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Influence on variation in process parameters for the design of xanthan-gum-facilitated ethyl cellulose microparticles for intestinal specific delivery

Abstract: Xanthan-gum-facilitated aspirin-loaded ethyl cellulose microparticles were prepared by multiple-emulsion solvent evaporation technology and the impact on variation in process parameters was investigated systematically. Scanning electron microscopy was performed to determine the surface morphology of the microparticles before and after dissolution study. X-ray diffraction (XRD), differential scanning calorimetry (DSC), Fourier transform infrared (FTIR) analysis were performed, and yield value, swelling study, encapsulation efficiency, flow properties and dissolution profiles of the prepared formulations were evaluated. The size of microparticles varied between 247 and 410 μm, and 58.34% drug entrapment efficiency was achieved depending on the variation in process parameters. The drug release in acid solutions was slower than in alkaline solution. The microparticles provided extended drug release in alkaline dissolution medium, and the drug release was found to be controlled by Fickian diffusion mechanism. XRD and DSC analyses revealed the amorphous nature of drug in the microparticles. FTIR data indicated the stable character of the encapsulated drug in the microparticles. Thus, variation in process parameters showed a slow and prolonged release of aspirin in simulated intestinal fluid.

Keywords: aspirin; ethyl cellulose; microparticles; multiple emulsions; xanthan gum.

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1 Introduction

Natural polymers provide great advantages in biomedical applications such as drug delivery and tissue engineering. They are biocompatible, nontoxic and biodegradable materials. Also, they have good potential to incorporate drugs, enzymes, bioactive components, etc. [1, 2]. Xanthan gum is a high-molecular-weight exopolysaccharide produced by *Xanthomonas campestris*. It has been widely used in oral topical formulations as a suspending and stabilizing agent and as a release-sustaining agent in pellets [3]. Ethyl cellulose, a nonbiodegradable and biocompatible polymer, is an extensively studied encapsulating material for the controlled release of pharmaceuticals. However, it has been little investigated by either conventional or modified (water-in-oil)-in-water (w/o/w) emulsion technology. Aspirin or acetylsalicylic acid is a nonsteroidal anti-inflammatory drug that acts by inhibition of prostaglandin synthesis. The involvement of prostaglandins in the pathology of various joint and ocular disorders is well proven. Therefore, aspirin is widely used in these disorders [4]. Encapsulation techniques have been used extensively to entrap drugs and bioactive compounds and control their release into the gastrointestinal tract. Several techniques were developed to produce encapsulated microparticles. A drug delivery system developed with microparticles might increase the life span of the active ingredients encapsulated inside and control the release. Because of their small size and large surface-to-volume ratio, microparticles are very much suitable for controlled delivery. Microencapsulation offers many advantages that include increased stability, prolonged *in vivo* half-life, reduction of possible adverse side effects, concentration of the drug resulting in lower

required doses, and ease of administration. Many techniques are available for microencapsulation such as ionotropic gelation method, emulsion cross-linking method, spray-drying technique, freeze-drying, solvent evaporation method and co-crystallization method. In this study, w/o/w multiple-emulsion solvent evaporation method was used to make encapsulation of xanthan-gum-facilitated aspirin-loaded ethyl cellulose microparticles, which is a relatively simple process, and final product characteristic depends mainly on the formulation and variation in process parameters. This technique has been proposed to obtain the desired properties of the microparticles, loaded with the water-soluble active principles, and include the use of enteric wall material in the oil phase [5, 6] and addition of nonsolvent into the external aqueous phase [7]. Simultaneously, research efforts have been made to incorporate water-insoluble drugs into polymeric microparticles. From the literature survey, it was observed that maximum research work has been done with the water-soluble active pharmaceutical principles into polymeric core such as melarsoprol-loaded poly(ε-caprolactone) microparticles [8], zidovudine-loaded poly(lactic-*co*-glycolic acid) PLGA microparticles [9], etc. Thus, in this present research work, our ultimate motivation is to incorporate water-insoluble medicaments into polymeric microparticles. To the best of our knowledge, no reports are available that describe the xanthan-gum-facilitated aspirin-loaded ethyl cellulose microparticles by w/o/w multiple-emulsion solvent evaporation method. Thus, the main endeavors of this research work were (1) to design a polymer matrix consisting of xanthan-gum-facilitated ethyl cellulose microparticles to encapsulate aspirin by w/o/w multiple-emulsion solvent evaporation method; (2) to characterize the compatibility of drug in xanthan-gum-facilitated ethyl cellulose microparticles through scanning electron microscopy (SEM), X-ray diffraction (XRD), differential scanning calorimetry (DSC) and Fourier transform infrared (FTIR) spectroscopy techniques; and (3) to study the influence on variation in process parameters systematically, which are likely to influence the physicochemical properties of microparticles.

2 Materials and methods

2.1 Materials

Aspirin (acetylsalicylic acid) was procured from Central Drug House Private Limited, New Delhi, India. Ethyl cellulose (Ethocel), xanthan gum and dichloromethane were purchased from HiMedia Laboratories Private Limited, Mumbai, India. Span 80 (sorbian monooleate) was purchased from Loba Chemie Pvt. Ltd., Mumbai, India. Tween 80 and acetone were obtained from SD Fine-Chem Limited, Mumbai, India. All other reagent-grade chemicals were purchased commercially and used as received without further purification.

2.2 Design of xanthan-gum-facilitated aspirin-loaded ethyl cellulose microparticles

Aspirin was dissolved in acetone and then uniformly dispersed in 2% (w/v) aqueous xanthan gum solution. The dispersion was added slowly into a 2% (w/v) solution of ethyl cellulose in dichloromethane containing Span 80 and emulsified with a magnetic stirrer (Sanjay Scientific Corporation, New Delhi, India). The resulting water-in-oil (w/o) primary emulsion was then transferred into 100 ml of water containing 0.5% (w/v) Tween 80 with continuous magnetic stirring at 400 rpm to form multiple w/o/w-type emulsion. The stirring was continued for 3 h to allow complete evaporation of the organic solvent from the multiple emulsion and led to the formation of microparticles. The resulting microparticles were separated by filtration and thoroughly washed with cold double-distilled water (5×100 ml) and finally dried in an oven (Macro Scientific Works, New Delhi, India) at 40°C overnight. Finally, the drug-loaded microparticles were stored in a vacuum desiccator fused with calcium chloride until further characterization and investigation.

The following variations in process parameters were determined:

1. Concentration of ethyl cellulose solution in organic solvent: 1.0% and 2.0% (w/v)
2. Concentration of Span 80 in ethyl cellulose solution: 0.0% and 1.0% (w/v)
3. Internal aqueous xanthan gum phase volume: 5 and 10 ml
4. External aqueous phase volume: 50 and 100 ml (while an internal aqueous xanthan gum phase volume is 10 ml).

2.3 SEM analysis

Before and after dissolution experiments the polymeric matrix structure of the xanthan-gum-facilitated aspirin-loaded ethyl cellulose microparticles was examined through a scanning electron microscope (Jeol-Datum, JSM-5200, Tokyo, Japan) at the required magnifications

with the secondary electron image as a detector and an accelerated voltage of 18 kV.

2.4 FTIR spectroscopy analysis

FTIR spectra of pristine drug, drug-unloaded microparticles and drug-loaded microparticles were recorded with a Perkin-Elmer FTIR spectrometer (Model FTIR-8400s, Shimadzu, Japan) in the wave number region between 4000 and 400 cm^{-1} at a resolution of 4 cm^{-1} with a scan speed of 1 cm/s using KBr pellets.

2.5 XRD

Samples of pristine drug, drug-unloaded microparticles and drug-loaded microparticles were scanned at 2θ plane from 5° to 50° using a wide angle X-ray diffractometer (X-Pert, Philips, The Netherlands) with a scan speed of 1°/min.

2.6 DSC study

DSC thermograms of pristine drug, drug-unloaded microparticles and drug-loaded microparticles were recorded using a Perkin-Elmer instrument (Pyris-Diamond TG/DTA, Singapore). Each sample (4–8 mg) was heated in the range between 30°C and 250°C at a heating rate of 10°C/min in a nitrogen atmosphere with a flow rate of 20 ml/min.

2.7 Identification of multiple-emulsion structure

The internal aqueous xanthan gum phase and external aqueous phase were colored with amaranth. Then, a drop of multiple emulsions was put on a microscopic slide and observed under an optical microscope (Olympus model HB, Mumbai, India).

2.8 Percent yield of microparticles

The percent yield of the microparticles was calculated as a percentage of the total amounts of polymers and drug employed during the preparation. The percentage yield of the beads was calculated using the formula [10]:

$$\%\ \text{Yield}=[(\text{amount of microspheres})/(\text{amount of drug}+\text{amount of polymer})]\times 100 \quad (1)$$

2.9 Particle size analysis

Particle size analysis of the aspirin-loaded ethyl cellulose microparticles was done by optical microscopy method (Olympus Model HB, India). A standard stage micrometer was used to calibrate the eyepiece micrometer. Dried microparticles were placed in a glass slide and the number of divisions of the calibrated eye piece was counted. A hundred beads were randomly selected from each formulation and the individual particle diameter was calculated based on this formula [10]:

$$1\ \text{eyepiece division}=[(\text{number of stage micrometer divisions}/\text{number of eyepiece micrometer divisions})\times(10\ \mu\text{m}) \quad (2)$$

2.10 Determination of drug entrapment efficiency

Accurately weighed, 10-mg aspirin-loaded ethyl cellulose microparticles were dissolved in 2 ml of dichloromethane; 50 ml of phosphate buffer (PB) solution (pH 7.4) was added and stirred for 60 min with a magnetic stirrer. The mixture was heated at 60°C for 45 min in a water bath to remove organic solvent. After that, the volume was adjusted to 50 ml with fresh PB solution (pH 7.4) heated at 50–55°C. The solution was cooled, filtered, and an aliquot, after suitable dilution, was analyzed spectrophotometrically at 230 nm [11]. The estimation of percentage drug encapsulation efficiency was calculated by following the equation [12]:

$$\text{Drug encapsulation efficiency}\ (\%)=(\text{actual drug content}/\text{theoretical drug content})\times 100 \quad (3)$$

2.11 Determination of flow property

The flow property of microparticles was evaluated by measuring angle of repose (θ), Carr's index (*C*) and Hausner ratio (*H*) reported previously [10].

2.12 Swelling study

Dried drug-free microparticles (50 mg) were immersed in 100 ml of pH 1.2 acid solutions or pH 7.4 PB solutions at 37°C. Microparticles were allowed to swell completely for 24 h to attain equilibrium. Then, the microparticles were removed from the swelling medium after 24 h by filtration and blotted carefully to remove excess surface water. The swollen microparticles were weighed. The equilibrium

water absorbency (Q) of the microparticles was calculated by an equation reported previously [13, 14].

$$\% \text{ Equilibrium water uptake } (Q) = (\text{mass of swollen sample-mass of dried sample}/\text{mass of dried sample}) \times 100 \quad (4)$$

2.13 *In vitro* drug release study

Samples of xanthan-gum-facilitated aspirin-loaded ethyl cellulose microparticles were placed in a digital USP type II dissolution rate test apparatus (Electro Lab TDT-68L, Mumbai, India) containing 900 ml of either pH 1.2 acid solutions or pH 7.4 PB solutions at 37°C (±2.0°C). Elution fluids were collected and the same volume of fresh buffer was replaced at regular intervals. Collected elution fluids were used for determination of drug concentration at 230 nm.

2.14 Release kinetics modeling

The *in vitro* drug release mechanism was determined from the values of diffusional exponent (n) by modeling the first 60% of the drug release into the Korsmeyer-Peppas model:

$$F = k_P t^n \quad (5)$$

where F represents the drug fraction released in time t, k_P is the rate constant and n is the diffusional exponent; this indicates the drug release mechanism [15].

3 Results and discussion

The formation of w/o/w multiple-emulsion structure by this technology is shown in Figure 1. As a number of variations in process parameters were involved for the design of xanthan-gum-facilitated ethyl cellulose microparticles from multiple emulsion templates, it can be assumed that the characteristics of microparticles could be altered. Thus, the focal point of this research work was especially intended for the systematic examination of these variations in process parameters, which could influence the nature of microparticles.

3.1 Influence of ethyl cellulose concentration in organic solvent

Two different concentrations of ethyl cellulose [1.0% and 2.0% (w/v)] in dichloromethane were prepared to examine the influence in percentage yield, particle size, drug entrapment efficiency and drug release behavior. The yield of microparticles was improved from 80.16% to 92.02% (Table 1). This could be due to the increase in viscosity in the polymeric solution when the concentration of the polymer was increased, thereby producing bigger droplets during emulsification, which ultimately increased the quantitative weight of the formulations. Increasing the weight of polymer in a fixed volume of organic solvent resulted in an increase in mean particle diameter of microparticles from 247.56 to 381.16 µm (Table 1). It could be postulated that the higher concentration of polymer in the sample led to an increased frequency of collisions, resulting in fusion of semiformed particles and, finally, increasing the size of the microparticles. The percent encapsulation efficiency showed a dependence on ethyl cellulose content. By increasing the concentration of ethyl cellulose, the increase in percent encapsulation efficiency was from 16.46% to 49.05% (Table 1). Probably, the high viscosity of the organic phase tended to restrict migration of the inner aqueous/drug phase to the external water phase and enhanced the drug entrapment efficiency. All the formulations showed that the values of angle of repose (θ), Carr's compressibility index (C) and Hausner ratio (H) were <25°, 10 and 1.25, respectively, which indicates excellent flow property (Table 1). The microcapsules were found to exhibit higher packing properties. The improvement in flow properties suggests that the microcapsules can be easily handled during processing. The variation in

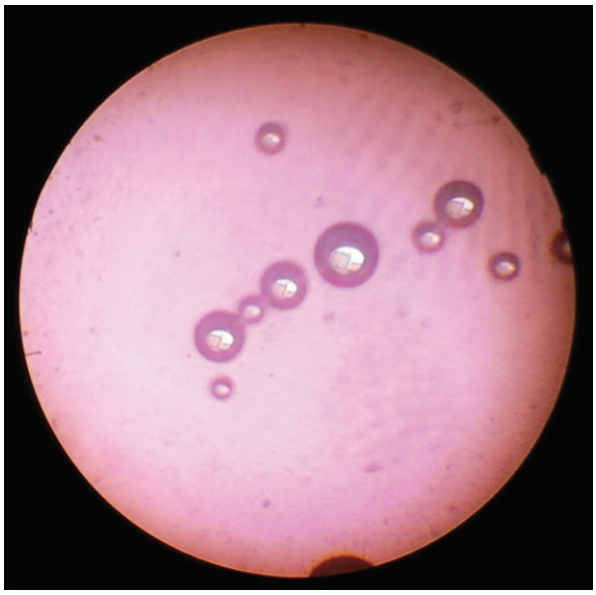

Figure 1 A photograph showing the presence of xanthan-gum-facilitated w/o/w emulsion structure; continuous aqueous phase (red); dispersed organic phase (white).

Processing variables	% Yield value	Mean size (μm)	% Entrapment efficiency (±SD, n=3)	Angle of repose (θ)	Carr's index (C)	Hausner ratio (H)	% Equilibrium swelling		Korsmeyer-Peppas model	
							pH 1.2	pH 7.4	*n*	r^2
Concentration of ethyl cellulose solution [% (w/v)]										
1.0	80.16	247.56	16.46±4.37	23.26	8.24	1.18	196	278	0.28	0.9785
2.0	92.02	381.16	49.05±2.11	24.70	7.14	1.07	139	264	0.32	0.9841
Concentration of Span 80 in oil phase [% (w/v)]										
0.0	81.35	353.05	17.18±5.57	22.69	9.78	1.20	188	269	0.36	0.9976
1.0	88.97	301.14	26.80±3.31	20.68	8.01	1.13	132	225	0.41	0.9704
Internal aqueous xanthan gum phase volume (ml)										
5	85.64	410.41	36.73±1.63	21.79	6.63	1.15	121	276	0.31	0.9914
10	78.01	349.17	25.71±2.68	19.09	7.82	1.28	98	203	0.45	0.9945
External aqueous phase volume (ml) (while internal aqueous xanthan gum phase volume=10 ml)										
50	84.07	341.06	37.43±2.38	23.17	9.2	1.13	159	238	0.34	0.9902
100	89.17	367.68	58.34±3.72	22.54	7.6	1.07	136	197	0.29	0.9878

Table 1 Influence on variation in process parameter on the *in vitro* physicochemical characteristics of aspirin-loaded xanthan-gum-facilitated ethyl cellulose microparticles.

polymer concentration affected the *in vitro* drug release profile. Formulations prepared with the highest polymer concentration ran always lower than those prepared with smaller concentrations either in pH 1.2 acid solutions or in pH 7.4 PB solutions (Figure 2A and B). The microparticles of 1% (w/v) ethyl cellulose showed rapid drug release in PB

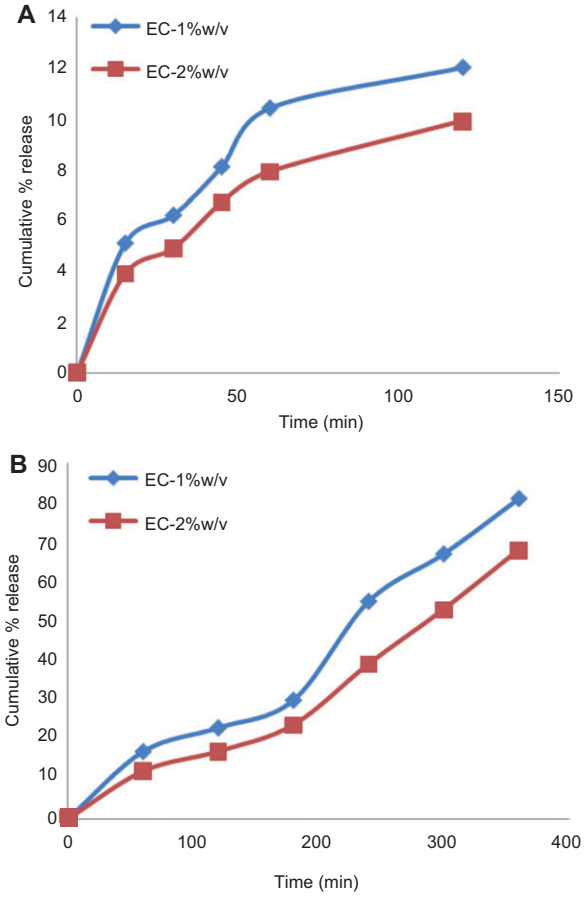

Figure 2 Release profiles of aspirin-loaded ethyl cellulose microparticles: variation of ethyl cellulose (A) in pH 1.2 acid solutions and (B) in pH 7.4 PB solutions.

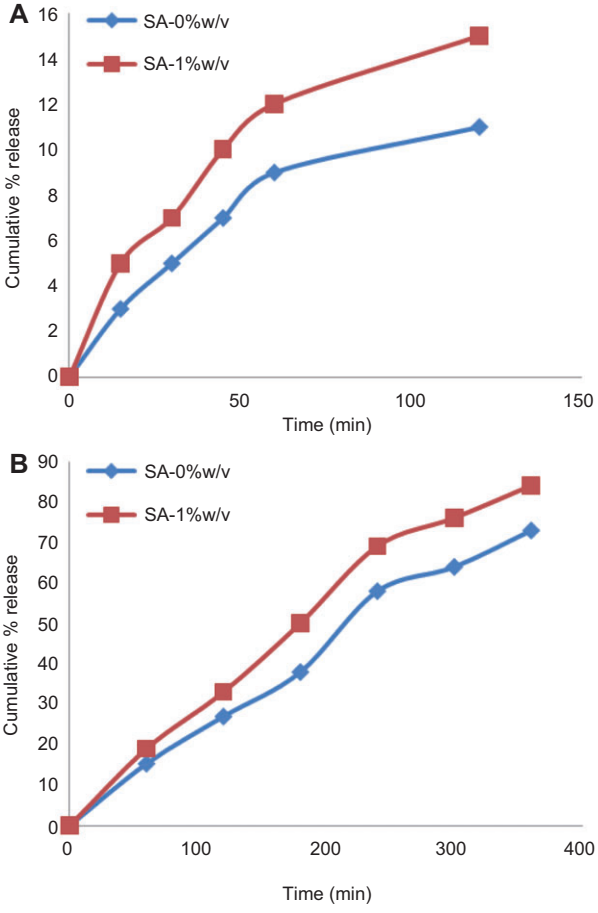

Figure 3 Release profiles of aspirin-loaded ethyl cellulose microparticles: variation of surfactant (A) in pH 1.2 acid solutions and (B) in pH 7.4 PB solutions.

solution compared to that in the remaining formulations. However, the rapid release was a little bit suppressed by a gradual increase in polymer concentration from 1% to 2% (w/v). A similar observation with protein-loaded PLGA microcapsules has been reported [16]. It may be attributed to an elevation in the concentration of ethyl cellulose that led to a dense, less porous polymeric phase and inhibited the rapid drug release. The equilibrium swelling behavior could be similarly explained by their pH-dependent drug release. The drug release was predominated by Fickian diffusion-controlled mechanism (Table 1).

3.2 Influence of Span 80 concentration in ethyl cellulose solution

Span 80 was mostly recommended as a non-ionic, lipophilic surfactant having an hydrophillic-lipophillic balance (HLB) value of 4.3. It was used here to stabilize the primary w/o emulsion by reducing the interfacial tension between the two phases. Two different concentrations of Span 80 [0.0% and 1.0% (w/v)] in ethyl cellulose were prepared, where one formulation was made by using only ethyl cellulose as the w/o primary emulsion stabilizer [17] and the remaining was made by using Span 80 [1.0% (w/v)]. The mean diameters of the microparticles were decreased from 353.05 to 301.14 µm, and the drug encapsulation efficiency was increased from 17.18% to 26.80% at the higher concentration of Span 80 in the oil phase (Table 1). Since the particle size and drug encapsulation efficiency are greatly related to the stability of the primary emulsion, this could be explained by the tensio-active properties of Span 80, which stabilized the primary emulsion and prevented the fast coalescence of the droplets [18, 19]. The influence of Span 80 on drug release behavior in both pH 1.2 acidic solution and pH 7.4 PB dissolution media are presented in Figure 3A and B. The concentration of Span 80 in ethyl cellulose solution showed an influence in controlling drug release from the microparticles. The faster drug

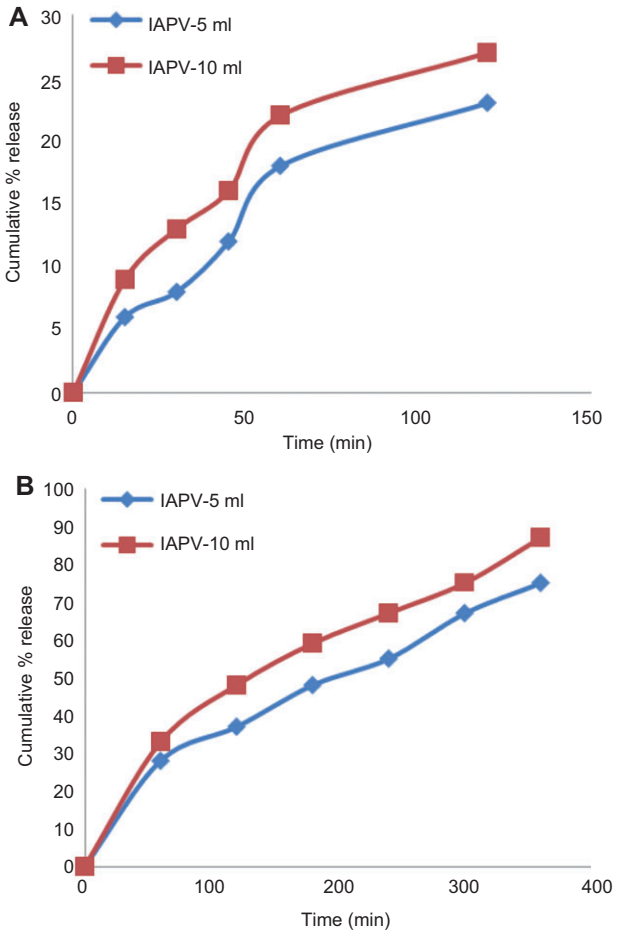

Figure 4 Release profiles of aspirin-loaded ethyl cellulose microparticles: variation of internal phase volume (A) in pH 1.2 acid solutions and (B) in pH 7.4 PB solutions.

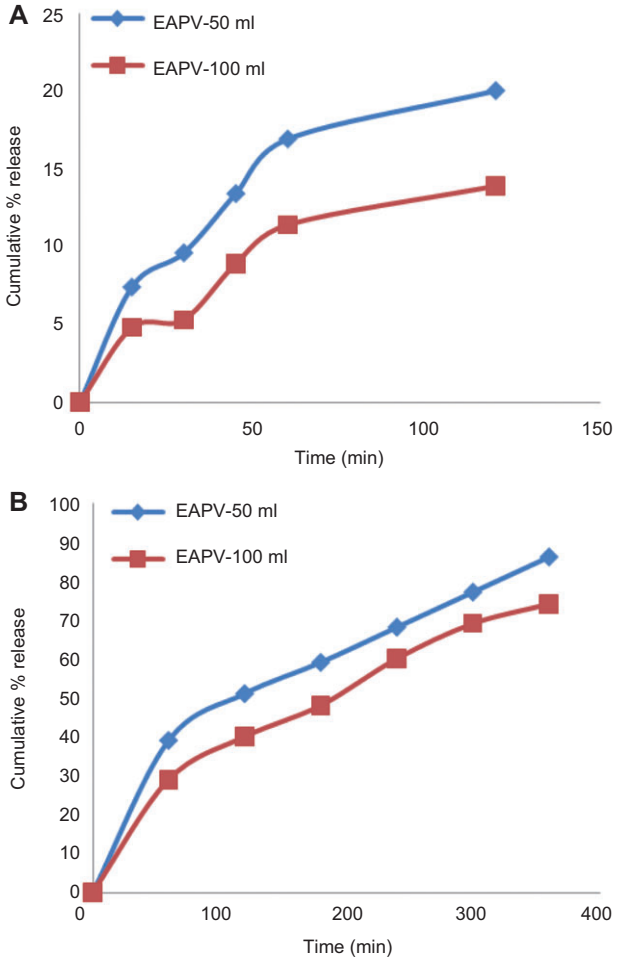

Figure 5 Release profiles of aspirin-loaded ethyl cellulose microparticles: variation of external phase volume (A) in pH 1.2 acid solutions and (B) in pH 7.4 PB solutions.

release in both media was achieved by 1.0% (w/v) Span 80 concentration. This phenomenon may be due to the formation of smaller particles at higher concentration of Span 80, which may enhance the effective surface area of the microparticles and lead to an increase in the dissolution rate. The drug release from the microparticles showed Fickian transport mechanism (Table 1).

3.3 Influence of internal aqueous xanthan gum phase volume

As the internal aqueous xanthan gum phase volume of the primary w/o-type emulsion increased, the percentage yield of the microparticles was decreased from 85.64% to 78.01%. A similar observation obtained with fluconazole-loaded ethyl cellulose microspheres has been reported earlier [12]. This may be due to the increase in internal aqueous xanthan gum phase volume that caused a decrease in mean particle diameter of the formulations (Table 1). The droplet size of the primary w/o-type emulsion may decrease with aqueous phase volume of the primary emulsion, which in turn decreases the mean particle diameter. However, this finding was just opposite to the earlier reports [20]. The drug entrapment efficiency of the microparticles showed a decreasing tendency from 36.73% to 25.71% (Table 1). Similar observations have been reported earlier [20, 21]. The microparticles prepared with higher aqueous internal xanthan gum phase volume released their content at a much faster rate than those prepared with lower internal phase volume in both the dissolution media (Figure 4A and B). Due to an increase in volume of the inner aqueous phase in the primary emulsion, the porosity of the microparticles increased and contributed to the faster drug release rates associated with the use of higher internal aqueous phase volume. The internal aqueous xanthan gum phase volume of primary w/o emulsion had no apparent influence on the drug release mechanism. The values of diffusional exponent (Table 1) indicated that the drug release from the microparticles followed Fickian diffusion mechanism.

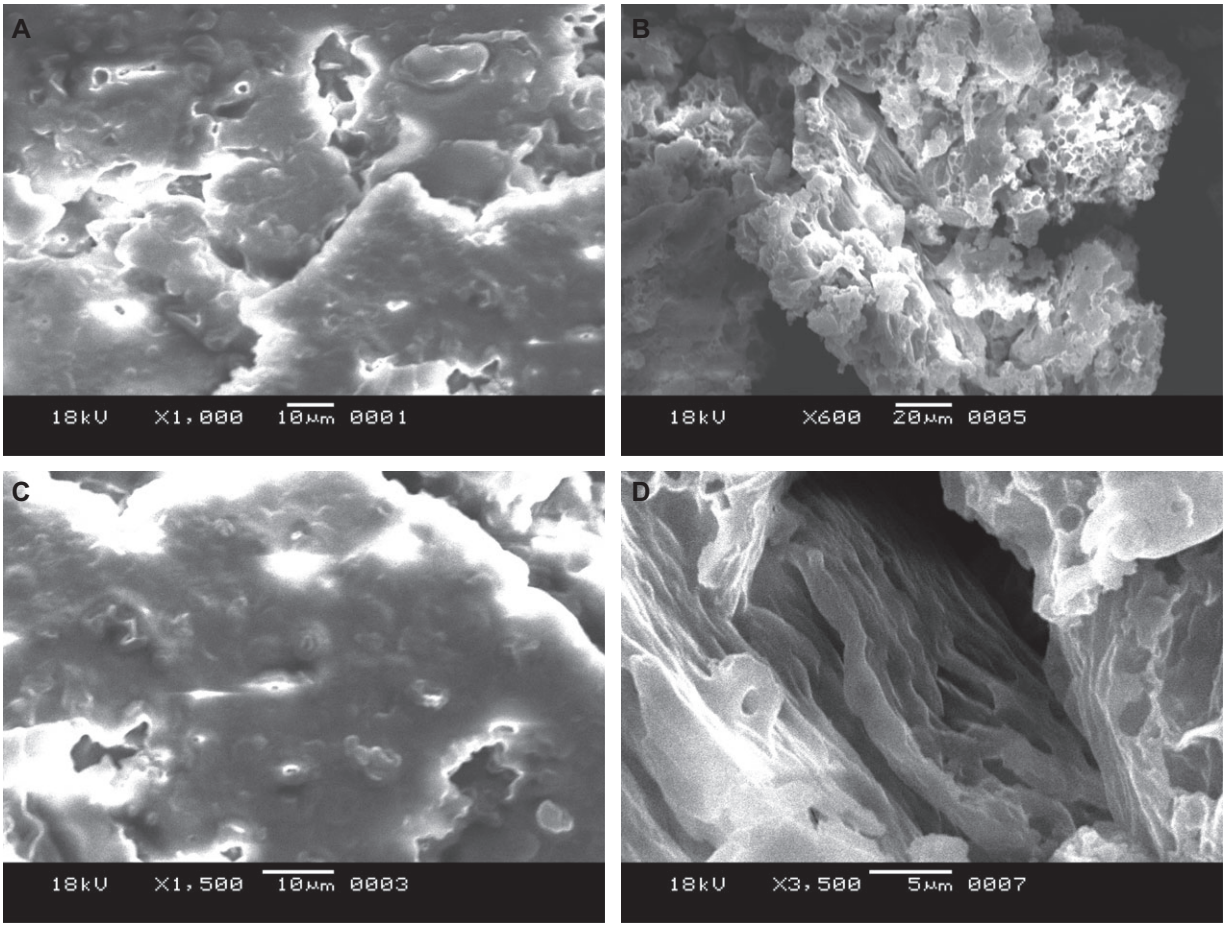

Figure 6 SEM of (A) surface before dissolution in pH 1.2, (B) surface after dissolution in pH 1.2, (C) surface before dissolution in pH 7.4 and (D) surface after dissolution in pH 7.4.

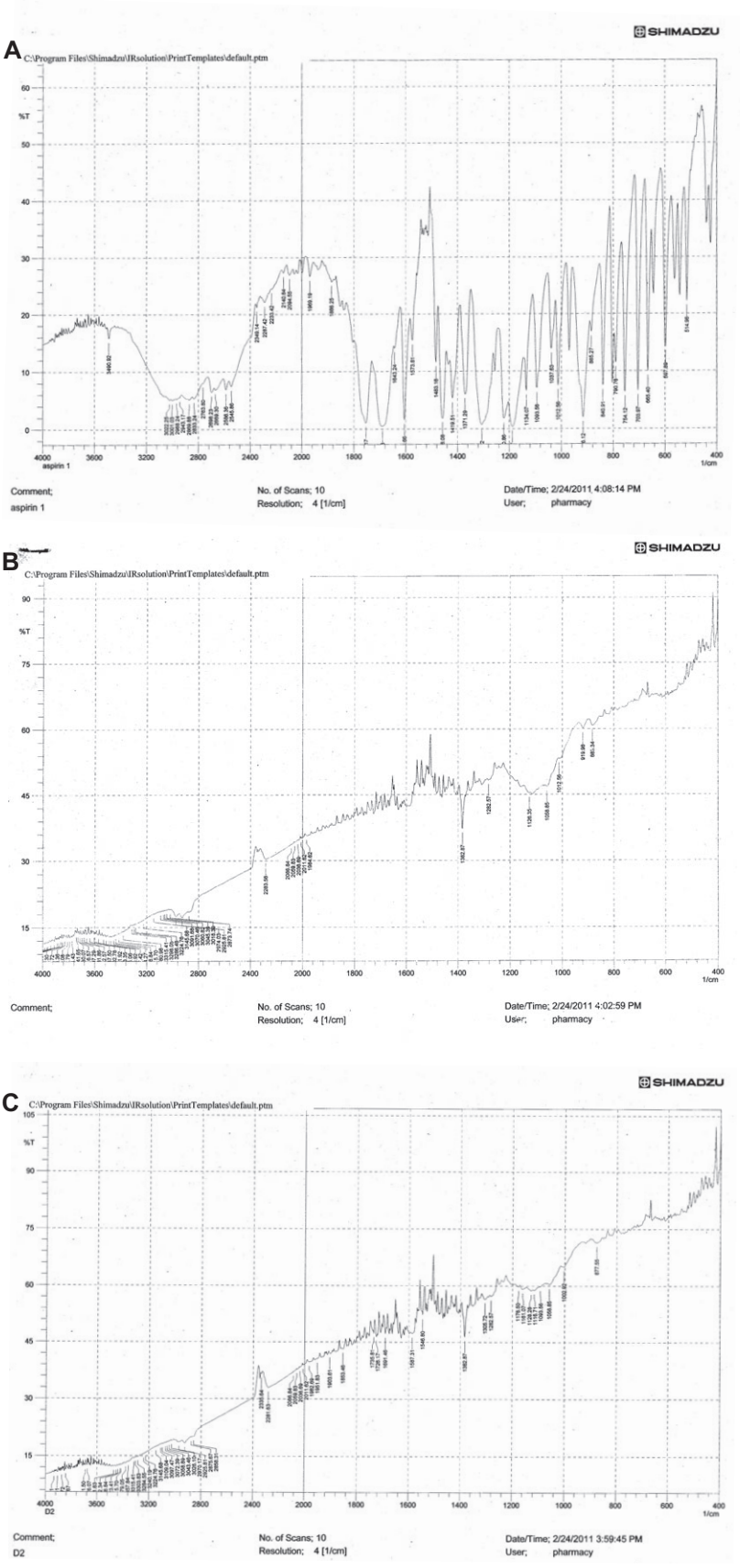

Figure 7 FTIR spectra of (A) pure aspirin, (B) blank ethyl cellulose microparticles and (C) aspirin-loaded ethyl cellulose microparticles.

3.4 Influence of external aqueous-phase volume

As the external aqueous-phase volume was increased from 50 to 100 ml, this resulted in an increase in percent yield and drug entrapment efficiency of the microparticles (Table 1). This similar phenomenon may be attributed to the slower rate of drug leaching from the internal aqueous xanthan gum phase volume of primary w/o emulsion to the external aqueous phase volume of the secondary w/o/w-type emulsion; because of the increase in external aqueous phase volume there was a decrease in mixing efficiency, which may be likely due to decrease in agitation, and ultimately, the particle size of the microparticles was increased (Table 1). A decrease in mixing efficiency most likely produced bigger emulsion droplets, which could form large microparticles [22]. The differences between release profiles of drug-loaded microparticles in acidic and alkaline dissolution media with increasing external phase volume are presented in Figure 5A and B, respectively. In 50 ml of external aqueous phase, higher drug release profile was observed in pH 7.4 alkaline medium, followed by 100 ml. The equilibrium swelling behavior of the microparticles was comparatively higher in alkaline medium (Table 1), and higher drug release could be expected in alkaline dissolution medium. The release behavior from microparticles satisfied the Korsmeyer-Peppas semi-empirical model, and the drug release was Fickian type, irrespective of external phase volume (Table 1). Surface analysis of the drug-loaded microparticles by SEM before (Figure 6A and C) and after dissolution (Figure 6B and D) study revealed a large number of pores and supported micropore diffusion controlled drug release mechanism.

The values of Carr's index and Hausner ratio were also within limits to indicate good flow property of these microparticles (Table 1). The compatibility of aspirin in this formulation was evaluated qualitatively through FTIR analysis. In the FTIR spectrum of pure aspirin (Figure 7A), several strong vibrations were presented at 1770 cm^{-1} (C=O stretch), 1600 cm^{-1} (C=C stretch), 1573 cm^{-1} (OCO antisymmetric stretch), 1419 cm^{-1} (OCO symmetric stretch) and 1238, 1200, and 1184 cm^{-1} (C-O and C-C stretching modes). Similar vibrational peaks of aspirin were detected in the spectrum of aspirin-loaded microparticles with minor differences in frequencies (Figure 7C). This suggested that the drug was apparently stable in the microparticles. The physical state of drug in these microparticles was examined by XRD and DSC analysis. The important crystallographic characteristics of aspirin were observed at prime scattering angles of 6° and 18° (Figure 8A). In the case of aspirin-loaded microparticles, they showed very sharp signals at scattering angles of 6° and 18° (Figure 8C). DSC thermograms of pure aspirin showed a clear endothermic peak associated with crystal melting at a temperature of 140.1°C (Figure 9A). However, the DSC thermogram of aspirin-loaded ethyl cellulose microparticles did not show a clear endothermic peak associated with crystal melting at this temperature, which reflects that the drug is

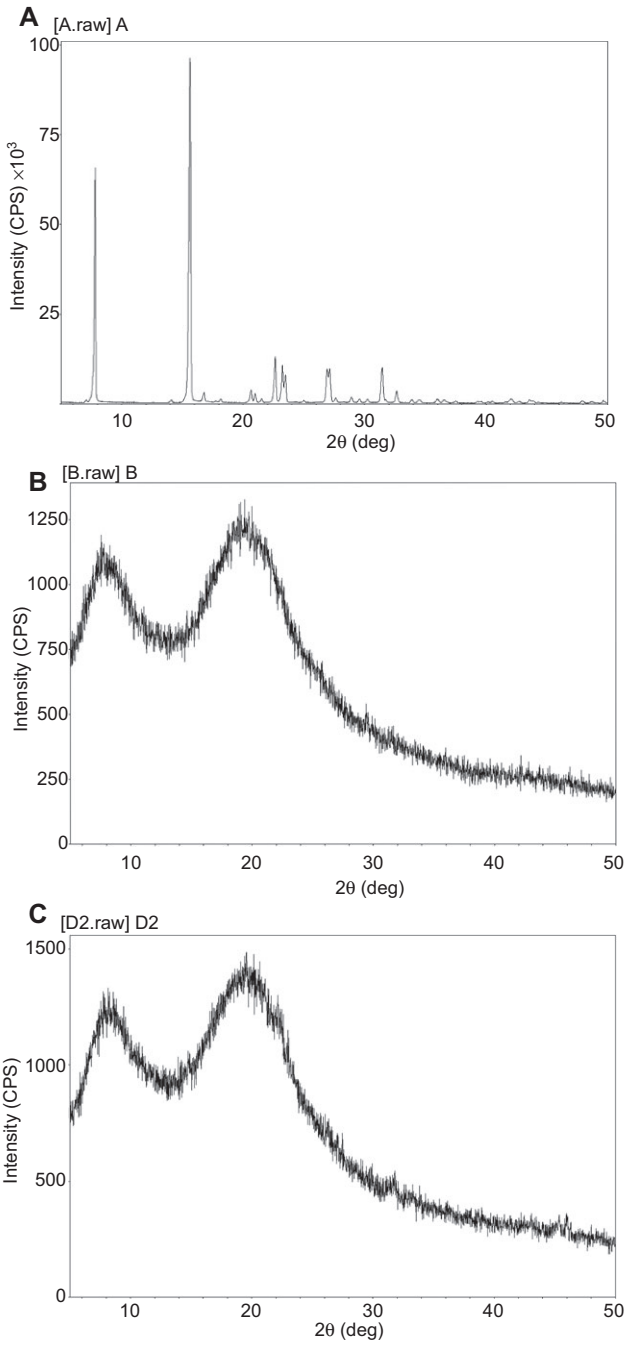

Figure 8 X-ray diffraction pattern of (A) pure aspirin, (B) blank ethyl cellulose microparticles and (C) aspirin-loaded ethyl cellulose microparticles.

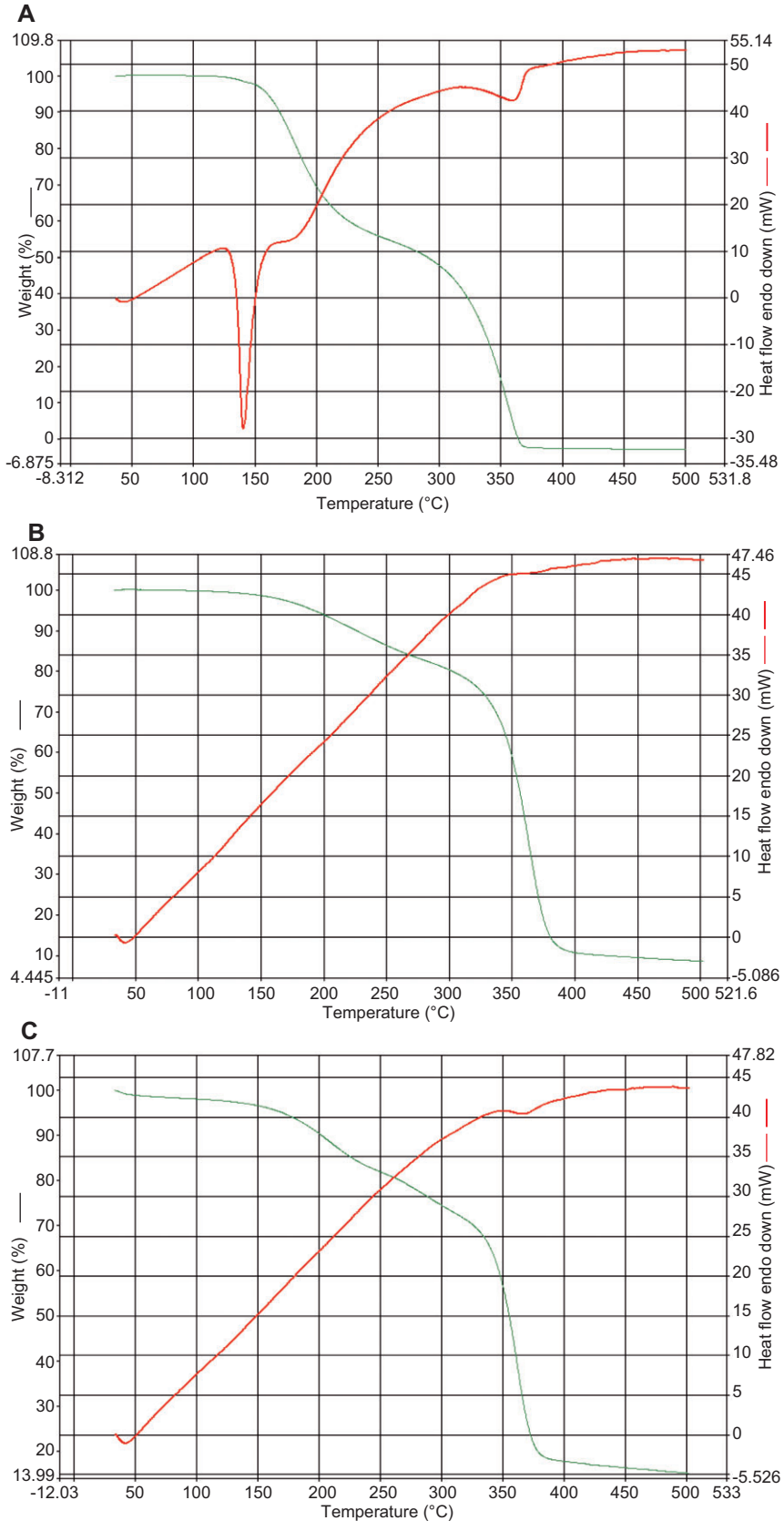

Figure 9 DSC thermograms of (A) pure aspirin, (B) blank ethyl cellulose microparticles and (C) aspirin-loaded ethyl cellulose microparticles.

homogeneously distributed in the matrix (Figure 9C). The thermal behavior coupled with the X-ray crystallographic data suggested that the drug was able to disperse almost homogeneously in the microparticles.

4 Conclusions

The influence on variation in process parameters of the microparticles has provided an understanding of the effects on different evaluation parameters. Proper control of such variation in process parameters enabled the formulation of free-flowing microparticles in nature with a desired micrometer size range. These xanthan-gum-facilitated aspirin-loaded ethyl cellulose microparticles were able to provide prolonged drug release in pH 7.4 alkaline solution, which can ultimately avoid the gastric side effects of aspirin. The drug release from these microparticles was predominantly controlled by Fickian diffusion mechanism. XRD and DSC analysis indicated the stable nature of the drug after microencapsulation and homogeneous distribution in these microparticles. Therefore, it may be concluded that proper control of the variation in process parameters involved for the design of xanthan-gum-facilitated ethyl cellulose microparticles from multiple emulsion showed a slow and prolonged release of aspirin in simulated intestinal fluid, indicating the potential for further *in vivo* studies in animals.

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