Bulletin of Pharmaceutical Research 2013;3(3):112-20
An Official Publication of Association of Pharmacy Professionals
ISSN: 2249-6041 (Print); ISSN: 2249-9245 (Online)

RESEARCH ARTICLE

FORMULATION AND *IN VITRO* EVALUATION OF EUDRAGIT® RS 100 MICROSPHERES CONTAINING LORNOXICAM PREPARED BY EMULSION-SOLVENT EVAPORATION METHOD

Lalit Kumar Tyagi[1] and Mohan Lal Kori[2]*

[1]*Research Scholar, Institute of Pharmaceutical Science and Research Center, Bhagwant University, Ajmer-305 004, Rajasthan, India*
[2]*Vedica College of B. Pharmacy, A Constituent Institute of RKDF University, Bhopal-462 033, Madhya Pradesh, India*

**E-mail*: mlkori.research@gmail.com
Tel.: +91 9893968611.

Received: September 09, 2013 / Revised: October 26, 2013 / Accepted: October 28, 2013

The aim of present study was to prepare sustained release Eudragit® RS 100 microspheres containing lornoxicam using emulsion-solvent evaporation technique. The influence of drug concentration, polymer concentration, emulsifier concentration and stirring speed on particle size, shape, % yield, entrapment efficiency and in vitro release characteristics of microspheres were investigated. SEM studies confirmed that microspheres were spherical and uniform in shape. The results showed that % yield, particle size and entrapment efficiency of prepared microspheres was found to be in the range of 68.75±0.82 to 84.83±0.88%, 132.52±5.24 to 214.92±4.24 μm and 65.18±1.66 to 85.28±1.60% respectively. It was found that particle size and entrapment efficiency of microspheres were enhanced with increasing polymer ratio but reduced with increasing stirring speed and surfactant concentration. The *in vitro* release studies showed that Eudragit® RS 100 microspheres showed sustained effect up to 12 h.

Key words: Eudragit RS 100, Lornoxicam, Microspheres, Polymethacrylate, Sustained release.

INTRODUCTION

Over the past few decades, microspheres have been one of the particulate delivery systems that is widely accepted to achieve oral (Sahoo *et al* 2007) and parenteral (Chowdary *et al* 2004) sustained or controlled drug delivery system, improved bioavailability, stability and target the drug to specific sites. Microspheres also offer advantages such as limiting fluctuation within a therapeutic range, reduction in side effects, decreased dose frequency and hence improved patient compliance (Ritschel, 1989). One of the popular methods for the encapsulation of drugs within water insoluble polymers is the emulsion solvent evaporation method. This technique offers several advantages and is preferable to other preparation methods such as spray drying, sonication and homogenization because it requires only mild conditions such as ambient temperature and constant stirring. Thus, a stable emulsion can be formed without compromising the activity of the drugs. Literature describes various methods as well as types of polymers showing potential for sustained and controlled drug delivery (Choi *et al* 2002; Kim *et al* 2002; Atyabi *et al* 2005; Dahiya and Gupta, 2011; Kumar and Dureja, 2011; Basarkar *et al* 2013). There are several formulation and process parameters that, when modified during the manufacture of microspheres by emulsion-

solvent evaporation technique, may affect the properties of microspheres.

Eudragit polymers are copolymers synthesized from acrylic and methacrylic acid esters available in different ionic forms. These polymers are well tolerated by the skin and have been used in the formulation of dosage forms especially matrix tablets for oral sustained release (Takka *et al* 2001) and in tablet coating (Gupta *et al* 2001). Eudragit® RS 100 is insoluble and slightly permeable to water and digestive juice, that is widely used as a wall material in the microencapsulation of drugs for sustained release (Kim *et al* 2002; Perumal, 2001; Sahoo *et al* 2005). This is due to its biocompatibility, good stability, easy fabrication and low cost. Lornoxicam (Lxm) is a member of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs) with extremely potent anti-inflammatory and analgesic activities (Homdrum *et al* 2006). It is widely used for the symptomatic treatment of pain and inflammation in patients with rheumatoid arthritis and osteoarthritis (Kidd and Frenzel, 1996). Lxm has a short biological half-life from 3 to 5 h; the usual oral dosage regimen is 4 to 8 mg and parentral dosage regimen is 4 mg/ml to be taken 3 to 4 times a day (Balfour *et al* 1996; Skjodt and Davies, 1998), repeated dosing can lead to local irritation and ulceration which is the cause of patient's noncompliance. Thus it is more suitable candidate to be designed as an oral sustained drug release formulation. Therefore, the aim of present study was to develop sustained release Lxm loaded microspheres using Eudragit® RS 100 by the emulsion solvent evaporation method in order to increase its biological half and to investigate the influence of formulation variables (Drug to polymer ratio, polymer to drug ratio, emulsifier concentration) and process variable (stirring speed) on shape, particle size, % yield, drug entrapment efficiency, flow property and drug release behavior.

MATERIALS AND METHODS

Materials

Lornoxicam (Lxm, Batch No.: KA0028003) was received as gift sample from M/s Zydus Cadila, Ahmedabad, Gujarat, India. Eudragit RS® 100 (ERS) was received from Evonik Degussa India Pvt. Ltd., Mumbai, India. All other chemicals used were of pharmaceutical or analytical grade.

Preparation of Lxm loaded Eudragit® RS 100 microspheres

Lxm loaded Eudragit® RS 100 microspheres (LERSM) were prepared by emulsion solvent evaporation method with some modification (Behera *et al* 2008; Haznedar and Dortunc, 2004; Basu and Adhiyaman, 2008). In this procedure, different amounts of ERS were dissolved in 10 ml acetone. The core material, Lxm, was added to the polymer solution and mixed for 15 min by using a magnetic stirrer. The resultant mixture was slowly poured in a thin stream to a mixture of 90 ml light liquid paraffin and 10 ml *n*-hexane contained in a 250 ml beaker, and was emulsified using Span 80, which acts as the external (continuous) phase. The system was stirred using mechanical stirrer at room temperature for an hour, until acetone evaporated completely. After evaporation of acetone, the paraffin was decanted off and microspheres formed were filtered using Whatman no.1 filter paper. The residue was washed 4-5 times with n-hexane. The product was then dried in a desiccator under vacuum at room temperature for 24 h. The different Lxm loaded ERS microspheres were prepared which are summarized in **Table 1** and effects of various formulation and process variables such as drug to polymer ratio, polymer concentration, emulsifier concentration and stirring speed on microspheres characteristics were investigated for optimization.

Characterization of Lxm loaded Eudragit® RS 100 microspheres

Shape and surface morphology analysis

Microspheres were suspended in water; a drop was placed on a glass slide, covered with a cover slip and viewed under the optical microscope to examine their shape. In order to examine the surface morphology, the microspheres were viewed under scanning electron microscope (SEM) (JEOL JSM-1600, Tokyo, Japan). The samples for SEM were prepared by lightly sprinkling the microspheres powder on a double adhesive tape, which was stuck on an aluminum stub. The stubs were then coated with gold to thickness of about 300 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then randomly scanned and photomicrographs were taken.

Determination of percentage yield and particle size analysis

The percentage yield value of microspheres was determined from the ratio of amounts of

Table 1. Formulation and process variables of Lornoxicam Loaded Eudragit® RS100 Microspheres

Formulation code	Lxm (mg)	Eudragit® RS 100 (mg)	Drug: Polymer ratio	Emulsifier concentration (%)	Stirring speed (rpm)
LERSM-D1	200	800	1:4	1.5	750
LERSM-D2	400	800	2:4	1.5	750
LERSM-D3	600	800	3:4	1.5	750
LERSM-D4	800	800	4:4	1.5	750
LERSM-P1	200	200	1:1	1.5	750
LERSM-P2	200	400	1:2	1.5	750
LERSM-P3	200	600	1:3	1.5	750
LERSM-P4	200	800	1:4	1.5	750
LERSM-P5	200	1000	1:5	1.5	750
LERSM-E1	200	800	1:4	1.0	750
LERSM-E2	200	800	1:4	1.5	750
LERSM-E3	200	800	1:4	2.0	750
LERSM-S1	200	800	1:4	1.5	500
LERSM-S2	200	800	1:4	1.5	750
LERSM-S3	200	800	1:4	1.5	100

*Effect of drug concentration (D_1-D_4); Effect of polymer concentration (P_1-P_5); Effect of emulsifier (surfactants) concentration (E_1-E_3); Effect of stirring speed (S_1- S_3)

solidified total microsphere to total solid material used in the inner phase, multiplied by 100 (Eq. 1) (Garud and Garud, 2012; Singh and Chaudhary, 2011):

$$\text{Yield (\%)} = (W_m/W_{dp}) \times 100 \quad \text{Eq. 1}$$

where, W_m is weight of the microspheres and W_{dp} is the expected total weight of drug and polymer.

Microspheres were studied for their size using optical microscopy. In this method, the sample was mounted on a slide and placed on a mechanical stage micrometer. The mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer (Martin, 1993).

Determination of flow property

The flow properties of prepared microspheres were investigated by measuring the bulk density, tapped density, Compressibility (Carr's) index, Hausner's Ratio and Angle of repose (Garud and Garud, 2012; Martin, 1993). Bulk and tapped densities were measured using a 10 ml graduated measuring cylinder. The sample placed in the cylinder and the initial volume (bulk) noted. The cylinder was then, tapped 100 times and the final volume (tapped) was again noted.

The bulk and tapped densities were calculated from the ratio of their respective weight and volume. Compressibility (Carr's) index and Hausner's ratio of microspheres were computed by using Eq. 2 and 3 respectively:

$$\text{Carr's index (\%)} = (D_t - D_b) / D_t \times 100 \quad \text{Eq. 2}$$

$$\text{Hausner's ratio} = D_t/D_b \quad \text{Eq. 3}$$

where, D_t is tapped density and D_b is the bulk density of the microspheres.

Angle of repose (θ) of different microspheres formulations were measured according to the fixed funnel standing method and calculated according to Eq. 4:

$$\theta = \tan^{-1} h/r \quad \text{Eq. 4}$$

where, r is the radius of the cone base and h is the height of the base.

Determination of drug content and entrapment efficiency

About 50 mg of accurately weighed microspheres were crushed in a glass mortar and pestle, and the powdered microspheres were suspended in 50 ml phosphate buffer solution (PBS, pH 6.8). The resulting mixture was shaken in a mechanical shaker. At the end of 2 h, it was filtered, the filtrate was diluted appropriately with PBS (pH 6.8) and analyzed for drug content spectrophotometrically (n = 3) at 376 nm using UV-Visible double beam spectrophotometer (Shimadzu 1700, Japan). Entrapment efficiency is percent of drug that is encapsulated in any microsphere formulations, which was calculated on the basis of ratio of drug in the final microspheres to the drug

entering the process *i.e.* entrapment efficiency was computed by using Eq. 5 (Sahoo *et al* 2005):

Entrapment efficiency (%) = (A/T) × 100 Eq. 5

where, A is actual drug concentration and T is the theoretical drug concentration.

In vitro drug release study

The drug dissolution test of microspheres was carried out by the paddle method (USP-XXIII). The *in-vitro* drug release profiles of the various microsphere formulations were studied in simulated gastrointestinal pH conditions *viz.* simulated gastric fluid (0.1 N HCl, pH 1.2) for the first 2 h followed by simulated intestinal fluid (phosphate buffer solution, PBS, pH 6.8) up to 12 h. The content was rotated at 100 rpm and thermostatically controlled at 37±0.5°C. Samples (5 ml) were withdrawn at various time intervals, and replaced with the same volume of test medium to maintain sink conditions. The withdrawn samples were suitably diluted where necessary, filtered through a 0.45 μ membrane filter and analyzed spectrophotometrically (Shimadzu 1700, Japan). All the tests were carried out in triplicate.

Differential scanning calorimetry (DSC) study

Thermal analysis using DSC was carried out on drug (Lxm), Eudragit® RS 100, physical mixture of Lxm and Eudragit® RS 100, blank Eudragit® RS 100 microsphere and Lxm loaded Eudragit® RS 100 microsphere using a Pyris Diamond DSC-4 (Perkins Elmer, Wellesley, MA) in order to assess the drug excipient compatibility. Accurately weighed samples were loaded into aluminum pans and sealed. All samples were run at a heating rate of 10°C min^{-1} conducted over a temperature range of 25-350°C in a liquid nitrogen environment. The results obtained from the heating were recorded.

RESULTS AND DISCUSSION

Lxm loaded Eudragit® RS 100 microspheres were prepared by emulsion solvent evaporation method, which is quite simple and involves two major steps, the formation of stable droplets of the drug-containing polymer solution and the subsequent removal of solvent from the droplets.

In this method, Acetone has a dielectric constant of 20.7 and was therefore chosen as the dispersed or internal phase, since solvents with dielectric constants between 10 and 40 showed poor miscibility with liquid paraffin. Eudragit® RS 100 is very slightly soluble in liquid paraffin. Therefore, liquid paraffin was used as the dispersion media or external phase along with Span 80 (Sengel *et al* 2006). Span 80 is soluble in mineral oil (like liquid paraffin) which acts as a droplet stabilizer and prevents coalescence of the droplets by localizing at the interface between the dispersed phase and dispersion medium (Singh and Chaudhary, 2011). In practice, however, reproducible manufacturing of microspheres with the desired properties (sphericity, good yield, flow property, encapsulation efficiency, suitable particle size and release profile), can be affected by the various factors such as concentration of drug, polymer, emulsifier and stirring speed etc.

Shape and surface morphology analysis

Scanning electron microscopy (SEM) was performed to determine whether the microspheres formed had been spherical and also to examine their internal and external surface. The use of SEM is also important for establishing the degree of porosity. The results of SEM analysis showed that Lxm loaded ERS microspheres were discrete, spherical, and uniform with presence of pores and few drug crystals on the surface of the microspheres **(Figure 1a, 1b)**.

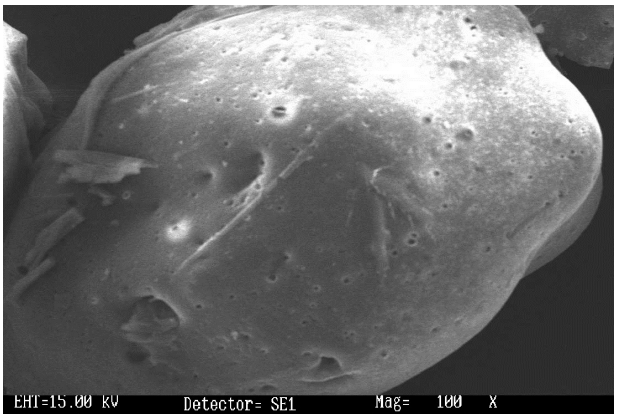

Fig. 1a. SEM images of Lxm Loaded Eudragit® RS 100 microspheres at 100x magnification

It was also evident that the microspheres exhibited porous surfaces, probably due to the high concentration of drug, since increased degree of porosity was observed with increased drug to polymer ratio. Microspheres that formulated with low concentrations of ERS that is 1:1 drug: polymer concentrations (LERSM-P_1) were small, soft, irregular and non spherical **(Table 2)**. These results showed that the

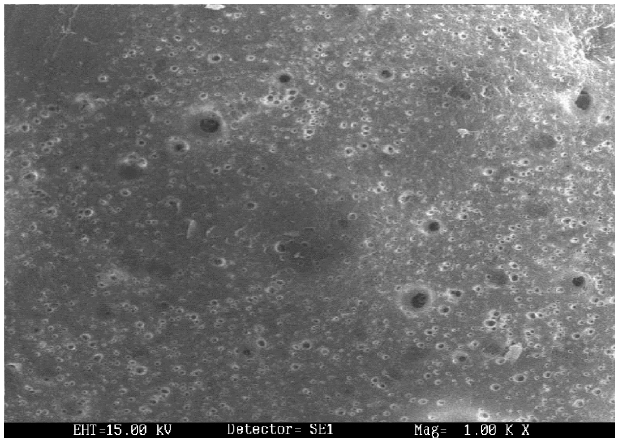

Fig. 1b. SEM images of Lxm loaded Eudragit® RS 100 microspheres at 1000x magnification

amount of solid and the viscosity of the inner phase is an important factor for the preparation of microspheres. When keeping the drug amount and the solvent volume constant, the spherical and uniform microspheres were formed as the polymer concentration was increased in formulations with 1:2 and 1:4 drug: polymer ratios. However, the irregular shapes of microspheres were observed when polymer concentration was further increased to 1:5 drug: polymer ratio (LERSM-P_5) because high polymer concentration was not completely dispersed in the outer phase. It was also observed that an optimum concentration of emulsifier *i.e.* 1.50 % (LERCM-E_2) is required to produce stable droplet resulting spherical microspheres, but in case of decreasing its concentration to 1.0 % (LERCM-E_1) led to increased extent of coalescence, resulting in irregular microspheres. Above the optimum concentration, microsphere having rough surface was observed (Maia *et al* 2004).

During processing, it was observed that the shapes of microspheres were irregular at 500 rpm, due to inadequate agitation of the media to disperse the inner phase in form of discrete droplets within the outer phase (Haznedar and Dortunc, 2004). Moreover, stirrer speed of 1000 rpm, resulted in high turbulence causing frothing and adhesion of the microspheres to the container walls and blade surfaces. The desired spherical microspheres with good surface characteristics were obtained at stirring speed of 750 rpm; therefore, this speed was used during manufacture of all the microspheres.

Table 2. Summary of effects of formulation and process variables on formulated microspheres

Formulation code	Shape	Product yield* (%)	Average particle size* (μm)	Drug entrapment efficiency* (%)	Drug release over the period of 12 h* (%)
LERSM-D_1	Spherical	83.60 ± 0.56	198.94 ± 2.86	82.38 ± 1.61	72.92 ± 1.68
LERSM-D_2	Spherical	78.50 ± 1.24	205.74 ± 4.45	76.58 ± 1.81	77.23 ± 1.86
LERSM-D_3	Spherical	75.07 ± 0.68	210.12 ± 3.54	72.45 ± 2.09	80.97 ± 2.43
LERSM-D_4	Spherical	71.87 ± 1.15	214.92 ± 4.24	69.72 ± 1.10	85.18 ± 2.15
LERSM-P_1	Irregular shape	68.75 ± 0.82	132.52 ± 5.24	65.18 ± 1.66	87.48 ± 1.42
LERSM-P_2	Spherical	74.16 ± 1.14	153.74 ± 4.53	73.83 ± 1.92	82.48 ± 2.68
LERSM-P_3	Spherical	78.12 ± 0.95	171.48 ± 5.34	77.57 ± 1.43	78.36 ± 1.82
LERSM-P4	Spherical	83.60 ± 0.56	198.94 ± 2.86	82.38 ± 1.61	72.92 ± 1.68
LERSM-P_5	Irregular shape	84.83 ± 0.88	207.56 ± 4.18	81.05 ± 1.48	70.26 ± 2.3
LERSM-E_1	Irregular shape	83.20 ± 0.62	204.87 ± 3.68	84.66 ± 1.86	70.15 ± 2.3
LERSM-E_2	Spherical	83.60 ± 0.56	198.94 ± 2.86	82.38 ± 1.61	72.92 ± 1.68
LERSM-E_3	Rough surface	80.90 ± 0.83	182.36 ± 5.08	76.31 ± 2.41	79.56 ± 2.15
LERSM-S_1	Irregular shape	84.10 ± 0.74	202.16 ± 4.62	85.28 ± 1.60	70.68 ± 1.63
LERSM-S_2	Spherical	83.60 ± 0.56	198.94 ± 2.86	82.38 ± 1.61	72.92 ± 1.68
LERSM-S_3	Spherical	81. 70 ± 0.91	190.82 ± 3.14	74.55 ± 2.45	78.35 ± 2.02

*Values are average of 3 readings ± standard deviation

Percentage yield and particle size analysis

In microsphere preparation, % yield was gradually decreased by increasing the drug to polymer ratio as it increased the viscosity of the solution in which solvent get evaporated rapidly before mixing with continuous phase, therefore forming as fibers and aggregates which further reduced the % yield. However, % yields slightly increased as the polymer ratio increased. The maximum yield was found to be 84.83±0.88% and the resulting average particle size of microspheres were found to be 132.52 ± 5.24 to 214.92±4.24 μm **(Table 2)**. The average particle size of microspheres increased with increasing

Lxm concentration might be due to increased content of the internal phase (drug and polymer) leading to bigger emulsion droplets resulting in a comparative increase in size of microspheres. Therefore, increasing the polymer:drug ratio caused the microsphere size to shift towards a higher size.

This may be due to higher concentration of polymer produced a more viscous dispersion which formed larger droplets and consequently larger microspheres (Pongpaibul *et al* 1984). Increased surfactant concentration led to the formation of particles with a lower mean particle size due to 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 optimum concentration, the dispersed globules/droplets were 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. Increasing the speed of stirring decreased the particle sizes and % yield of microspheres (Babay *et al* 1988).

Drug entrapment efficiency

The value of drug incorporation efficiency was found to be in the range of 65.18±1.66 to 85.28±1.60% **(Table 2)**. Results showed that drug entrapment efficiency decreased with increase in the drug proportion of the preparation.

This may be due to the reason that at higher concentration, drug might not uniformly dispersed in the polymer matrix. The increased entrapment efficiency was seen with increasing concentrations of polymer because increased polymer content provides more binding sites for the drug molecules and more particles of drug would be coated leading to higher encapsulation efficiency (Khan *et al* 2010).

Flow property of microspheres

Angle of repose, bulk and tapped density, Carr's index and Hausner's ratio were determined to predict the flow properties of microspheres formulations.

The value of bulk density and tapped density of microspheres were varied in the range of 0.385±0.015 to 0.612±0.021 g/cm^3 and 0.417±0.017 to 0.811±0.036 g/cm^3 **(Table 3).**

Table 3. Effects of formulation and process variables on flow property of formulated microspheres

Formulation Code	Bulk density* (g/cm^3)	Tapped density* (g/cm^3)	Compressibility (Carr's) index* (%)	Hausner's Ratio*	Angle of Repose*
LERSM-D_1	0.441 ± 0.011	0.484 ± 0.013	8.884 ± 0.217	1.097 ± 0.002	15.10 ± 1.070
LERSM-D_2	0.411 ± 0.009	0.447 ± 0.011	8.053 ± 0.309	1.087 ± 0.003	17.20 ± 2.250
LERSM-D_3	0.400 ± 0.016	0.435 ± 0.019	8.045 ± 0.357	1.087 ± 0.004	16.50 ± 1.851
LERSM-D_4	0.385 ± 0.015	0.417 ± 0.017	7.673 ± 0.167	1.083 ± 0.002	15.44 ± 2.145
LERSM-P_1	0.612 ± 0.021	0.811 ± 0.036	24.537 ± 0.826	1.325 ± 0.014	29.35 ± 2.211
LERSM-P_2	0.535 ± 0.016	0.600 ± 0.021	10.833 ± 0.381	1.121 ± 0.005	19.44 ± 1.784
LERSM-P_3	0.492 ± 0.013	0.545 ± 0.016	9.724 ± 0.233	1.107 ± 0.002	18.76 ± 1.025
LERSM-P_4	0.441 ± 0.011	0.484 ± 0.013	8.884 ± 0.217	1.097 ± 0.002	15.10 ± 1.070
LERSM-P_5	0.405 ± 0.009	0.484 ± 0.013	16.322 ± 0.473	1.195 ± 0.006	25.47 ± 1.178
LECM-E_1	0.416 ± 0.017	0.492 ± 0.013	15.447 ± 1.884	1.182 ± 0.025	23.74 ± 0.960
LECM-E_2	0.441 ± 0.011	0.484 ± 0.013	8.884 ± 0.217	1.097 ± 0.002	15.10 ± 1.070
LECM-E_3	0.411 ± 0.025	0.500 ± 0.025	17.800 ± 1.306	1.216 ± 0.019	27.42 ± 2.705
LERSM-S_1	0.422 ± 0.010	0.508 ± 0.015	16.929 ± 1.398	1.203 ± 0.005	26.70 ± 1.147
LERSM-S_2	0.441 ± 0.011	0.484 ± 0.013	8.884 ± 0.217	1.097 ± 0.002	15.10 ± 1.070
LERSM-S_3	0.517 ± 0.011	0.577 ± 0.019	10.398 ± 0.366	1.116 ± 0.004	19.27 ± 1.530

*Values are average of 3 readings ± standard deviation

The Carr's index and Hausner's ratio for all formulations (except LERSM-P_1 formulation) were less than 17.800±1.306 and 1.216±0.019 respectively, which are within the normal acceptable value. This is further substantiated by the values of angle of repose which was in the

range from 15.10±1.070 to 29.35±2.211, indicating excellent flow characteristics of the microspheres, suggesting that all the microspheres formulations can be easily handled during processing.

In vitro drug release study

The percentage of drug release after 12 h was found between 70.15 ± 2.3 to 87.48 ± 1.42 % for all microspheres formulations. It was found that the drug release was prolonged up to 12 h. **Figure 2** showed the effect of drug to polymer ratio on Lxm release from the prepared microspheres.

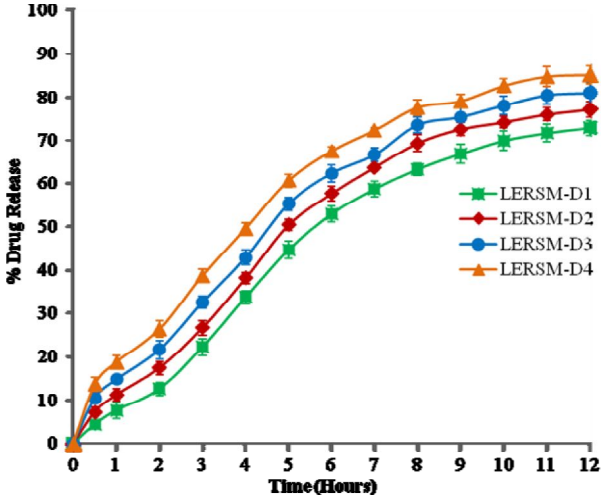

Fig 2. Effect of drug concentration on Lxm release from microspheres

The results revealed that, the release profiles of microspheres prepared with 1:1 drug to polymer ratio (LERSM-D_1) showed the most retarded release patterns. Moreover, increasing the drug concentration produced faster drug release because as the amount of drug content is increased, the matrix become more porous as drug leached out from the polymer and thus faster drug release rate occured (Song *et al* 1981). The rate of drug release from the microspheres depends on the polymer concentration as shown in **Figure 3**, which indicated that the release of Lxm from the microspheres was decreased with increasing content of the polymer and can be explained by a decreased amount of drug presented close to the surface and also by the fact that the amount of uncoated drug decreased with increase in polymer concentration (Alex and Bodmeier, 1990). Drug release rates from Eudragit RS 100 microspheres were also affected by emulsifier concentration and stirring speed of the system.

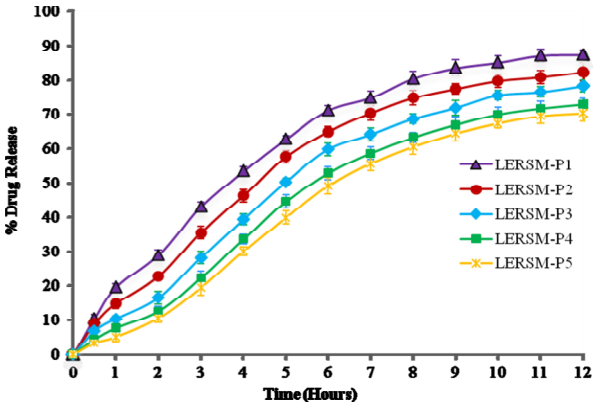

Fig. 3. Effect of polymer concentration on Lxm release from microspheres

The results revealed that the rate and amount of drug release increased, as the concentration of the emulsifier was increased **(Figure 4)**. This is due to the increase in wettability and better solvent penetration as the surfactant is increased and may also lead to the increase in amount of drugs deposited at the surface. Increasing the stirring speed of the system decreased the mean particle size as mentioned before and this led to an increase of release rate **(Figure 5)** as would be expected from surface area relationship (Pongpaibul *et al* 1984).

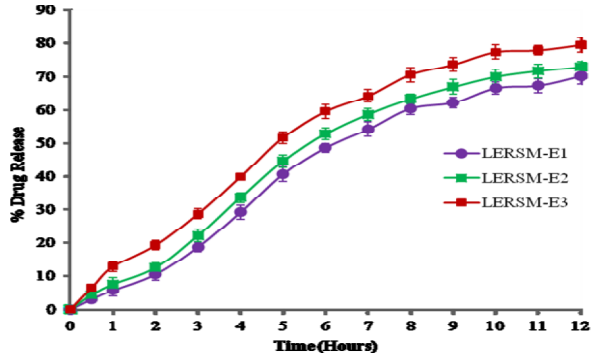

Fig. 4. Effect of emulsifier (surfactant) conc. on Lxm release from microspheres

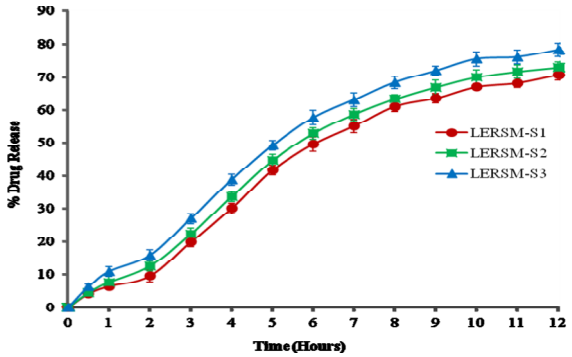

Fig. 5. Effect of stirring speed on Lxm release from microspheres

Differential scanning calorimetry study

The thermal behavior of drug, ERS, physical mixture of drug and ERS, blank ERS microspheres and Lxm loaded ERS microsphere are presented in **Figure 6**.

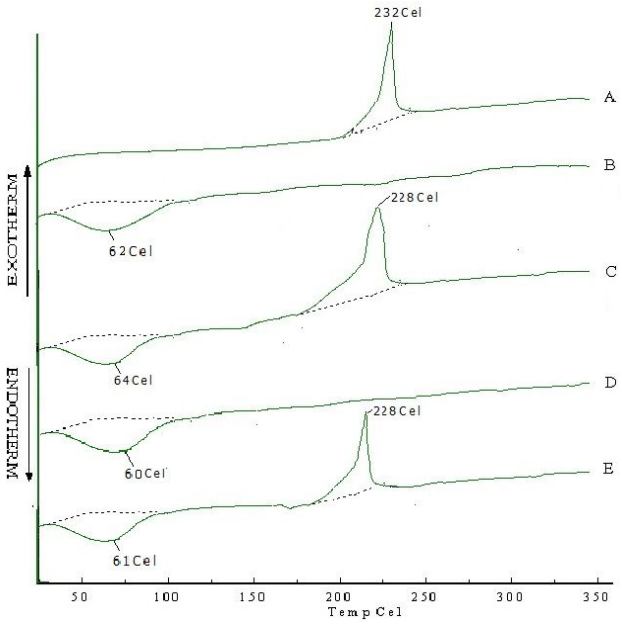

Fig. 6. DSC thermo grams of pure Lxm (A), Eudragit RS 100 (B), physical mixture of Lxm and Eudragit RS 100 (C), Blank Eudragit RS 100 microspheres (D) and Lxm-loaded Eudragit RS 100 microsphere (E).

In the thermogram, the pure Lxm exhibiting a sharp exothermic peak at 232°C corresponded to the melting point of drug in the crystalline form. The DSC of ERS showed a peak at 62°C, indicating its glass transition temperature.

In the DSC curve of physical mixture of Lxm and ERS, and Lxm loaded microspheres formulation, the characteristic peaks of drug(s) were observed. The result showed that there was no incompatibility between the drug and polymers.

CONCLUSION

Lornoxicam loaded Eudragit® RS 100 microspheres were prepared successfully using emulsion solvent evaporation techniques. The formulated microspheres were found to be satisfactory with respect to micromeritic properties as well as drug release. The studies suggested that judicious selection of optimum formulation and process variables are necessary to obtain microspheres with desired properties. It was concluded that Eudragit® RS 100 can be successfully employed to load and entrap lornoxicam for retarding the drug release from particulate drug delivery system such as microspheres.

ACKNOWLEDGEMENT

The authors are grateful to Zydus Cadila, Ahmedabad (GJ) for providing sample of Lxm.

REFERENCES

Alex R, Bodmeier R. Encapsulation of water-soluble drugs by a modified solvent evaporation method. I. Effect of process and formulation variables on drug entrapment. *J. Microencapsul.* 1990;7(3):347-55. [DOI: 10.3109/02652049009021845]

Atyabi F, Mohammadi A, Dinarvand R. Preparation of nimodipine loaded microspheres: Evaluation of parameters. *Iranian J. Pharm. Sci.* 2005;1(3):143-52.

Babay D, Hoffman A, Benita S. Design and release kinetic pattern evaluation of indomethacin microspheres intended for oral administration. *Biomaterials* 1988;9 (6):482-8. [http://dx.doi.org/10.1016/0142-9612(88)90042-7]

Balfour JA, Fitton A, Barradell LB. Lornoxicam. A review of its pharmacology and therapeutic potential in the management of painful and inflammatory conditions. *Drugs* 1996;51(4):639-57.

Basarkar GD, Shirsath GN, Patil SB. Development of microspheres containing diclofenac diethylamine as sustained release topical formulation. *Bull. Pharm. Res.* 2013;3(1):14-22.

Basu SK, Adhiyaman R. Preparation and characterization of nitrendipine loaded eudragit RL 100 microspheres prepared by an emulsion-solvent evaporation method. *Trop. J. Pharm. Res.* 2008;7(3):1033-41.

Behera BC, Sahoo SK, Dhal S, Barik BB, Gupta BK. Characterization of glipizide-loaded polymethacrylate microspheres prepared by an emulsion solvent evaporation method. *Trop. J. Pharm. Res.* 2008;7(1): 879-85.

Choi HS, Seo SA, Khang G, Rhee JM, Lee HB. Preparation and characterization of fentanyl-loaded PLGA microspheres: *In vitro* release profiles. *Int. J. Pharm.* 2002;234(1-2):195-203. [DOI: http://dx.doi.org/10.1016/S0378-5173(01)00968-1]

Chowdary KPR, Koteshwara Rao N, Malathi K. Ethyl cellulose microspheres of glipizide: Characterization, *in vitro* and *in vivo* evaluation. *Indian J. Pharm. Sci.* 2004; 66(4):412-6.

Dahiya S, Gupta ON. Formulation and *in vitro* evaluation of metoprolol tartrate microspheres. *Bull. Pharm. Res.* 2011; 1(1):31-9.

Garud N, Garud A. Preparation and *in-vitro* evaluation of metformin microspheres using non-aqueous solvent evaporation technique. *Trop. J. Pharm. Res.* 2012;11(4): 577-83. [http://dx.doi.org/10.4314/tjpr.v11i4.8]

Gupta VK, Beckert TE, Price JC. A novel pH- and time-based multi-unit potential colonic drug delivery system. I. Development. *Int. J. Pharm.* 2001;213(1-2):83-91. [http://dx.doi.org/10.1016/S0378-5173(00)00649-9]

Haznedar S, Dortunc B. Preparation and *in vitro* evaluation of eudragit microspheres containing acetazolamide. *Int. J. Pharm.* 2004;269(1):131-40. [http://dx.doi.org/10.1016/j.ijpharm.2003.09.015]

Homdrum E-M, Likar R, Nell G. Xefo® Rapid: A novel effective tool for pain treatment. *Eur. Surg.* 2006;38(5):342-52. [DOI: 10.1007/s10353-006-0272-6]

Khan SA, Ahmad M, Murtaza G, Aamir MN, Rehman N, Kousar R, Rasool F, Akhtar M. Formulation of nimesulide floating microparticles using low-viscosity hydroxypropyl methylcellulose. *Trop. J. Pharm. Res*. 2010;9(3):293-9.

Kidd B, Frenzel W. A multicenter, randomized, double blind study comparing lornoxicam with diclofenac in osteoarthritis. *J. Rheumatol.* 1996;23(9):1605-11.

Kim BK, Hwang SJ, Park JB, Park HJ. Preparation and characterization of drug-loaded polymethacrylate microspheres by an emulsion solvent evaporation method. *J. Microencapsul.* 2002;19(6):811-22. [DOI: 10.1080/02652040210000022770]

Kumar M, Dureja H. Development and characterization of factorially designed 5-fluorouracil microspheres. *Bull. Pharm. Res.* 2011;1(1):54-61.

Maia JL, Santana MHA, Re MI. The effect of some processing conditions on the characteristics of biodegradable microspheres obtained by an emulsion solvent evaporation process. *Braz. J. Chem. Eng.* 2004;21(1):1-12. [DOI: 10.1590/S0104-66322004000100002]

Martin AN. Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences, 4th edition, Lippincott Williams & Wilkins: USA, 1993.

Perumal D. Microencapsulation ibuprofen and eudragit® RS 100 by the emulsion solvent diffusion technique. *Int. J. Pharm*. 2001;218(1-2):1-11. [http://dx.doi.org/10.1016/S0378-5173(00)00686-4]

Pongpaibul Y, Price JC, Whitworth CW. Preparation and evaluation of controlled release indomethacin microspheres. *Drug Dev. Ind. Pharm.* 1984;10(10):1597-1616. [DOI: 10.3109/03639048409039070]

Ritschel WA. Biopharmaceutics and pharmacokinetic aspects in the design of controlled release peroral drug delivery systems. *Drug Dev. Ind. Pharm*. 1989;15(6-7):1073-1103. [DOI: 10.3109/03639048909043666]

Sahoo SK, Mallick AA, Barik BB, Senapati PC. Formulation and *in vitro* evaluation of eudragit® microspheres of stavudine. *Trop. J. Pharm. Res.* 2005;4(1):369-75.

Sahoo SK, Mallick AA, Barik BB, Senapati PC. Preparation and *in vitro* evaluation of ethyl cellulose microspheres containing stavudine by the double emulsion method. *Pharmazie* 2007;62(2):117-21. [DOI: http://dx.doi.org/10.1691/ph.2007.2.6076]

Sengel CT, Hascicek C, Gonul N. Development and *in-vitro* evaluation of modified release tablets including ethylcellulose microspheres loaded with diltiazem hydrochloride. *J. Microencapsul.* 2006;23(2):135-52. [DOI: 10.1080/02652040500286474]

Singh V, Chaudhary AK. Preparation of Eudragit E100 microspheres by modified solvent evaporation method. *Acta Pol. Pharm.* 2011;68(6):975-80.

Song SZ, Cardinal JR, Kim SM, Kim SW. Progestin permeation through polymer membrane. V: Progestrone release from monolithic hydrogel devices. *J. Pharm Sci*. 1981;70(2):216-9. [DOI: 10.1002/jps.2600700226]

Skjodt NM, Davies NM. Clinical pharmacokinetics of lornoxicam. A short half-life oxicam. *Clin. Pharmacokinet.* 1998;34(6):421-8. [DOI: 10.2165/00003088-199834060-00001]

Takka S, Rajbhandari S, Sakr A. Effect of anionic polymers on the release of propranolol hydrochloride from matrix tablets. *Eur. J. Pharm. Biopharm.* 2001;52(1):75-82. [DOI: http://dx.doi.org/10.1016/S0939-6411(01)00147-3]

*****