Dissolution of Paracetamol Crystallized in the Presence of Poly(Vinyl acetate-co-Maleic Anhydride)

D. A. RAVAL, D. N. PARIKH[1] AND V. M. PATEL[2]

Sarvoday Kelavani Samaj, Yogidham, Rajkot-360 005, [1]Department of Industrial Chemistry, ISTAR, [2]N. V. P. College of Pure and Applied Sciences, Vallabh Vidyanagar-388 120, India.

Copolymer of vinyl acetate and maleic anhydride, poly (vinyl acetate-co-maleic anhydride) was prepared by precipitation polymerization and characterized. Paracetamol was crystallized in presence of different concentrations of poly (vinyl acetate-co-maleic anhydride). Crystals were characterized by sieve analysis, solubility and dissolution study. Crystallization of paracetamol in presence of poly (vinyl acetate-co-maleic anhydride) caused a marked enhancement in its dissolution rate with increase in concentration of poly (vinyl acetate-co-maleic anhydride) in crystallization medium.

The development of a meaningful dissolution procedure for drug products with limited water solubility has been a challenge to both the pharmaceutical industry and the agencies that regulate them. Drug release is usually the rate limiting process for absorption of low solubility oral drugs. Both *In-vivo* physiology and the physicochemical characteristics of the drug are important to the oral absorption of poorly water-soluble drugs. In the body, natural surfactants aid in the dissolution and subsequent adsorption of drugs with limited aqueous solubility[1]. *In vitro*, various methods have been used to enhance dissolution rates of poorly water-soluble drugs[2]. The methods include, for example, micronization, formation of water soluble salts of compounds, solid dispersion,

***For correspondence**

E-mail: deardipeshparikh@rediffmail.com

TABLE 1: CHARACTERIZATION OF COPOLYMER (VAMA)

Parameters	Values
Feed composition (moles) VA::MA	0.25::0.25
Copolymer composition (moles) VA::MA	0.27::0.11
Yield (g)	35
Acid values (mg of KOH/g)	394
Softening point	165°
Molecular weight	1056
Bulk density (g/ml)	0.327

TABLE 2: CHARACTERIZATION OF CRYSTALLIZED PARACETAMOL

Concentration of VAMA in crystallization medium (%)	Bulk density (g/ml)	Solubility in methanol (ml/g)	%Release within 4 min	Weight fraction of particles retained	
				> 700 microns	700-400 microns
0.0	0.602	6.3	67.5	0.292	0.248
0.1	0.605	6.3	72.9	0.225	0.265
0.2	0.660	6.2	87.3	0.221	0.408
0.4	0.686	6.0	92.2	0.126	0.533

spherical crystallization and crystallization of drugs in the presence of surfactants or hydrophilic polymers. Present work deals with the investigation of dissolution properties of paracetamol crystallized in the presence of different concentrations of poly (vinyl acetate-co-maleic anhydride) (VAMA).

The copolymers of vinyl acetate with maleic anhydride, VAMA, was prepared by precipitation polymerization as per the method reported in our earlier work[3]. The copolymer was characterized by its acid value, softening point, solubility, molecular weight and bulk density measurement[4]. The dried copolymer was powdered and sieved to get uniform particle size (200 mesh) before use.

Crystallization was carried out by adding a solution of paracetamol (5 g/12 ml) in hot methanol to 50 ml of water containing 0, 0.1, 0.2 and 0.4% VAMA. The mixture was cooled to 3° and after 15 min, the resulting crystals were collected by filtration. Crystals were characterized by solubility, sieve analysis and dissolution study. Dissolution study was carried out using USP dissolution apparatus 1 in simulated gastric fluid (pH 1.2) at 37°. In a typical experiment, 1 g of crystallized paracetamol was suspended in 900 ml of acid buffer and kept stirred at 50 rpm. The percentage of paracetamol dissolved at the end of 4 min of dissolution test was determined by withdrawing the liquid sample (10 ml) and measuring its absorbance at 430 nm using Spectronic 21 UV/Vis spectrophotometer[5].

The copolymer VAMA is a light, white powder. Characterization of copolymer sample prepared from equimolar ration of monomers reveals that it is a copolymer with low molecular weight (1056), which was measured as relative value by gel permeation chromatography using polystyrene as standard. The softening point is 165°. The acid value of copolymer sample was found to be 394 mg of KOH/g of the copolymer. Calculated from this value, the relative molar composition of the copolymer was found to be 0.27:0.11 (vinyl acetate:maleic anhydride). The molar composition of the copolymer reveals that the maleic anhydride content is lower in the resulting copolymer than that in the feed (Table 1). VAMA is soluble in dimethyl formamide, tetrahydrofuran, butanol, ethanol, methanol, acetone and water, whereas it is insoluble in hexane, toluene and xylene. Crystallization of paracetamol in the presence of VAMA caused a marked enhancement in its dissolution rate. With increasing concentration of VAMA in crystallization medium, the obtained crystals exhibited faster dissolution profiles. The percentage of paracetamol dissolved within the first 4 min of dissolution test increased from 67.5% for untreated paracetamol to 92.2% for paracetamol crystallized in presence of 0.4% VAMA (Table 2)

The enhancement of dissolution rate is attributed to adsorption of VAMA onto the surface of paracetamol crystals, which increases their wettability. Adsorption of VAMA also resulted into higher bulk density of the crystallized material. Decrease in average particle size of paracetamol obtained in presence of VAMA is another reason for the higher dissolution rate. There was no significant difference between the methanol solubility of untreated paracetamol and that of samples crystallized in the presence of VAMA.

REFERENCES

1. Chiou, W.L., Chen. S.J. and Athanikar, N., **J. Pharm. Sci**., 1976, 65, 1702.
2. Rao, B.S. and Murthy, K.V.R., **Int. J. Pharm**., 2002, 231, 72.
3. Patel, H., Raval, D.A., Madamvar, D. and Sinha, T.J.M., **Angew. Makromol. Chem**., 1997, 245, 1.
4. Mark, H.F., In; Encyclopedia of Polymer Science and Engineering, John Wiley and Sons, 1987, 3.
5. Jefferey, G.H., In; Quantitative Chemical Analysis, 5th Edn., Longmann Sci. and Tech., 1989, 678.

Accepted 16 February 2006
Revised 2 April 2005
Received 19 April 2004
Indian J. Pharm. Sci., 2006, 68 (1): 93-94