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Studies on in vitro release behaviour of indomethacin-loaded polystyrene microparticles

S. Tamilvanan, B. Sa *

Department of Pharmaceutical Technology, Jadavpur University, Calcutta 700 032, India

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Abstract

Indomethacin-loaded polystyrene microparticles were prepared by emulsion-solvent evaporation method from an aqueous system. The effect of different parameters like concentration of aqueous phase emulsion stabilizer, volume of the organic disperse phase and initial drug loading on drug content and release of drug were investigated. Keeping the drug-polymer ratio constant, variation in the concentration of emulsion stabilizer and volume of the organic disperse phase did not produce any significant change either in the actual drug content or in the drug release. The initial drug loading, however, greatly influenced the drug release which, as revealed by different analyses, was due to the presence of drug in different physical forms in the microparticles. Physical characterization using thin layer chromatography and infrared spectroscopy apparently revealed the absence of drug degradation and sizeable interaction between the drug and the polymer. Regardless of lack of interaction, thermodynamic properties such as solubility of the drug in the polymer and fraction of the drug present in crystalline form were determined by using differential scanning calorimetry and was further substantiated with scanning electron micrography and X-ray diffraction analysis.

Keywords: Indomethacin; Polystyrene microparticles; Drug release; Soluble form; Crystalline form

1. Introduction

Indomethacin, a non-steroidal anti-inflammatory drug, has been successfully used in the treatment of soft tissue problems associated with trauma, osteoarthritis and rheumatoid arthritis (Marion, 1973). However, drug therapy with this agent is associated with several adverse effects (Borta and Koff, 1992) and the frequency and the severity of the adverse effects are well correlated with the plasma concentration of the drug (Alvan et al., 1975; Bechgaard et al., 1982). Clinical study revealed that conventional dose-dumping indomethacin capsules induce several adverse effects like epigastric pain, peptic ulcer, vertigo, headache (Rowe and Carless, 1981a). On the other hand, controlled release indomethacin capsules maintain adequate therapeutic plasma level of the drug avoiding peaks and troughs (Rowe and Carless, 1981b) and thereby, minimize the emergence of

* Corresponding author. Tel.: +91-32-1855660; fax: +91-33-4720964.

E-mail address: mediacom@satyam.net.in (B. Sa)

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adverse effects and increase patient compliance by reducing the frequency of administration. However, when compared with single unit sustained release tablets, multiunit controlled release dosage forms pass through the gut as if a solution avoiding the vagaries of gastric emptying and different transit rates (Beckett, 1980) and release drugs in a more predictable manner (Follonier and Doelkar, 1992). Moreover, a multiunit system spreads in a large area of the absorbing mucosa and prevents exposure to a high drug concentration, when compared to single unit dosage form on chronic dosing (Davis et al., 1984).

Preparation of multiunit controlled release microparticles by the conventional emulsion–solvent evaporation method requires large volume of hazardous organic solvents (Sa, 1991; Bodmeier et al., 1994). To avoid this problem, the above method has been modified where aqueous system have been used to keep the volume of the organic solvent to a minimum (Barkai et al., 1990; Sa et al., 1996). In the previous paper (Tamilvanan and Sa, 1998), we reported the effect of various parameters on the development of indomethacin-loaded polystyrene microparticles from an aqueous system containing methylcellulose as emulsion stabilizer.

The objective of this work was to study the effect of different formulation variables on the release of indomethacin from polystyrene microparticles with a view to optimize a formulation which could be useful as controlled release dosage form. Polystyrene was selected as a model polymer.

2. Materials and methods

2.1. Materials

Indomethacin (Indian Pharmacopoeia) and polystyrene (Grade McG-100, general purpose) were sample gifts. Methylcellulose (3000–4000 mps, Loba Chemi, India) and all other analytical reagent grade chemicals were obtained commercially and used as received.

2.2. Methods

2.2.1. Preparation of microparticles

The method of preparation of indomethacin-loaded polystyrene microparticles by emulsion–solvent evaporation method using an aqueous system has been reported previously (Tamilvanan and Sa, 1998). In brief indomethacin was dissolved or dispersed in dichloromethane solution of polystyrene at 15°C and was emulsified at 500 rev min^{-1} in 150 ml methylcellulose mucilage and stirred for 2 h. The resulting microparticles were poured in 600 ml cold distilled water and was stirred for a further 2 h. The microparticles were filtered, washed with water and vacuum dried. The experimental parameters varied were concentration of methylcellulose, volume of the organic disperse phase and drug loading.

2.2.2. Sizing of microparticles

Microparticles were separated into different size fraction by sieving for 15 min on a mechanical shaker using a nest of standard sieves.

2.2.3. Determination of indomethacin content

Actual amount of indomethacin present in different sized microparticles was determined following the method reported previously (Sa et al., 1996). In brief accurately weighed amount (≈ 25 mg) of indomethacin-loaded polystyrene microparticles was dissolved in 25 ml of chloroform and was assayed spectrophotometrically at 321 nm using a double beam spectrophotometer (model 200-20 Hitachi, Japan). The polymer did not interfere with the assay.

2.2.4. Drug release study

Release of indomethacin from the microparticles were studied following the USP paddle method. About 100 mg of the microparticles, accurately weighed, were immersed in USP phosphate buffer solution (pH 6.8, 900 ml, 37 ± 1°C) and rotated at 75 rev min^{-1}. Aliquots (10 ml) of the dissolution medium were withdrawn at predetermined time and were replenished immediately with same volume of fresh medium. Withdrawn samples, following suitable dilution, were assayed spectrophotometrically at 320 nm.

2.2.5. Thin layer chromatography (TLC)

Qualitative TLC was carried out using 10×10 cm precoated silica gel 60 aluminium backed TLC sheets with layer thickness of 0.25 mm. A dichloromethane solution of an accurately weighed amount of indomethacin and drug-loaded microparticles was applied, using a sample applicator (Camag Nanomet 11 with 1 μl capillary and holder), directly onto the TLC sheet, leaving 2 cm from the edge. The sheet was developed with Benzene–Ether–Glacial acetic acid–Methanol $(120 + 60 + 18 + 1)$ system in Camag chamber for 20 min. After development, the sheet was air dried and examined under UV light. The experiment was duplicated under identical conditions.

2.2.6. Infrared spectroscopy

Infrared spectra of indomethacin and drug-loaded microparticles were determined in the range of 4000–650 cm^{-1} using an I.R. spectrophotometer (model IR-700, Jasco, Tokyo, Japan) from KBr pellets.

2.2.7. Scanning electron microscopy (SEM)

The dried microparticles following sputter coating with silver (Edward S150 model, UK) were examined with a scanning electron microscope (Jeol JSM 35CF, Japan) for surface topography.

2.2.8. Differential scanning calorimetry (DSC)

DSC scans of indomethacin and drug-loaded microparticles were performed in an atmosphere of nitrogen in the following way: weighed amount (≈ 5 mg) of sample were kept in hermetically sealed aluminium pans and were heated at a scan speed of 10°C min^{-1} over a temperature range of 135–175°C in a differential scanning calorimeter (Perkin–Elmer, DSC-2 calibrated with Indium) at a chart speed of 10 mm min^{-1}.

2.2.9. X-ray diffraction study

Indomethacin and drug-loaded microparticles were subjected to X-ray diffraction study in a X-ray diffractometer (ISO-DEBYEFLEX 3000, CuK_{α} radiation, 10–50°2θ) fitted with SEIFERT X DAL 3000 software.

3. Results and discussion

Indomethacin-loaded polystyrene microparticles were prepared by emulsion-solvent evaporation method from an aqueous system containing methylcellulose as emulsion stabilizer. Post-manufacturing sieving revealed that the microparticles were confined within the size range of 177–550 μm. Although the geometric mean diameter of the microparticles were found to vary depending on methylcellulose concentration in the aqueous phase, volume of dichloromethane in the organic disperse phase and the initial drug load (Tamilvanan and Sa, 1998), microparticles having mean diameters of 275, 327.5 and 427.5 μm were considered for evaluation. The effect of variation in the concentration of methylcellulose, used as

Table 1
Effect of methylcellulose concentration in aqueous dispersion medium on indomethacin content of polystyrene microparticles[a]

Methylcellulose concentration (% w/v)	Actual drug content (mean + S.D., $n = 4$) of microparticles having average diameter		
	275 μm	327.5 μm	427.5 μm
0.00625	43.19 ± 1.08	43.88 ± 1.62	43.19 ± 2.13
0.0125	44.52 ± 0.87	42.92 ± 1.24	45.32 ± 0.38
0.025	45.52 ± 0.32	44.67 ± 0.30	46.02 ± 0.43
0.05	44.10 ± 0.86	44.75 ± 1.08	43.76 ± 1.63
0.10	44.33 ± 0.42	44.61 ± 0.94	43.63 ± 0.22
0.20	45.27 ± 1.22	44.40 ± 0.35	42.34 ± 2.06

[a] The theoretical drug content in each case was 45% w/w.

Table 2
Effect of initial drug loading on indomethacin content of polystyrene microparticles prepared with 0.10% w/v methylcellulose concentration in aqueous dispersion medium

Theoretical drug load (% w/w)	Actual drug content (mean + S.D., $n = 4$) of microparticles having average diameter		
	275 μm	327.5 μm	427.5 μm
20	20.08 ± 1.05	18.38 ± 0.99	19.06 ± 1.17
30	30.79 ± 3.09	30.29 ± 0.41	29.99 ± 1.20
40	41.03 ± 0.42	40.79 ± 0.32	42.89 ± 0.54
50	51.80 ± 2.91	50.34 ± 1.76	51.60 ± 1.08
60	60.42 ± 6.03	60.93 ± 1.19	61.97 ± 0.88
70	71.88 ± 1.56	71.33 ± 1.24	70.07 ± 1.56

aqueous phase emulsion stabilizer, on actual drug content in different sized microparticles have been represented in Table 1. The actual drug contents were found to be very close to the theoretical drug contents in each of the sizes studied. Keeping the methylcellulose concentration and theoretical drug loading constant at 0.1 and 45% respectively, increase in the volume of dichloromethane in the disperse phase from 5 to 11 ml with an increment of 2 ml varied the actual drug content from 41.77 to 44.19% in different sized microparticles. Further, a variation in the initial drug loading from 20 to 70% did not produce any significant change in actual drug contents from their respective theoretical drug loads (Table 2). These observations indicated that methylcellulose concentration, volume of dichloromethane and theoretical drug loading did not affect the actual drug content in the microparticles. The juxtapositioning of the actual and theoretical drug contents could be due to insignificant partitioning of the water insoluble drug in aqueous phase during solvent evaporation stage of microparticles formation.

When the amount of drug released from the microparticles prepared with variable concentration of methylcellulose were plotted against time, the resulting release profiles were found to be almost superimposable indicating, apparently, that methylcellulose did not produce any predictable change in drug release pattern. In order to ascertain that methylcellulose had no effect on drug release characteristics, a more stringent statistical analysis in the form of two criteria classification of analysis of variance (ANOVA) was done. By using data in the form of percent indomethacin released from three different batches of each formulation (Table 3), ANOVA was calculated at the first, third and fifth hour

Table 3
Amount of indomethacin released in phosphate buffer (pH 6.8) from polystyrene microparticles (275 μm) having 45% w/w drug load and prepared with variable concentrations of methylcellulose[a]

Methylcellulose concentration (% w/v)	% Indomethacin released at		
	Hour 1	Hour 3	Hour 5
0.00625	22.54 (± 0.69)	36.34 (± 1.55)	43.40 (± 1.99)
0.0125	20.53 (± 3.80)	32.07 (± 5.33)	41.21 (± 5.02)
0.025	22.73 (± 0.82)	36.31 (± 0.85)	43.28 (± 1.02)
0.05	19.87 (± 4.39)	32.82 (± 4.77)	41.06 (± 4.38)
0.10	19.95 (± 4.05)	32.46 (± 6.18)	41.60 (± 4.51)
0.20	22.42 (± 1.79)	35.06 (± 1.65)	44.26 (± 1.31)

[a] Figures in parentheses indicate standard deviation (n = 3).

and was used as a representative of the entire dissolution profile. Table 4 shows that, at all the times studied, the calculated $F_{5,10}$ values for indomethacin release from the microparticles, prepared with variable concentration of methylcellulose as aqueous phase emulsion stabilizer, did not exceed the tabular $F_{5,10}$ value at 95% confidence limit. Similarly, the calculated $F_{2,10}$ values for the release of indomethacin from different batches of microparticles did not exceed the tabular $F_{2,10}$ value at 0.95 level. Similar observations were noted for the microparticles having different sizes. This led to the conclusion that there was no significant difference among the release of indomethacin from the microparticles prepared with different concentrations of methylcellulose as aqueous phase emulsion stabilizer. Further, a variation in the volume of dichloromethane in the organic disperse phase did not show any appreciable change in drug release (Fig. 1).

While 90% indomethacin powder dissolved within 60 min, the release of the drug from the microparticulate dosage form extended over a period of time depending on the drug loads in the microparticles (Fig. 2). However, the drug loads influenced the release pattern in a peculiar manner. The release of indomethacin from 20% drug-loaded microparticles was the highest. Increase in drug load from 20 to 50% with an increment of 10% decreased the release gradually. Further increase in drug load above 50% in the microparticles resulted in higher release. It appears that upto 50% drug load, indomethacin was dispersed into polystyrene microparticles and no more than 50% drug could be incorporated into the microparticles. At 60 and 70% drug loads, indomethacin, in excess of 50%, might have been surface absorbed which resulted in the higher anamalous release. Before proceeding for further studies, the compatibility of the drug with the polymer and any possible drug decomposition or drug-polymer interaction were checked through qualitative thin-layer chromatography and infrared spectroscopy. Qualitative TLC analyses showed that the *Rf* value of the drug obtained from the microparticles was the same as that of the pure drug. Infrared spectroscopy studies revealed that the characteristic absorption bands for different functional groups of indomethacin present in the microparticles were similar to those obtained from the pure drug and to the reported values (Table 5). Although inconclusive without further evaluation, these studies explained that the drug was compatible with the polymer and neither any decomposition of the drug nor any drug-polymer interaction occurred in the microparticles containing 20–70% drug load.

DSC thermograms of indomethacin and the microparticles containing variable amount of drug load are presented in Fig. 3. While indomethacin showed a sharp endothermic peak at 160° which was close to the reported melting point (160–161°C) of Form I of the drug (Lund, 1994), the microparticles containing 20% drug did not show any endothermic peak. This suggests that, at this concentration, the drug was dispersed at a molecular level in the polymer, at least so at its melting temperature. Babay et al. (1988) and Benita et al. (1988) reported that at low concentration, indomethacin was present in a molecular dispersion or solid solution state in ethylcellulose and ethyl-

Table 4
F values[a] for release of indomethacin at selected times from polystyrene microparticles (275 μm) prepared with variable concentrations of methylcellulose

Time (h)	Calculated $F_{5,10}$ values for methylcellulose concentration	Tabular $F_{5,10}$ values at 0.95 level	Calculated $F_{2,10}$ values for different batches	Tabular $F_{2,10}$ value at 0.95 level
1	0.38		0.54	
2	0.44	3.33	0.49	4.10
3	0.27		0.26	

[a] Calculated from two criteria classification of anlaysis of variance.

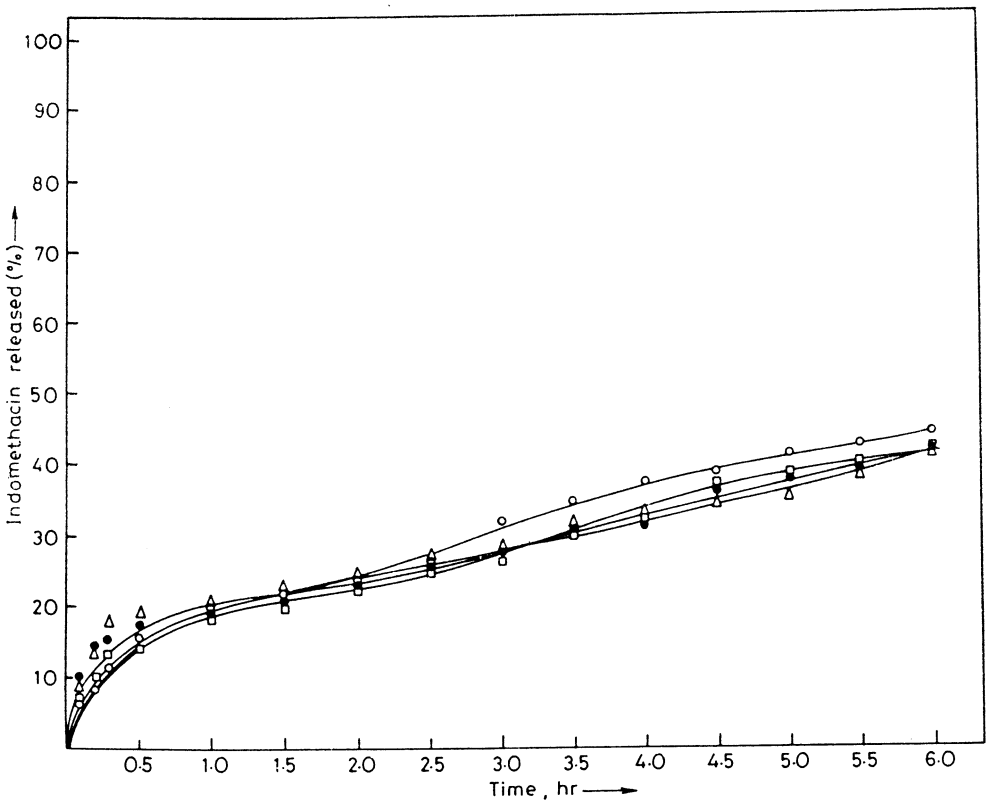

Fig. 1. Effect of volume of dichloromethane in the disperse phase on indomethacin release from polystyrene microparticles (275 μm) having 45% drug load. Key, (○), 5 ml; (□), 7 ml; (△), 9 ml and (●), 11 ml.

cellulose-poly (ethylene glycol) microspheres respectively. On the other hand, the thermal events corresponding to the melting of indomethacin in the high drug-loaded microparticles were clearly observed in the DSC thermogram at a temperature close to that obtained from the pure drug. The heats of melting of the entrapped drug in the microparticles containing more than 20% of the drug were measured by taking the overall areas of the endothermic peak between 135 and 175°C using the conventional paper cutting method and the equation for energy calculation is given below

$$\Delta H_S = \Delta H_{In} \times \frac{W_{In}}{W_S} \times \frac{A_S}{A_{In}} \times \frac{R_S}{R_{In}} \times \frac{S_{In}}{S_S} \quad (1)$$

where ΔH is change of entropy, ΔH_{In} is 134 m Cal, W_S is sample weight in milligram, W_{In} is 3.05 mg, A_S is peak area in square inches, A_{In} is 19.66 mg, R_S is range sensitivity in m Cal s^{-1}, R_{In} is 10 m Cal s^{-1}, S_S is chart speed in inch s^{-1}, S_{In} is 40 mm min^{-1}, In is indium and S is sample. When the values of ΔH were plotted against the encapsulation ratios, a straight line relationship was obtained (Fig. 4). By using this calibration data, the concentration of indomethacin in any other sample of polystyrene microparticles can be determined by simply measuring the endothermic heat (Theeuwes et al., 1974). This plot also allowed to calculate the exact amount of the drug soluble in the polymer as the concentration at which the heat of melting is zero. For this, linear regression analysis of the plot in Fig. 4 was performed and an equation of the straight line was obtained as follows;

$$Y = (0.6075)\ X + 18.5331, \text{ correlation coefficient} = 0.9920 \quad (2)$$

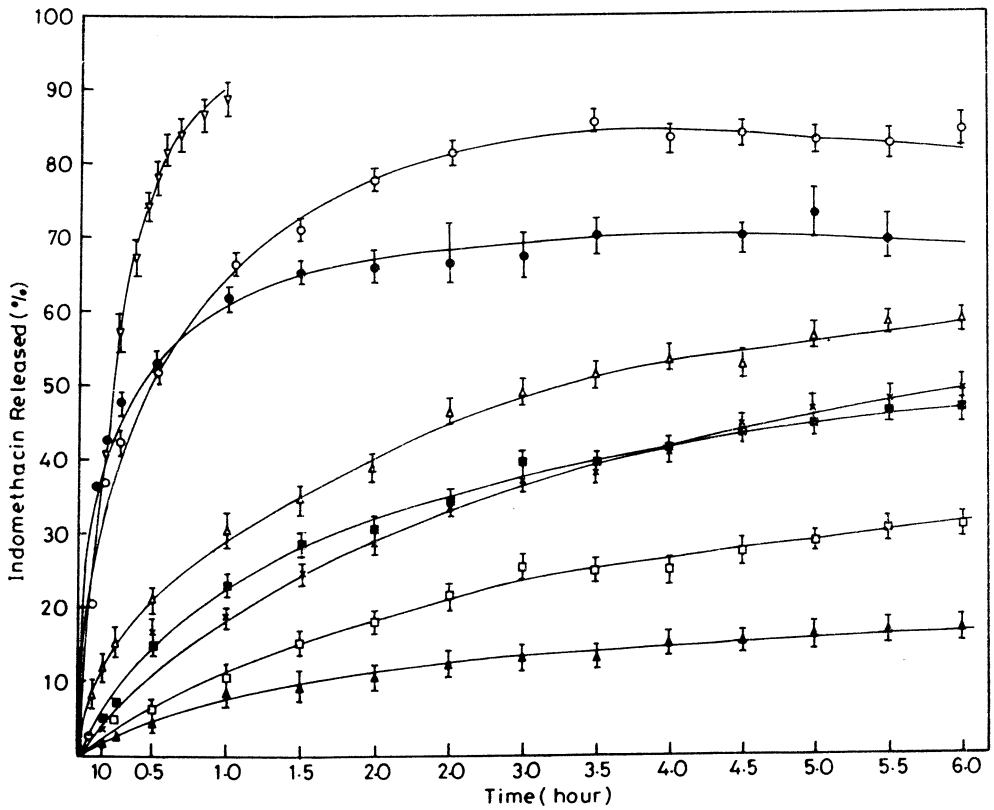

Fig. 2. Effect of initial drug loading on indomethacin release in pH 6.8 from polystyrene microparticles having 427.5 μm diameter. Key, (○), 20%; (●), 30%; (△), 40%; (X), 45%; (▲), 50%; (□), 60%; (■), 70% w/w and (▽), indomethacin powder.

In Eq. (2), values 0.6075 and 18.5331 represent the slope and the intercept of the line, respectively in Fig. 4. The value of the intercept was the solubility of indomethacin in polystyrene at its melting temperature. Since, at 20% drug loading, the entrapment efficiency was $99.68 \pm 0.38\%$ (Tamilvanan and Sa, 1998), the amount of indomethacin dissolved in the polymer was equal to

Table 5
Characteristic group absorption frequencies, obtained from infra-red spectroscopy studies, for functional groups of indomethacin (IMC) and IMC-loaded polystyrene microparticles

Functional group	Bands occurring at wave numbers cm^{-1}			
	IMC	30% IMC-loaded microparticles	70% IMC-loaded microparticles	Reported values[a]
Carboxylic OH deformation	927	925	927	925
C = O stretch (ketone)	1719	1719	1717	1715
Aromatic C = C stretch	1593	1602	1598	1600
C–Cl vibration	754	754	754	750
O–CH_3 deformation	1457	1453	1454	1450

[a] O'Brien et al., 1984.

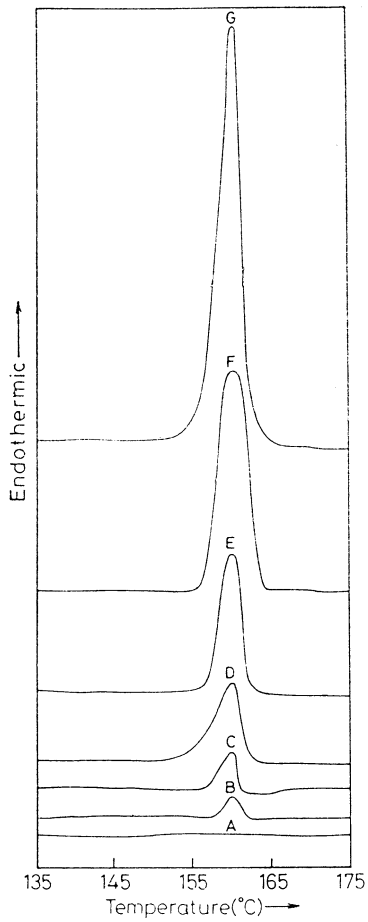

Fig. 3. DSC thermograms of polystyrene microparticles containing 20% (A), 30% (B), 40% (C), 50% (D), 60% (E), 70% (F) w/w indomethacin and of indomethacin (G).

18.5331 g 100 g^{-1} of microparticles, and was close to the theoretical value (20%). However, the soluble fraction obtained from this study was lower than that obtained by Babay et al. (1988) for indomethacin-loaded ethylcellulose microspheres. This difference may be related to the higher miscibility of indomethacin with ethylcellulose than with polystyrene.

In order to substantiate that the drug was present in solid solution state in the polymer matrix, X-ray diffraction analysis and scanning electron micrography were conducted with microparticles containing 20% indomethacin. X-ray diffraction study, however, demonstrated the presence of a few very faint X-ray diffraction bands (Fig. 5). SEM also showed the existence of only a few drug crystals on the smooth surface (Fig. 6A). If indomethacin was present entirely in a stable molecular form (solid solution) in the microparticles containing 20% drug loading, there should not be either any peaks in the X-ray diffractogram or any drug crystals on the surface of the microparticles. The estimation of soluble fraction of indomethacin, as described earlier, revealed that 92.67% of the drug at 20% drug loading was entirely present in a state of stable molecular dispersion and hence, only 7.33% might be present in crystalline state. This small amount of crystalline indomethacin present in 20% drug-loaded microparticles might have been responsible for the generation of X-ray diffraction peaks of very low intensity (Fig. 5) and only a few crystals in SEM (Fig. 6A).

Irrespective of drug loadings ranging from 30 to 70% w/w, the unique endothermic peaks originated from polystyrene microparticles between 135 and 175°C (Fig. 3) indicating that, from 30% loading onwards, indomethacin was present in crystalline form along with the dissolved form. This suggests that appreciable crystallinity (as refers to the ratio of crystalline regions of the drug to amorphous regions) existed in the mi-

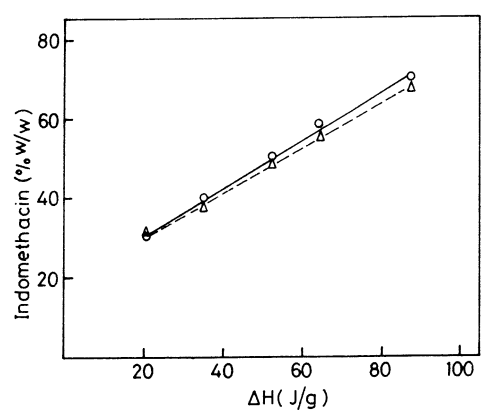

Fig. 4. Relationship between heat of melting (△H) of the entrapped indomethacin and drug concentration in polystyrene microparticles. Key, —— o —— o ——, line from experimental data; ------ △ ------ △ ------, calculated line from the drug solubility intercept and heat of melting of the pure drug.

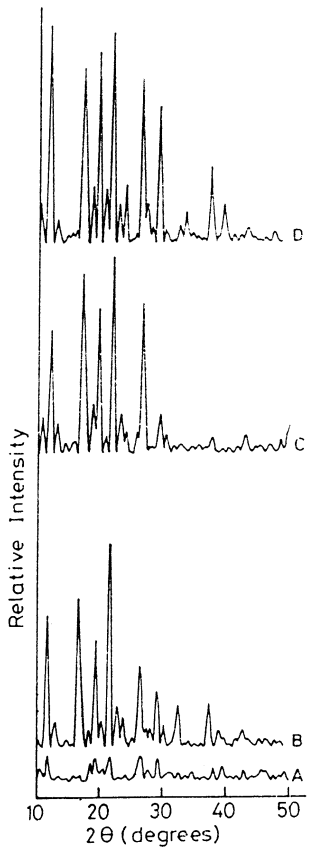

Fig. 5. X-ray diffraction patterns of indomethacin-loaded polystyrene microparticles having (A) 20%, (B) 50%, (C) 70% w/w drug load and (D) indomethacin powder.

croparticles within these drug loadings. The X-ray diffraction patterns of microparticles, as depicted in Fig. 5, demonstrated that the number and location of peaks of indomethacin obtained from microparticles containing 30–70% drug loading were the same and similar to those obtained from the pure drug. The observed diffraction peak values (2θ) were consistent with the reported values of Form I of indomethacin (O'Brien et al., 1984). The relative intensity of the peaks obtained from microparticles were, however, less than those obtained from the pure drug (Fig. 5). A similar reduction in peak intensity was observed in polymethylmethacrylate microparticles (Sa and Mondal, 1998). This reduction in peak intensity may be due to inhibition or retardation of indomethacin crystallization by the polymer

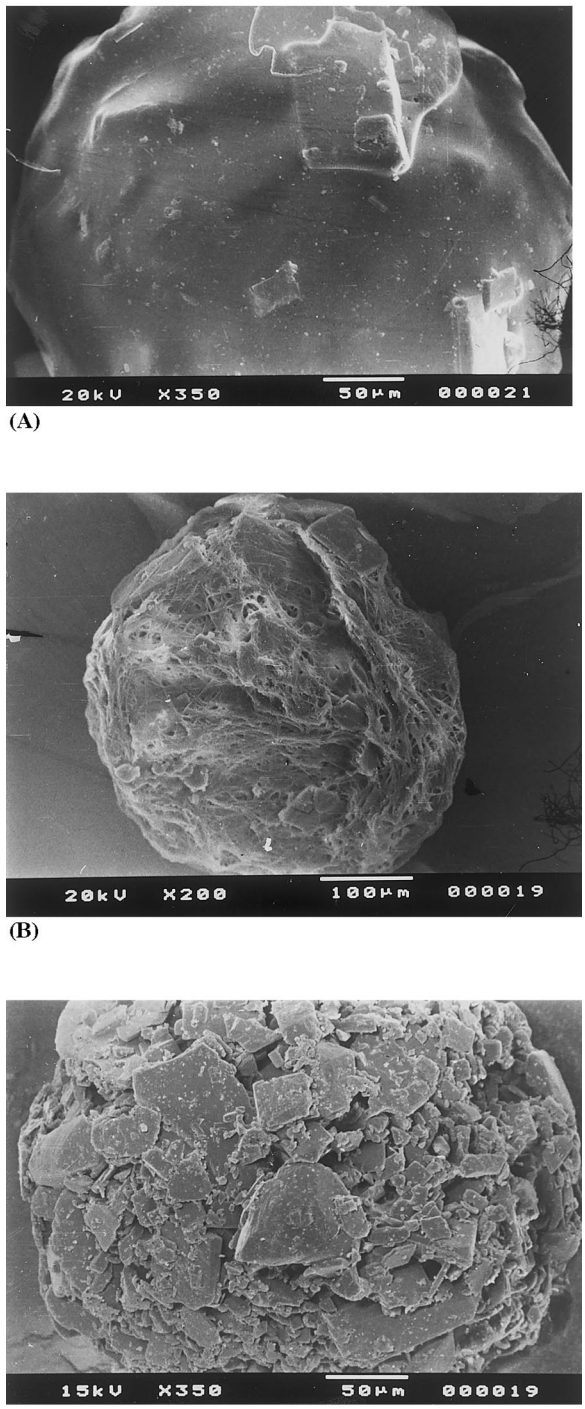

Fig. 6. Scanning electron micrographs of indomethacin-loaded polystyrene microparticles. Key, (A) 20%, (B) 50% and (C) 70% w/w drug load.

Table 6
Crystallinity of indomethacin in polystyrene microparticles at various drug load calculated from DSC thermograms

Drug load% (w/w)	Crystallinity[a] (%)
20	ND[b]
30	22.13
40	33.86
50	42.58
60	59.06
70	87.78

[a] The percentage crystallinity calculated from the area of endothermic peaks normalized per gram of indomethacin.
[b] ND-Not detected as indicated by peakless thermogram.

(Sekikawa et al., 1978). SEM illustrated how external morphology of the microparticles varied with drug loadings (Fig. 6). Increase in drug load from 30 to 70% gradually produced an irregular and textured surface in which indomethacin crystals were embedded. The precent crystallinity, a measure of crystalline dispersion state of the drug in the polymeric matrix as a function of drug loading was calculated by the methods described by Gupta and Purwar (1984) and is given in Table 6. From Fig. 3, Fig. 5 and Table 6, it was apparent that peak area of the melting transition endotherm, relative intensity of the diffraction pattern and crystallinity of the drug respectively increased with increase in drug loading in the microparticles. Since, the amount of polymer for all the formulations during preparation of microparticles was kept constant (0.5 g) the gradual augmentation of the overall areas of endothermic peak between 135 and 175°C, the relative intensity and the crystallinity with increase in drug loadings were attributed to the increase in crystalline domain of the drug in the microparticles.

By deducing the soluble fraction of the drug, calculated from Eq. (2), with total amount of drug entrapped in each of the drug loading levels, the exact crystalline fractions of the drug were calculated. Further, the heat of melting of one gram of indomethacin (115.10 J g^{-1} at 160°C) was determined experimentally using Eq. (1) and was found close to the value reported for Form 1 of the drug (Venkataram et al., 1995). Multiplication of the value of exact crystalline fraction with the value of heat of melting of the drug gave the expected endothermic heat for each drug loading from the drug -polymer composition when other caloric processes have negligible heats. Fig. 4 demonstrated that the expected endothermic heat at each drug loading was always close to the value determined experimentally. Further, the heat of mixing, as defined by the difference between the observed and expected endothermic heats at each drug loading, was calculated and was found to be in the same order of magnitude (0.2–1.09). It was, therefore, concluded that at 20% drug loading, indomethacin was present in solid solution form and 30% onwards, crystalline domain of the drug existed in equilibrium with the solid solution. Further, at all the drug concentrations studied, no evidence of metastable molecular dispersion form of the drug was found. Thus presence of the drug at a molecular level at 20% loading boosted the drug release and as the formation of crystalline domain increased with increase in drug loading, the release of the drug from the microparticles decreased. Although increase in drug loading above 50% further increased the crystalline domain of indomethacin, the release of the drug increased instead of decreasing. Presence of large amount of crystalline form of the surface absorbed drug led to the formation of porous matrix (Fig. 6C). As a result, penetration of dissolution fluid, dissolution of drug crystals and transport of drug solution towards the sink solution were facilitated and this was responsible for enhancement of release characteristics.

4. Conclusion

This study revealed that although the formulation variables like concentration of emulsion stabilizer and volume of organic disperse phase did not influence the drug release pattern considerably, the physical form of the drug depending on its concentration in the microparticles may have significant effect on the release pattern.

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