitates

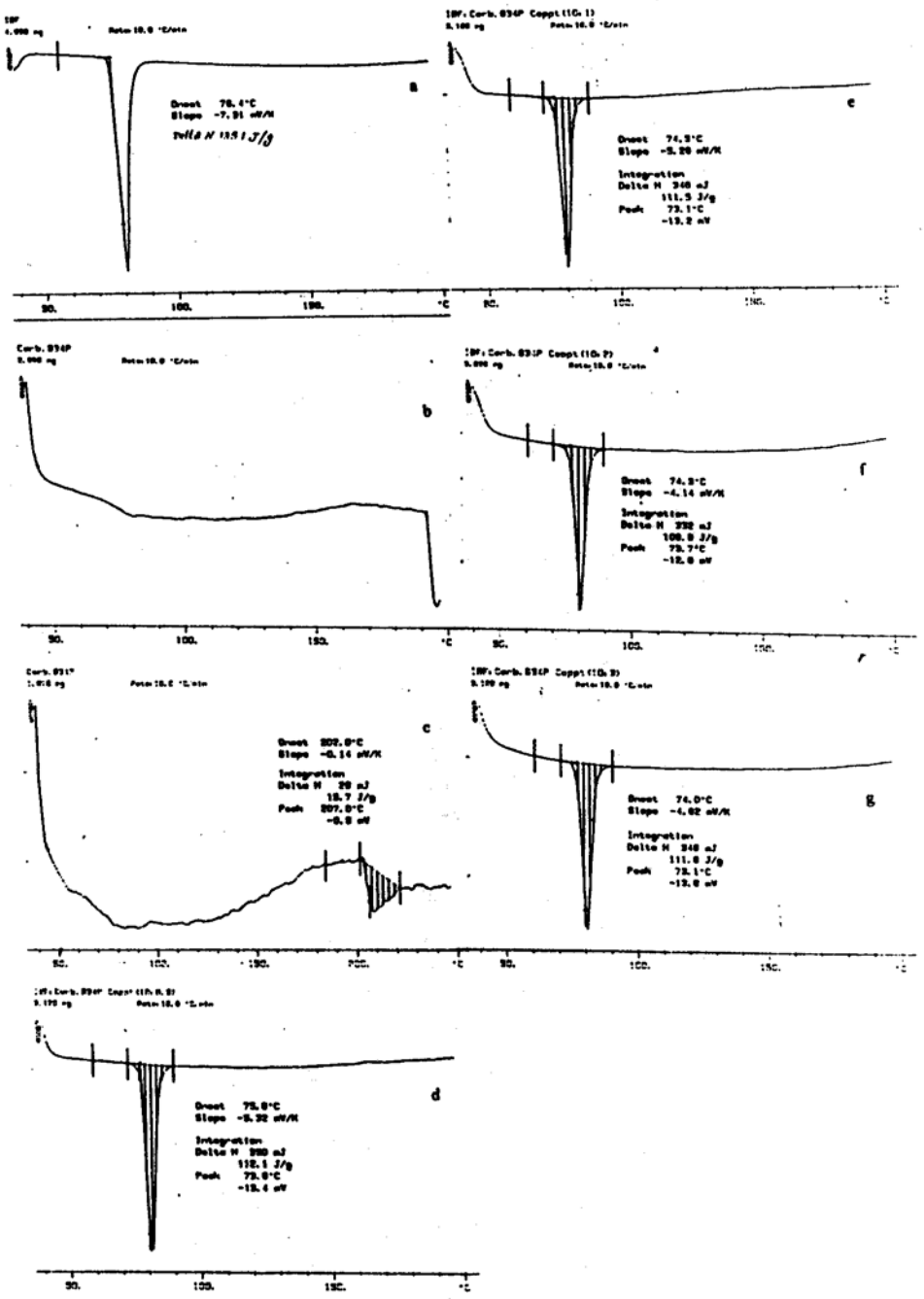

Fig. 2: DSC thermograms of (a) IBF, (b, c) Carbopol 934P and IBF/Carbopol 934P. CR Coprecipitates (d) 10:05, (e) 10:1, (f) 10:2, and (g) 10:3.

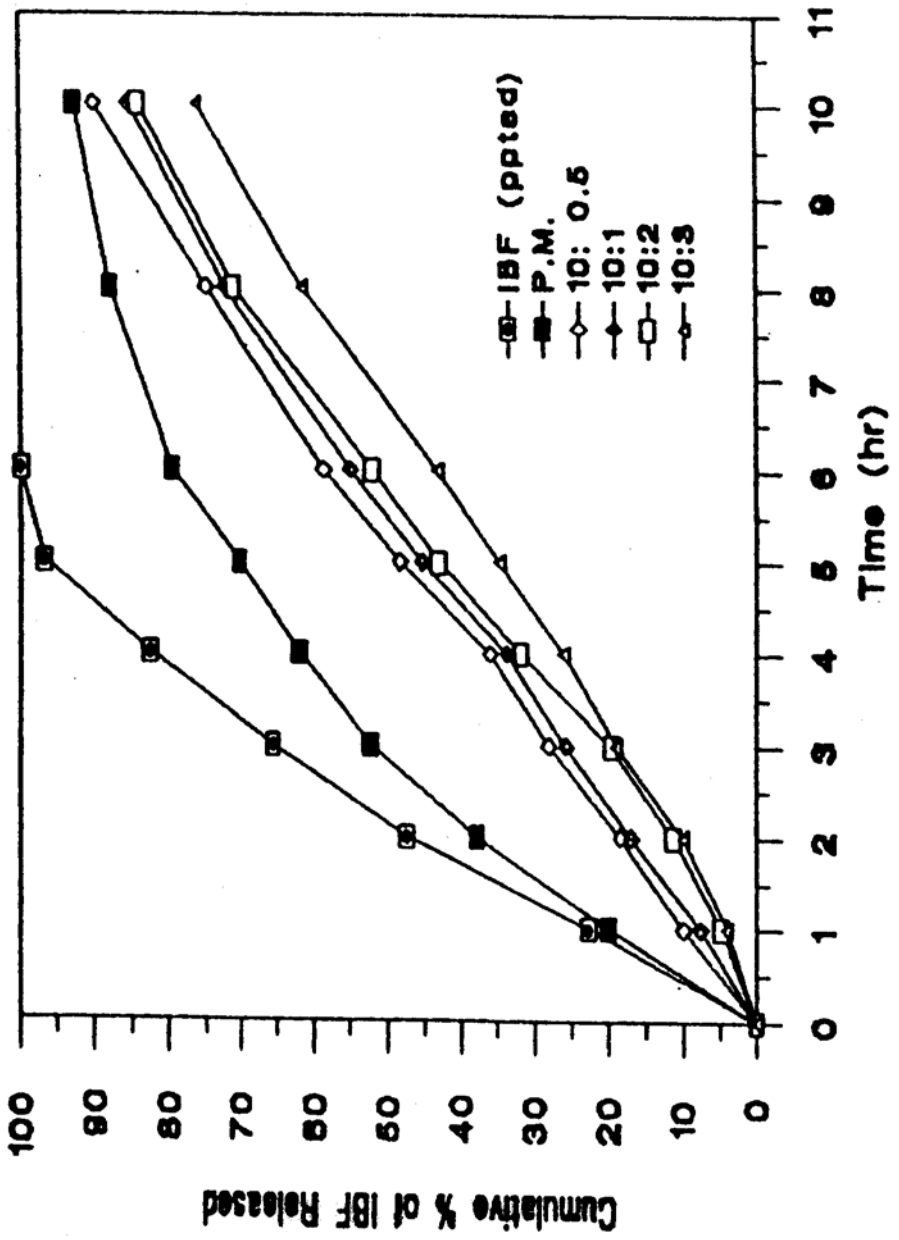

Fig. 3: Release Profiles of IBF (precipitated from ethanol), IBF and Carbopol 934P Physical Mixture (10:1), and CR Coperecipitates from pH 7.2 Phosphate Buffer Solution (method A).

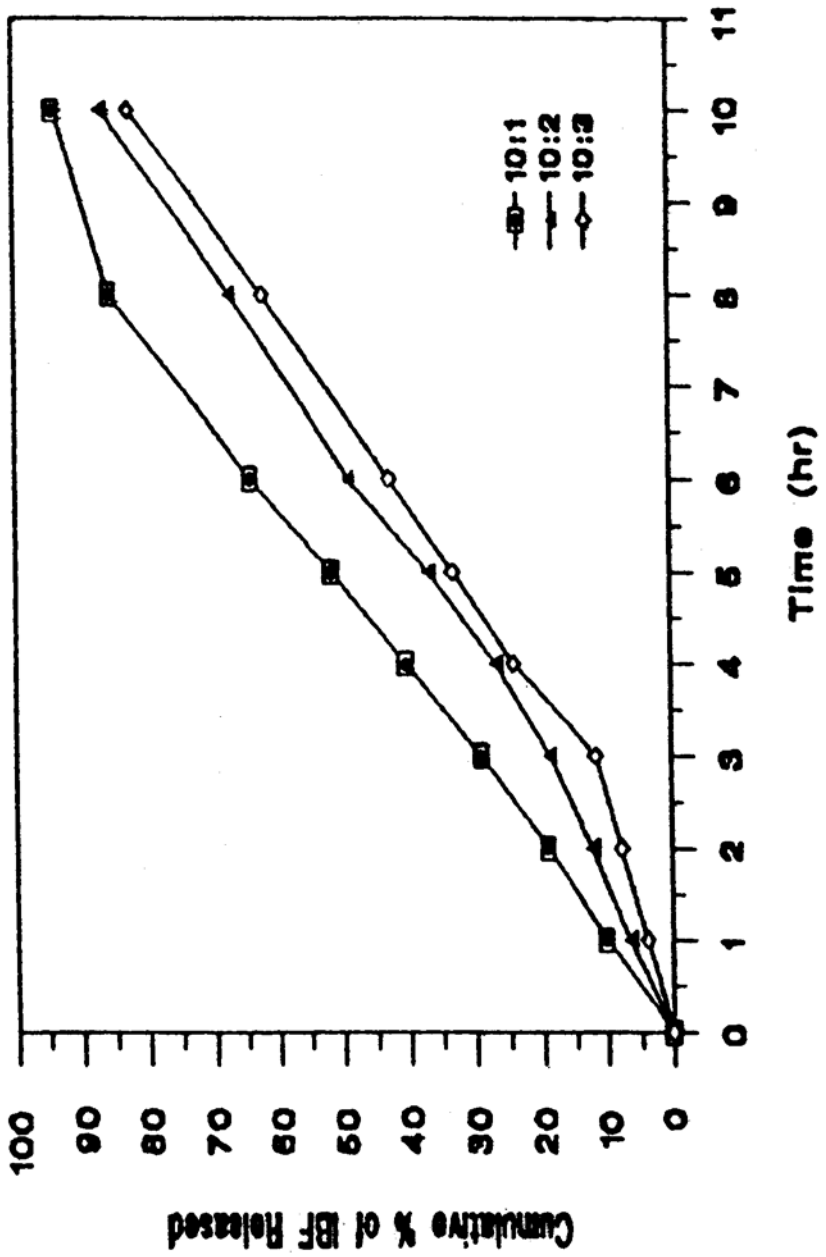

Fig. 4: Release Profiles of IBF/Carbopol 934P CR Coprecipitates from pH 7.2 Phosphate Buffer Solution (method B).

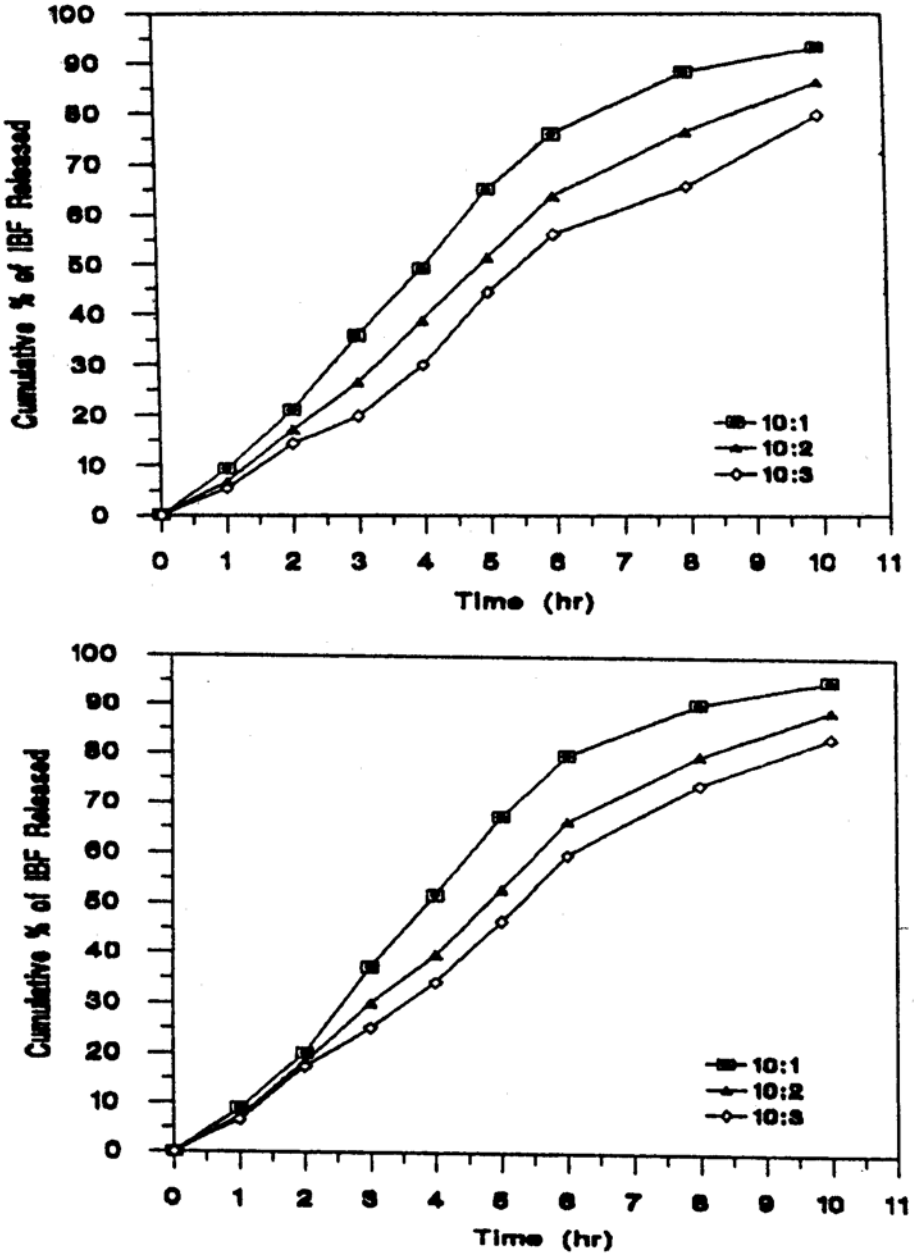

Fig. 5: Release Profiles of IBF/Carbopol 934P-NF CR Coprecipitates from Distilled Water (Upper) Method A, (Lower) Method B.

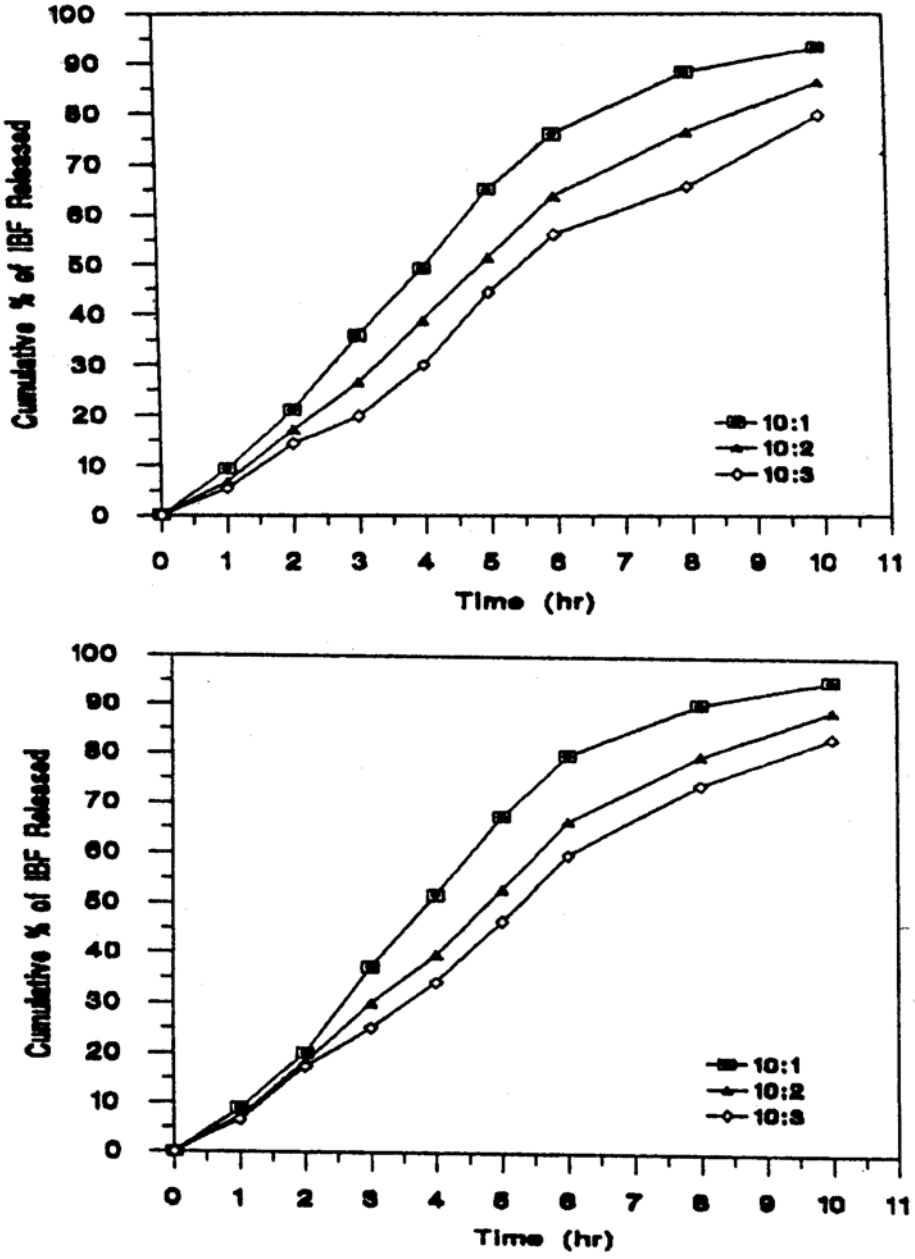

Fig. 6: Release Profiles of IBF/Carbopol 934P Controlled Release Coprecipitates from SGF (pH 1.2) (Upper) Method A (Lower) Method B.

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