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Full Length Research Paper

Development and *in-vitro* characterization of lornoxicam loaded ethyl cellulose microspheres prepared by emulsion solvent evaporation method

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Advancement in drug delivery could come from innovating improvement to the existing drug delivery system. Lornoxicam (Lxm) loaded ethyl cellulose microspheres were prepared by emulsion solvent evaporation technique and also to investigate the effect of variations in drug concentration, polymer concentration, internal phase volume, continuous phase volume and emulsifier concentration on the particle size, shape, % yield, percent entrapment efficiency and *in vitro* drug release behavior. The scanning electron microscopy (SEM) revealed that microspheres had good spherical geometry with smooth surface. The result showed that the maximum yield of the microspheres was found to be 64.23 ± 0.25%, with particle size in the range of 64.24 ± 1.82 to 81.83 ± 3.43 µm and encapsulation efficiency was found to be in a range of 60.34 ± 1.63 to 71.61 ± 1.20%. The average particle size and entrapment efficiency of microspheres were enhanced with increasing polymer concentration but reduced with increasing internal phase volume, external phase volume and emulsifier concentration. *In vitro* release profile of microspheres was in the range of 75.65 ± 2.3 to 87.78 ± 2.3% at the end of 12 h. It was concluded that Lxm loaded ethyl cellulose microspheres formulation showed sustained effect over a period of 12 h.

Key words: Ethyl cellulose, lornoxicam, microspheres, solvent evaporation, sustained release.

INTRODUCTION

In the last few decades, advancement in controlled/ sustained drug delivery systems has led to attainment of more effective therapy, that is delivery of drug over a long period of time, avoiding the large fluctuations and reducing the need of several administrations (Duarte et al., 2007). Over the past few decades, microspheres are one of the microparticulate systems which have shown tremendous potential and are used for sustained or controlled drug delivery and to improve the therapeutic efficacy (Davis and Illum, 1988; Ritschel, 1989). Ethyl cellulose (EC) is a water insoluble, biocompatible and nontoxic cellulose polymer and is studied extensively as encapsulating agent for sustained release of drugs (Chowdary et al., 2004; Wu et al., 2003).

Lornoxicam (Lxm), also known as chlortenoxicam, is a member of the oxicam group widely used for the symptomatic treatment of pain and inflammation in patients with rheumatoid arthritis and osteoarthritis. However, Lornoxicam usefulness is limited due to its short half-life that ranges from 3 to 5 h (Skjodt and Davies, 1998). Hence

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Table 1. Formulation variables of Lxm loaded ethyl cellulose microspheres (LECM).

Formulation code*	Lxm (mg)	EC (mg)	Drug:polymer ratio	DCM (ml)	Distilled water (ml)	Emulsifier concentration (%)
LECM-D_1	200	600	1:3	10	100	1.0
LECM-D_2	400	600	2:3	10	100	1.0
LECM-D_3	600	600	3:3	10	100	1.0
LECM-P_1	200	200	1:1	10	100	1.0
LECM-P_2	200	400	1:2	10	100	1.0
LECM-P_3	200	600	1:3	10	100	1.0
LECM-P_4	200	800	1:4	10	100	1.0
LECM-I_1	200	600	1:3	5	100	1.0
LECM-I_2	200	600	1:3	10	100	1.0
LECM-I_3	200	600	1:3	15	100	1.0
LECM-C_1	200	600	1:3	10	50	1.0
LECM-C_2	200	600	1:3	10	100	1.0
LECM-C_3	200	600	1:3	10	150	1.0
LECM-E_1	200	600	1:3	10	100	0.5
LECM-E_2	200	600	1:3	10	100	1.0
LECM-E_3	200	600	1:3	10	100	1.5

*Effect of drug concentration (D_1-D_3), polymer concentration (P_1-P_4), internal phase volume (I_1-I_3), external (continuous) phase volume (C_1-C_3), emulsifier concentration (E_1-E_3).

it requires repeated dosing which lead to local irritation and ulceration, and hence is the cause of the patient's non-compliance. To reduce the frequency of dosing and improve the patient compliance, controlled/sustained release formulation is desirable.

In the present investigation, we made an attempt to prepare various ethyl cellulose microspheres of Lxm by emulsion-solvent evaporation technique with varying various formulation variables like drug concentration, polymer concentration, volume of internal phase, volume of external phase and emulsifier concentration (Tween 80). The effect of the mentioned formulation variables on particle size, shape, % yield, drug entrapment efficiency and drug release behavior were investigated for the development of Lxm loaded ethyl cellulose microspheres to provide oral sustained drug delivery for a longer period of time.

MATERIALS AND METHODS

Chemicals

The drug, Lornoxicam was obtained as a gift sample from Zydus Cadila Healthcare Limited, India. EC was purchased from Central Drug House (P) Ltd., New Delhi, India. Dichloromethane (DCM) and Tween 80 procured from Central Drug House Pvt. Ltd., New Delhi, India. All other chemicals used were of analytical grade.

Preparation of Lxm loaded ethyl cellulose microspheres

The Lxm loaded ethyl cellulose microspheres were prepared by emulsion solvent evaporation method with some modification (Atyabi et al., 2005; Duarte et al., 2006). Weighed amount of polymer and Lxm were dissolved in dichloromethane as the internal phase. The prepared organic phase was then added drop wise to the water, containing Tween-80 (surfactant), which acts as external (continuous) phase. The mixture was stirred with mechanical stirrer at controlled stirring speed of 1000 rpm. The formed oil-in-water (o/w) emulsion was stirred continuously at room temperature until complete evaporation of dichloromethane and formation of solid microspheres. The prepared microspheres were filtered, washed with excess of distilled water and dried in a desiccator under vacuum at room temperature.

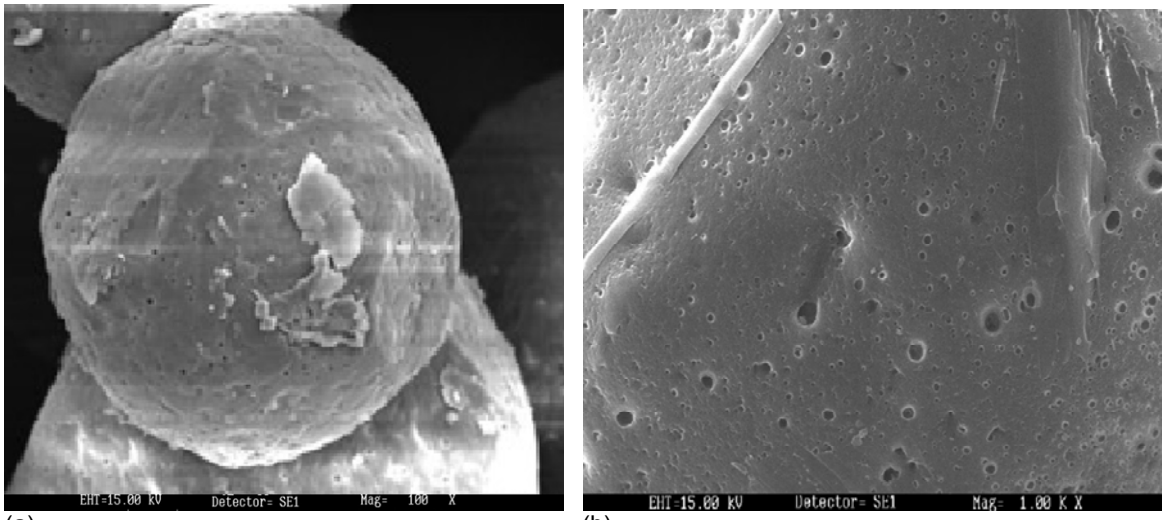
Optimization of Lxm loaded ethyl cellulose microspheres

Various formulation variables such as: drug concentration, polymer concentration, volume of internal phase, volume of external phase, emulsifier concentration, which could affect the preparation and properties such as particle size, shape, % yield, drug entrapment efficiency and *in vitro* drug release of the microspheres were studied for the development of Lxm loaded ethyl cellulose microspheres. The compositions and formulation code of the microspheres are given in Table 1.

Characterization of Lxm loaded ethyl cellulose microspheres

Shape and surface morphology

Shape and surface morphology of the formulations were studied by scanning electron microscopy (SEM) (JEOL JSM-1600, Tokyo, Japan) using a gold sputter technique. The samples for SEM were prepared by lightly sprinkling the microspheres on a double adhesive tape, which was stuck on an aluminum stub and coated with gold to a thickness of about 300 Å under an argon atmosphere in a high-vacuum evaporator. The coated samples were then randomly scanned and photomicrographs were taken.



(a) (b)

Figure 1. SEM images of Lxm loaded ethyl cellulose microspheres. (a): at 100× magnification, (b): at 1000× magnification.

Particle size analysis

Microspheres were studied microscopically for their size using a calibrated ocular eyepiece. In this method, the samples were mounted on a slide and placed on a mechanical stage. The calibrated ocular eyepiece was fitted with a micrometer by which the particle size of the sample was determined (Martin et al., 2005).

Determination of percent yield and entrapment efficiency

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by the following Equation 1 (Garud and Garud, 2012), where Wm is the weight of the microspheres and Wdp is the expected total weight of drug and polymer used for the preparation.

$$\text{Yield (\%)} = (Wm / Wdp) \times 100 \quad (1)$$

For the determination of entrapment efficiency, microspheres (100 mg) were accurately weighed and crushed and were suspended in 50 ml of phosphate buffer solution (PBS) (pH 6.8) and the resulting mixture was kept for shaking on mechanical shaker. At the end of 2 h, it was filtered, diluted appropriately and analyzed for drug content spectrophotometrically (n = 3) at 376 nm (Shimadzu 1700, Japan). Entrapment efficiency was calculated using Equation 2 (Garud and Garud, 2012), where A is actual drug concentration and T is the theoretical drug concentration.

$$\text{Entrapment efficiency (\%)} = (A / T) \times 100 \quad (2)$$

***In-vitro* drug release studies**

The drug dissolution test of microspheres was carried out by the paddle method specified in United States Pharmacopeial (USP) XXIII. The *in vitro* drug release of various microspheres formulations were studied in simulated gastrointestinal pH conditions: simulated gastric fluid (0.1 N HCl, pH 1.2) for the first 2 h, followed by simulating intestinal fluid (phosphate buffer solution, PBS, pH 6.8) up to 12 h, at 37 ± 0.5°C. Samples (1 ml) were withdrawn at regular time intervals and replaced with the same volume of test volume of test medium to maintain sink conditions. The withdrawn samples were suitably diluted, filtered through a 0.45 µ membrane filter and analyzed spectrophotometrically. All the tests were carried out in triplicate.

Differential scanning calorimetry study

The differential scanning calorimetry (DSC) of pure drug (Lxm), ethyl cellulose (EC), physical mixture of Lxm and EC, blank EC microsphere and Lxm loaded EC loaded microsphere was performed using a Pyris Diamond DSC-4 (Perkins Elmer, Wellesley, MA) in order to assess the drug excipient compatibility study. Thermograms were obtained at a scanning rate of 10°C min^{-1} conducted over a temperature range of 25 to 350°C in a liquid nitrogen environment.

RESULTS AND DISCUSSION

Ethyl cellulose microspheres of Lxm were successfully prepared by emulsion solvent evaporation method. SEM image of Lxm loaded ethyl cellulose microspheres showed that all microspheres were spherical and uniform with presence of some of the drug adhered to the surface of microspheres in its native crystalline form (Figure 1a and b).

Effect of drug concentration on particle size, percent yield and entrapment efficiency

The amount of drug was varied with respect to constant polymer concentration with drug to polymer ratio of 1:3 (LECM-D_1), 2:3 (LECM-D_2) and 3:3 (LECM-D_3) in order to investigate the effect of drug concentration, the resulting average particle size of microspheres were found to be 75.11 ± 1.12, 78.77 ± 2.92 and 81.83 ± 3.43 µm, respectively

Table 2. Effects of formulation variables on particle shape, size, % yield and drug entrapment efficiency of Lxm loaded ethyl cellulose microspheres.

Formulation code	Shape	Average particle size[$] (µm)	Yield[$] (%)	Drug entrapment efficiency[$] (%)
LECM-D_1	Spherical	75.11±1.12	64.23±0.25	71.61±1.20
LECM-D_2	Spherical	78.77±2.92	60.32±0.72	67.88±2.37
LECM-D_3	Spherical	81.83±3.43	58.27±0.45	61.47±1.43
LECM-P_1	Irregular shape	64.24±1.82	61.73±0.34	60.34±1.63
LECM-P_2	Spherical	67.38±2.02	62.32±0.08	65.15±1.06
LECM-P_3	Spherical	75.11±1.12	64.23±0.25	71.61±1.20
LECM-P_4	Spherical	76.25±1.36	65.02±0.58	70.19±2.06
LECM-I_1	Spherical	79.10±1.98	59.75±0.04	71.37±2.18
LECM-I_2	Spherical	75.11±1.12	64.23±0.25	71.61±1.20
LECM-I_3	Spherical	73.60±2.35	65.40±0.20	67.10±1.31
LECM-C_1	Spherical	79.32±2.06	67.04±0.45	70.97±2.34
LECM-C_2	Spherical	75.11±1.12	64.23±0.25	71.61±1.20
LECM-C_3	Spherical	71.45±1.68	59.09±0.48	65.64±2.21
LECM-E_1	Irregular shape	77.41±1.45	65.68±0.18	72.48±2.11
LECM-E_2	Spherical	73.11±1.12	64.23±0.25	71.61±1.20
LECM-E_3	Rough surface	72.29±1.79	61.26±0.37	68.24±1.60

[$]All data were expressed as mean ± SD. n = 3.

(Table 2). The average particle size of microspheres increased with increasing Lxm concentration may be due to increased content of the internal phase (drug and polymer) leading to bigger emulsion droplets resulting in a comparatively increase in size of microspheres. The percentage yield of microspheres gradually decreased with increasing the drug ratio, which might be due to increase in viscosity of internal phase and hence rapid solvent evaporation before formation of a continuous emulsion leading to and hence reduced percent yield. The drug entrapment efficiency was found to decrease progressively with increasing the drug ratio for preparation (Table 2), which might be attributed due to greater payload on polymer matrix which resulted in an increase in drug leaching into the continuous phase before the solidification could occur, moreover reduced % yield may be attributed to a reduction in drug entrapment efficiency. The highest entrapment efficiency was found with LECM-D_1 (1:3) that is, 71.61 ± 1.20 (Table 2), therefore this formulation was selected as optimum.

Effect of polymer concentration on particle size, percent yield and entrapment efficiency

The effect of increasing polymer concentration (drug to polymer ratio) from LECP-P_1 (1:1), LECP-P_2 (1:2), LECP-P_3 (1:3) and LECP-P_4 (1:4) on microspheres characteristics were shown in Table 2. The average particle size and percent yield of Lxm loaded ethyl cellulose microspheres were found to increase from 64.24 ± 1.82 to 76.25 ± 1.36 µm and 61.73 ± 0.34 to 65.02 ± 0.58% on varying drug: polymer ratio from 1:1 to 1:4, respectively. The average particle size was found to increase significantly with increasing the polymer concentration. With increasing the polymer concentration the internal phase viscosity increased which produced larger droplets upon emulsification, particle size were increased (Vasir et al., 2003). Percent yield was slightly increased on increasing polymer concentration. However, this increase was not significant. The entrapment efficiency was found to be in the range of 60.34 ± 1.63 to 71.61 ± 1.20% (Table 2).

The entrapment efficiency increased progressively with increasing polymer concentration because the increased polymer content provided more binding site for the drug molecules and more particles of Lxm were coated leading to higher encapsulation efficiency (Khan et al., 2010). EC microspheres (LECM-P_3) with drug: polymer ratio (1:3) shows highest entrapment efficiency that is, 71.61 ± 1.20%. However, further increase in the concentration of EC resulted in a decrease in the entrapment efficiency which may be due to aggregation of polymer matrix as a consequence of higher viscosity of internal phase in which drug did not uniformly dispersed in smaller droplets upon the induced shear for the preparation.

Effect of internal phase volume on particle size, percent yield and entrapment efficiency

In the preparation of Lxm loaded EC microspheres, when the volume of internal phase was increased from 5 ml to 15 ml (Table 2), percent yield of microspheres increase

may due to reduction in viscosity of internal phase as a consequence of a uniform dispersion, resulting in homogeneous emulsion and consequently increased yield upon its solidification. Before the formation of stable emulsion at given stress the emulsion droplets are not divided into smaller droplets resulting in lumps and hence reduced yield of microspheres. The average particle size of microspheres was decreased and found to be 79.10 ± 1.98, 75.11 ± 1.12 and 73.60 ± 2.35 on increasing internal phase volume of 5 ml (LECM-I_1), 10 ml (LECM-I_2) and 15 ml (LECM-I_3), respectively. Increase in internal phase volume from 5 to 15 ml also seemed to have decreased the entrapment efficiency from 71.61 ± 1.20 to 67.10 ± 1.31. This, which was due to the leaching of drug particle from internal phase to continuous phase was increased because of decreased viscosity of the drug-polymer solution. The internal phase volume of LECM-I_2 (10 ml) was found to be optimum for EC microspheres preparation, as the drug entrapment efficiency was highest (Table 2).

Effect of continuous (external) phase volume on particle size, percent yield and entrapment efficiency

Variations in continuous phase volume were also studied and results suggested that as the volume of the processing medium was increased from 50, 100 and 150 ml, the % yield and particle size decreased gradually and was found to be 67.04 ± 0.45, 64.23 ± 0.25, 59.09 ± 0.48% and 79.32 ± 2.06, 75.11 ± 1.12, 71.45 ± 1.68 µm, respectively (Table 2). This can be attributed to the fact that larger volumes of continuous phase resulted in less collisions between emulsion droplets and fine dispersement of emulsion, thereby yielding small and uniform microspheres (Saravanan et al., 2003). When the continuous phase volume was increased, entrapment efficiency of the drug was found to decrease. This may be due to increase of the partitioning of the drug into the increased volume of the continuous phase. Continuous phase volume of 100 ml (LECM-C_2) was found to be optimum for the preparation of EC microspheres (Table 2).

Effect of emulsifier concentration on particle size, percent yield and entrapment efficiency

The effect of emulsifier concentration on the formation of microspheres were examined, the average particle size and percent yield of microspheres was found to vary from 79.32 ± 2.06 to 71.45 ± 1.68 µm and 67.04 ± 0.45 to 59.09 ± 0.48% on varying emulsifier concentration (Tween 80) from 0.5 to 1.5%, respectively. Increased surfactant concentration led to the formation of globules with a lower average size and stabilization of the emulsion droplets avoiding their coalescence, resulting in smaller microspheres (Maia et al., 2004). An optimum concentration is required to produce finest stable dispersion. Below this concentration, the dispersed globules/droplets are fused to produce larger globules that require lower emulsifier concentration for stabilization (according to their reduced surface area). Above the optimum concentration, no significant decrease in particle size and microsphere having rough surface was observed. The drug entrapment efficiency varied from 72.48 ± 2.11 to 68.24 ± 1.60% during preparation of microspheres (Table 2), for the preparation of spherical shape and high entrapment efficiency. Required emulsifier concentration was 1.0% for Lxm loaded EC microspheres.

***In-vitro* drug release studies**

The effect of the drug to polymer ratio (LECM-D1 to LECM-D3) on the Lxm release from microspheres is shown in Figure 2, drug release from microspheres is notably affected by when the ratio of drug to the polymer is increased. It was found to increase with increasing drug content ratio. By increasing the amount of drug content, a point is reached when the solid drug particles upon dissolution begin to form continuous pores or channels within the matrix, ultimately leading to the diffusion of dissolution medium within polymer matrix and increasing the drug/dissolution medium interaction and hence increasing dissolution rate were observed (Song et al., 1981).

The results of effect of polymer concentration showed that the rate of Lxm release from LECM-P1, LECM-P2, LECM-P3 and LECM-P4 formulations was found to be 36.47 ± 0.98, 30.83 ± 1.44, 23.29 ± 1.46 and 20.59 ± 1.38% during the first 2 h in SGF, was significantly reduced and thereafter only LECM-P3 and LECM-P4 formulations followed the drug release pattern extending up to 12 h in dissolution medium SIF (pH 6.8). Lxm release from EC microspheres followed the order LECM-P1 > LECM-P2 > LECM-P3 > LECM-P4 (Figure 3). The study showed that the rate of Lxm release from EC microsphere was progressively decreased from 87.48 ± 2.68 to 75.65 ± 2.3% by increasing the polymer concentration, suggesting that the release from microspheres could be controlled by polymer concentration. This may be due to the increased density and thickness of polymer matrix at higher polymer concentrations that acted as a barrier for penetration medium, thereby retarding the diffusion of the drug, resulting in decreasing overall drug release from the polymer matrix (Al-Kassaa et al., 2007; Ramachandran et al., 2010).

The effect of the volume of internal phase and continuous phase on drug release (%) was shown in Figure 4 and 5, respectively. Internal phase volume does not have any significant effect on drug release. On the other hand, significant increase in the drug release rate was observed

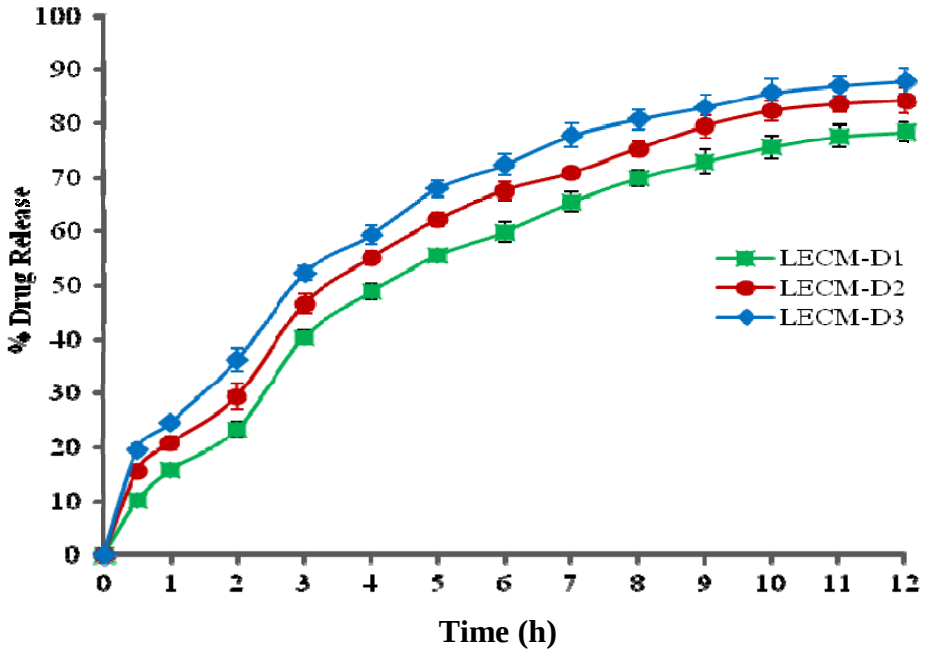


Figure 2. Effect of drug concentration on Lxm release from ethyl cellulose microspheres.

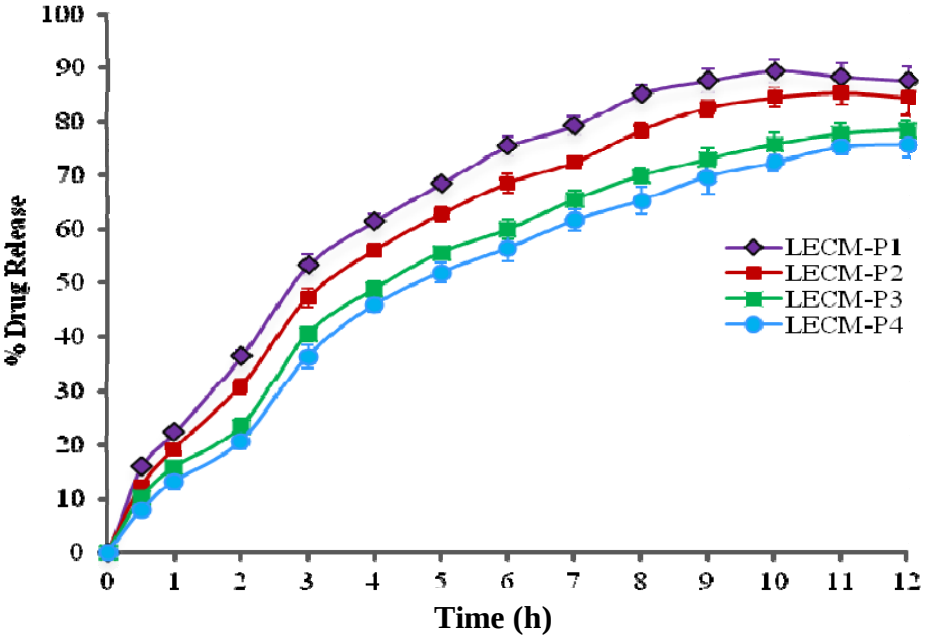


Figure 3. Effect of polymer concentration on Lxm release from ethyl cellulose microspheres.

with increased volume of continuous (external) phase. It may be due to a decreased size of the microspheres and hence a larger surface area exposed to dissolution (Dahiya and Gupta, 2011). The release of drug from EC microspheres also depends on the concentration of emulsifier (Tween 80), which was used at the time of preparation preparation as a stabilizer. As the concentration of Tween 80 increased from 0.5% (LECM-E1), 1.0% (LECM-E2) and 1.5% (LECM-E3), the release rate was increased (Figure 6). It may also be due to a decreased size of the microspheres and hence a larger surface area exposed to dissolution medium.

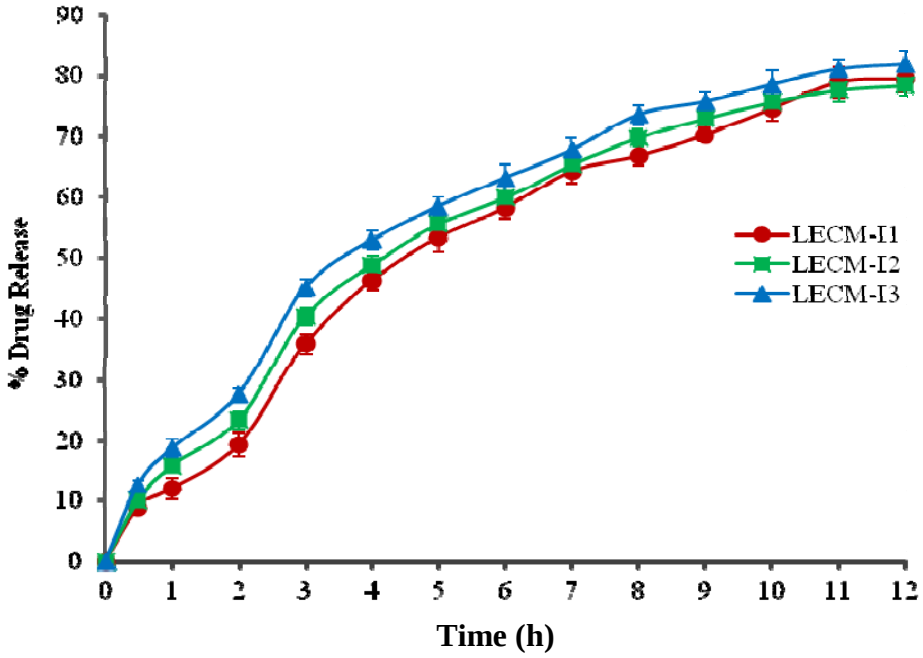


Figure 4. Effect of internal phase volume on Lxm release from ethyl cellulose microspheres.

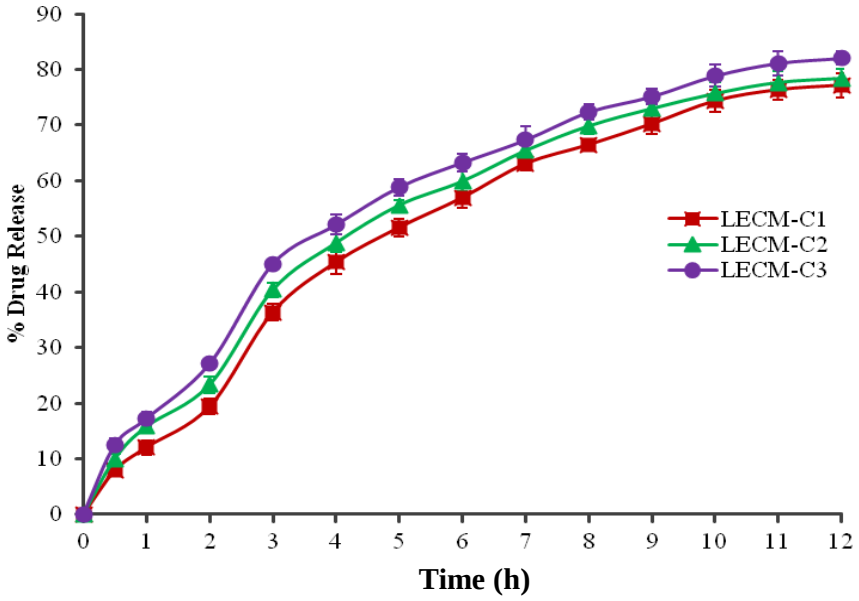


Figure 5. Effect of external (continuous) phase volume on Lxm release from ethyl cellulose microspheres.

Differential scanning calorimetry study

The DSC curves of pure Lxm (A), EC (B), physical mixture of Lxm and EC (C), blank EC microspheres (D) and Lxm-loaded EC microsphere (E) are shown in Figure 7. It was evident from the DSC profile that pure Lxm was typical of a crystalline substance, exhibiting a sharp exothermic peak at 232°C, corresponding to its melting. Thermogram of EC also displays a large exothermic peak around 180°C. The thermograms of the physical mixtures of Lxm with EC showed the existence of the drug exothermic peak, which could indicate the absence of interaction between Lxm and EC. The examination of EC empty microspheres revealed an exotherm peak due to the melting point of EC. The DSC profile of the drug appeared at the temperature corresponding to its melting

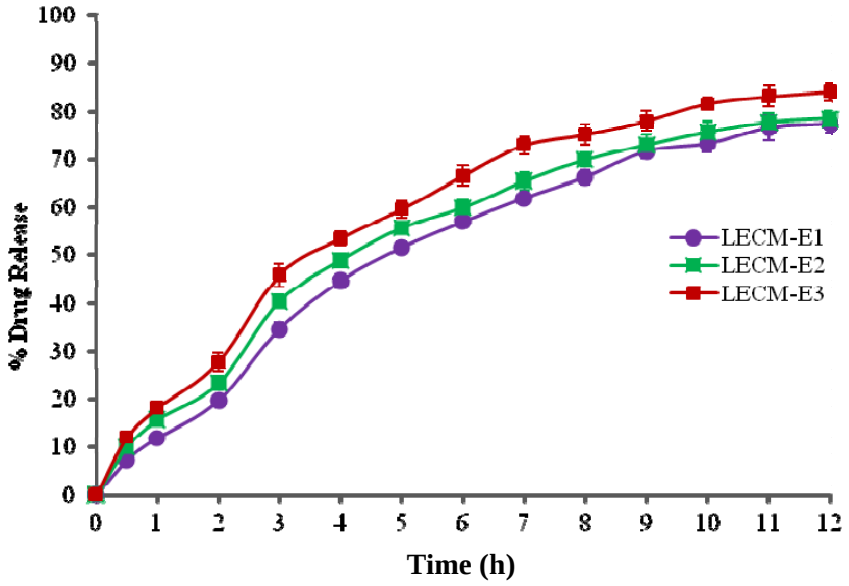


Figure 6. Effect of emulsifier concentration on Lxm release from ethyl cellulose microspheres.

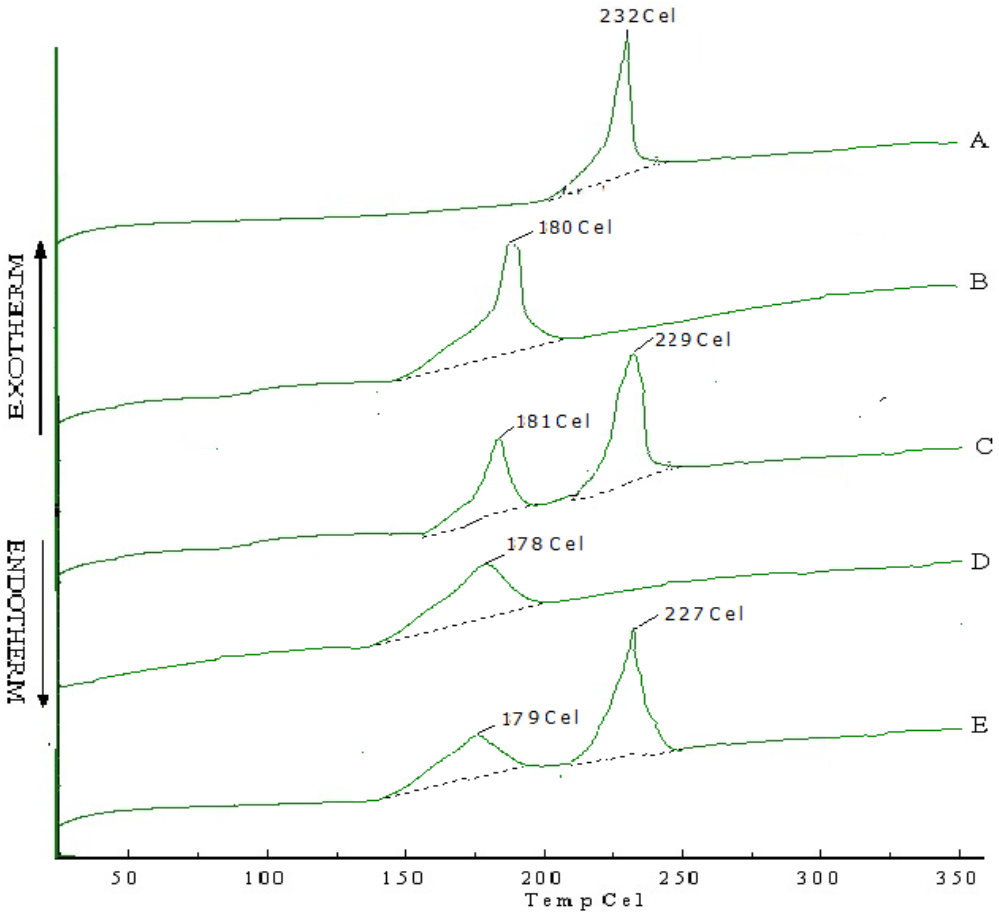


Figure 7. DSC thermo grams of pure Lxm (A), EC (B), physical mixture of Lxm and EC (C), blank EC microspheres (D) and Lxm- loaded EC microsphere (E).

point in the Lxm-loaded EC microspheres but with the loss of its sharp appearance. It appears that there is a significant reduction of drug crystallinity in the microspheres. The DSC study apparently revealed that the drug was compatible with the polymer and neither drug decomposition nor drug-polymer interactions occurred in the freshly prepared microspheres.

Conclusion

It can be concluded that the emulsification solvent evaporation method is a simple, reproducible method and the prepared microspheres had good spherical geometry. This study also concluded that ethyl cellulose microspheres formulation containing drug: polymer ratio (1:3), 10 ml internal phase volume, 100 ml continuous phase volume and 1.0% emulsifier concentration was optimized on the basis sphericity, highest entrapment efficiency and drug release study. The *in vitro* drug release studies showed that Lxm loaded ethyl cellulose microspheres formulation showed better sustained effect over a longer period of time. However, ability of ethyl cellulose microsphere to incorporate the drug and provide the sustained release for oral administration can be considered as one of the promising formulation technique for preparing a multiparticulate drug delivery system (polymer microsphere) of Lornoxicam, and the use of ethyl cellulose for the microsphere preparation has provided delays in drug release at a longer period which is suitable for oral drug delivery systems.

Conflict of interest

No competing interests were disclosed.

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