Research Paper

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Controlled Release Coprecipitates of Ibuprofen and Carbopol® 934p-NF: Preparation, Characterization and *in Vitro* Drug Release

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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, Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC) and Infra Red (I R) Spectroscopy. 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 was found between the constituents of coprecipitate. The methods of preparation of the coprecipitates are simple and practical. Both of them minimize the use of toxic organic solvents and have very promising potentials to be used in the production of controlled release tablets.

Key words: Ibuprofen, Carbopol 934P-NF, controlled release coprecipitates, *in vitro* drug release

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Introduction

Coprecipitates of drugs and polymers have been investigated extensively for enhancing the dissolution of poorly soluble compounds (Simonelli *et al*., 1969; Kawashima *et al*., 1995; Goracinova *et al*., 1995; Khan and Zhu, 1998). The use of this technique in sustaining/controlling release of drugs has recently been examined (Karnachi *et al*., 1995; Khan *et al*., 1996). Carbopol 934P-NF is a polymer of acrylic acid that is a cross-linked with polyalkenyl polyether. It is a high molecular weight polymer that readily hydrates 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 (1988) reported that the drug release from carbomer tablets appeared to follow a zero order release mechanism in most of the cases. Moreover, the investigations in the recent few years (Melley *et al*., 1987; Huang and Schwartz, 1995) and the patent formulations of carbomers, especially of the widely used Carbopol 934P-NF (DeCrosta *et al*., 1987; Ueda *et al*., 1987) showed that carbomers occupy an important position in the field of controlled release drug delivery systems and needs further investigation and more research work to be done.

The objective of this research work 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.

Materials and Methods

Materials: Ibuprofen (IBF) was purchased from Xin Hua Pharmaceutical Factory (Shandong, China); Carbopol 934P-NF was obtained as a gratis supply from BF Goodrich Specialty Chemicals (Ohio, USA).

Methods: IBF-Carbopol 934P-NF coprecipitates at different drug to polymer ratio (D:P) were prepared using the following two methods:

Method A: IBF and the required amount of carbopol 934P-NF (Table 1) were dissolved in 7.5 ml of C_2H_5OH (USP). To this alcoholic solution, 0.025% (w/v) aqueous solution (200ml) of sucrose fatty acid ester at room temperature was added while stirring at a rate of 600rpm for 15 minutes, using a constant velocity electric stirrer (Especial Medical Instruments Factory, Shanghai, 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 into 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 stored in labeled bottles in a desiccator till further use (Khan and Zhu, 1998).

Method B: In this method IBF was dissolved in 3ml of C_2H_5OH. Aqueous solutions of the carbomer (200ml) 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 600rpm for 15 minutes. The instantly coprecipitated spherical micro-matrices were processed similarly as mentioned in "method A"(Khan and Zhu, 1998).

Table 1: Amounts of IBF and Carbopol 934P-NF used in the preparation of CR coprecipitates

IBF: Carb.	Amount of Carbopol used (g)	Carbopol used (%)	Drug Loading (%)
10:0.5	0.1	4.76	95.24
10:1	0.2	9.09	90.91
10:2	0.4	16.67	83.33
10:3	0.6	23.08	76.92

Table 2: Dissolution data of IBF-Carbopol 934P-NF coprecipitates in media with different pH environments

Method of Preparation	Dissolution Medium	Formulation	Cumulative % Released 6 hrs	Cumulative % Released 10 hrs	T_{50} min.	T_{90} min.
	pH 7.2 Phosphate Buffer Solution	IBF(precipitated From Ethanol)	100	-----	130	270
		Physical Mixture (10 : 1)	73.5	92.8	170	528
Method A	pH 7.2 Phosphate Buffer Solution	Coprecipitates 10 : 0.5	58.8	90.0	310	598
		10:1	55.1	85.5	328	639
		10:2	52.1	84.1	347	651
		10.3	43.2	76.1	405	708
Method B		10:1	64.1	93.9	292	546
		10:2	48.8	86.7	366	623
		10:3	42.6	82.4	406	650
Method A	Distilled Water	10:1	75.8	93.3	242	530
		10:2	63.7	86.1	292	655
		10:3	56.1	79.6	328	700
Method B		10:1	79.8	95.1	230	488
		10:2	66.6	89.0	280	620
		10:3	59.9	83.4	310	680
Method A	SGF (pH 1.2)	10:1	86.4	98.4	186	421
		10:2	76.1	93.0	213	567
		10:3	64.7	88.7	255	620
Method B		10:1	90.6	99.5	158	360
		10:2	82.7	95.0	198	513
		10:3	79.6	90.0	210	600

Characterization and Evaluation of the Coprecipitates Scanning Electron Microscopy (SEM): The shape and topography of the ingredients and that of the coprecipitates were studied by SEM (ISI-SX-40, Akashi, Japan). The samples for SEM were mounted on sample-stubs with double-sided adhesive tape, vacuum coated with gold, and photographed at the suitable magnification.

Differential Scanning Calorimetry (DSC): DSC patterns were determined using a differential scanning calorimeter (DSC-25 Mettler, Switzerland). Each sample was heated between 40 and 200°C with a scanning rate of 10°C min^{-1}. DSC thermogram of the carbomer was also obtained between 40 and 250°C.

Infra Red (IR) spectroscopy: IR spectra of all the formulations prepared were scanned using Model 983 Perkin Elmer I R. Spectrophotometer (USA), from the KBr pellets. The scanning range used was 4000 to 400 cm^{-1}.

Compression of the Coprecipitates: Coprecipitates corresponding to 200mg of IBF were individually poured into a die. Tablets were compressed on a single punch machine (Shanghai Mechanical Equipment Factory), using 9mm diameter flat-surfaced beveled punches. The tablet hardness ranged from 7 to 9kg.

***In Vitro* Drug Release studies:** Drug release investigations were carried out using the USP basket method (Khan and Zhu, 1998) with ZRS-4 Intelligent Dissolution Tester (Tianjin University Radio Factory, Tianjin, China) with a rotation speed of 100rpm. 900ml of each simulated gastric fluid (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 (0.45μm) and analyzed using 752 C Spectrophotometer (The 3rd Analytical Instruments Factory, Shanghai, China) at 222nm. 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 IBF released was calculated. T_{50} and T_{90} were also determined (Table 2) (Khan and Zhu, 1998).

Results and Discussion

Scanning Electron Microscopy (SEM): Fig. 1 showed the SEM of IBF, Carbopol 934P-NF, and their coprecipitates. Analysis of the SEM revealed that the large elongated crystals of IBF and the relatively small sized polyhedral particles of the carbomer have been transformed in to the spherical matrix structures, demonstrating totally different picture than that of the ingredients.

Differential Scanning Calorimetry (DSC): The thermograms of IBF did not show any major change in the endothermic peak with the carbomer (Fig. 2). However, slight shifts at the peak location of IBF towards lower temperatures were demonstrated. The coprecipitates also showed slight changes in the heat of fusion (ΔH_f) values.

Infra Red (IR) Spectroscopy: The IR 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 (COOH) groups at 1730 and 1706 cm^{-1}, respectively In case of the coprecipitates overlapping of the characteristic peaks was

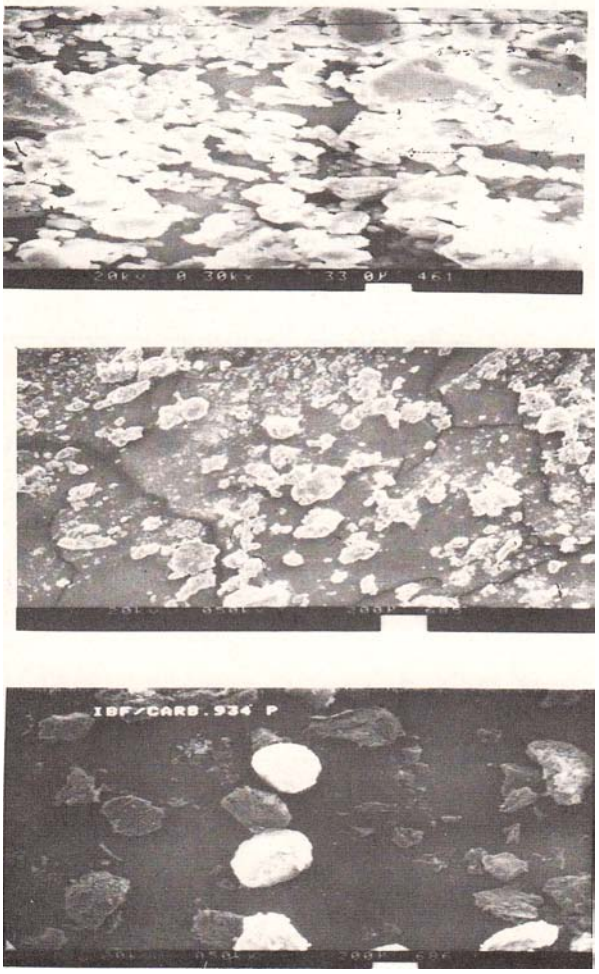

Fig. 1: Scanning Electron Photomicrographs of (a) IBF (precipitated from C_2H_5OH) (b) IBF/Carbopol 934P Physical mixture, and © CR Coprecipitates.

observed, indicating that no strong interaction exists between the drug and the carbomer.

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 structure 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.

***In Vitro* Drug Release Studies:** The release profiles of IBF (precipitated from C_2H_5OH), 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 (Figs. 3 to 6). T_{50}, T_{90} and the cumulative percent drug release at the end of 6h and 10 hrs are given in Table 2.

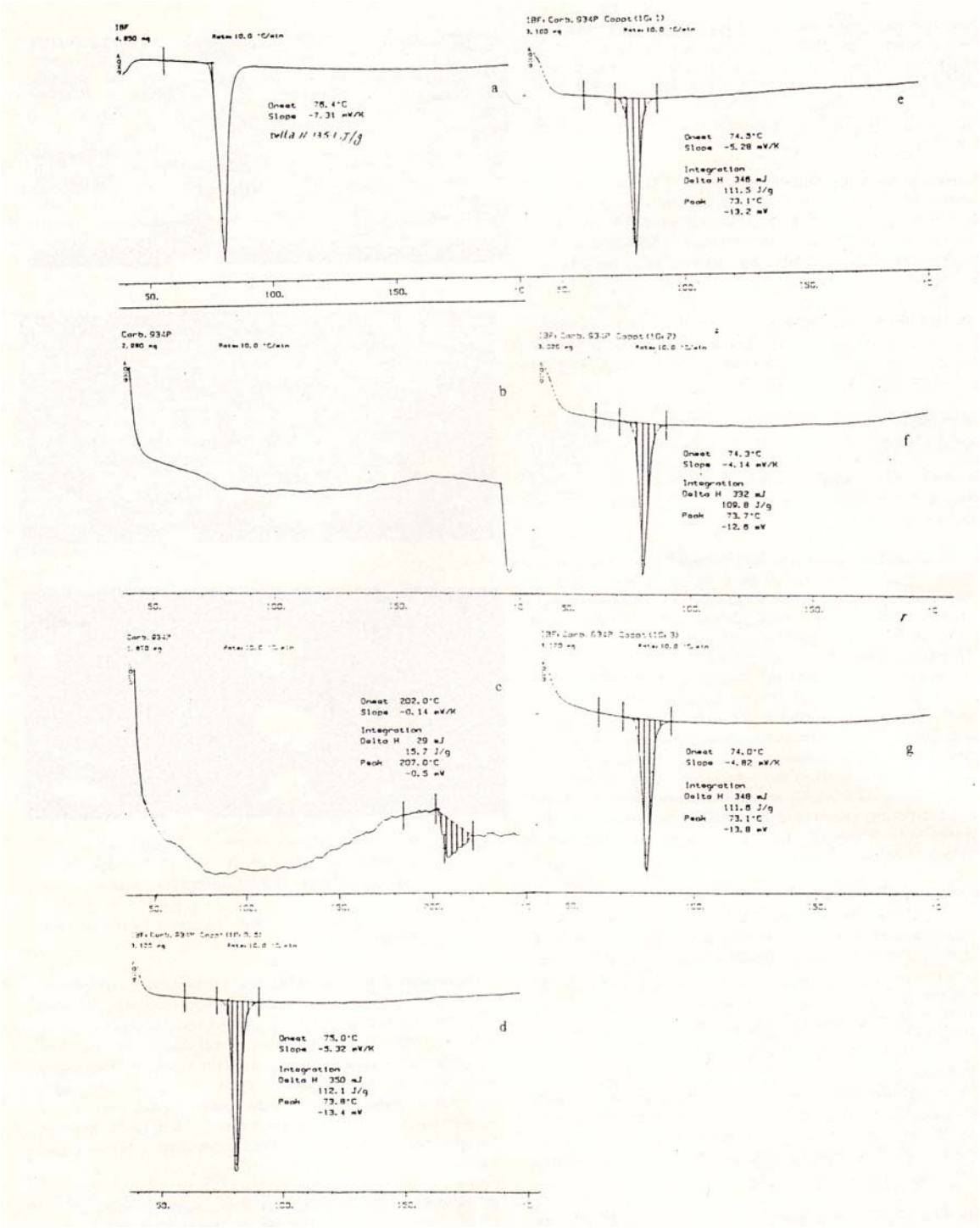

Fig. 2: DSC thermograms of (a) IBF, (b,c) Carbopol 934P, and IBF/Carbopol 934P CR coprecipitates (d) 10:0.5, (e) 10:1, (f) 10: 2 and (g) 10:3.

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. However, the degree of swelling in each of the medium was not the same. Peak swelling of the polymer was observed in pH 7.2 phosphate buffer solution. The reason for this effect is that 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, there is a shift from an anomalous behavior towards a Case II type release mechanism for the coprecipitates containing carbopol 934P-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 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 (COOH) groups causes maximum swelling, resulting in fewer and smaller regions of low microviscosity. 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 polymer, which results in a rapid decrease in its glass transition temperature (Tg) to the

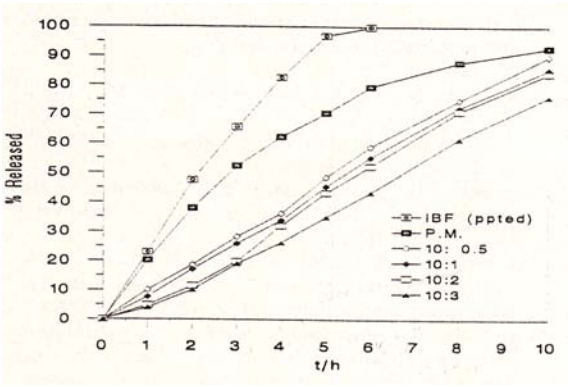

Fig. 3: Release profiles of IBF (precipitated from C_2H_5OH), IBF/Carbopol 934P physical mixture (10:1), and CR coperecipitates in pH 7.2 phosphate buffer solution (method A)

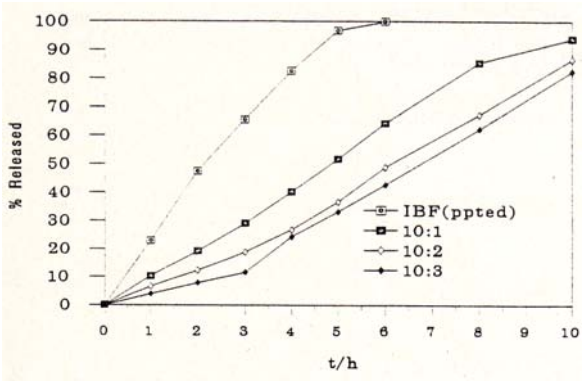

Fig. 4: Release profiles of IBF (precipitated from C_2H_5OH), IBF/Carbopol 934P physical mixture (10:1), and CR coperecipitates in pH 7.2 phosphate buffer solution (method B)

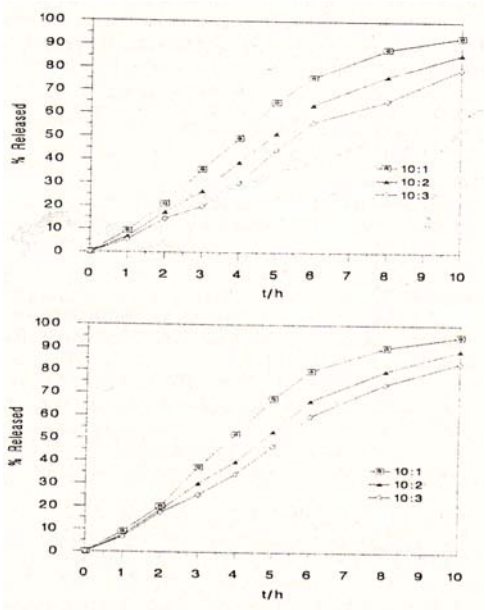

Fig. 5: Release profiles of IBF/Carbopol 934P CR coprecipitates in distilled water (upper) method A, (lower) method B.

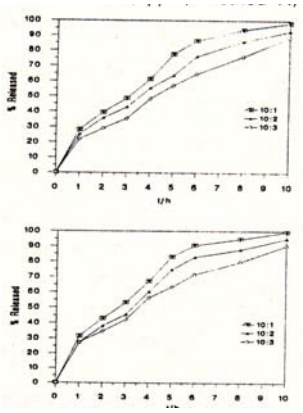

Fig. 6: Release profiles of IBF/Carbopol 934P CR coprecipitates SGF (pH 1.2) (upper) method A, (lower) method B.

temperature of the dissolution medium. Microscopically, there is a relaxation of the polymer chains due to the 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 (Ranga-Rao and Devi, 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 micropores. 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*. (1992) and several other authors who have studied the impact of concentration on dissolution kinetics (Capan *et al*., 1990; Seng *et al*., 1985).

From this research work concluded that 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.

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