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Encapsulation of Lornoxicam into spermaceti microspheres and comparative bioavailability study

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Abstract

In this study, Lornoxicam (LX) loaded spermaceti (SC) microspheres were prepared using meltable emulsified dispersion cooling induced solidification technique and the bioavailability of the marketed product (Flexispaz® capsule-reference-product A) was compared with the optimized formulation (lornoxicam loaded spermaceti microspheres–test–product B). Morphological studies of wax microspheres were evaluated using scanning electron microscopy (SEM). The SEM images showed the spherical shape of wax microspheres and more than 97% of the isolated microspheres were in the size range 309-317 μm. Differential scanning calorimetry (DSC), Fourier transforms infrared (FTIR) spectroscopy and stability studies showed that the drug after encapsulation with SC microspheres was stable and compatible. A single dose, randomized, complete cross over study of LX (8mg) microspheres were carried out on 10 healthy male and female Albino sheep's under fasting conditions. Plasma LX concentrations and other pharmacokinetic parameters obtained were statistically analyzed. Based on this study, it can be concluded that drug loaded LX microspheres and Flexispaz® capsule are bioequivalent in term of the rate and extent of absorption.

Keywords: Lornoxicam; Wax microspheres; Release kinetics; Bioavailability; Bioequivalence

Introduction

Lipophilic drugs are poorly water-soluble, but easily mix with waxy materials and exhibit good absorption rate[1]. However, reported methods are not suitable for all lipophilic drugs[2] at its end use and recent years different methods have been developed to design different types of waxy microspheres loaded with lipophilic drugs [2]. From the point of environmental concern and human safety, dosage forms should be free from toxic solvents during preparation. In the present study, meltable dispersed emulsified cooling induced solidification method was used to prepare wax microspheres which are free from toxic solvent.

LX is a non-steroidal, anti-inflammatory agent with analgesic properties [3]. and chemically as 3E–6–chloro-3[hydroxyl(pyrolin–2-2ylamine) methylene) –2- methyl -2- 3–hydro– 4H thieno [2,3 – e] [1,2] thiazin– 4– one 1,1 dioxide. LX has a molecular weight of 371.80 g/mol and molecular formula is $C_{13}H_{10}ClN_3O_4S_2$. LX is commercially available in the form of conventional immediate-release tablets (4 and 8 mg), rapid-release tablets (8 mg), and parenteral formulations (4 mg/ml) for intravenous and intramuscular use. Studies revealed that it is more effective than 10 mg morphine when used to control pain after oral surgery & its analgesic activity is comparable to that of opioids. It is effective in the treatment of post-operative pain and rheumatoid arthritis [4]. It differs from other oxicams by its potent inhibition of prostaglandin biosynthesis [5]. In ischemia and ischemia-reperfusion conditions LX has exhibit protective effects on the development of myocardial infarction in rats [6] & also demonstrated its protective effects against herpetic stromal keratitis [7]. LX should be dosed at least 2 times a day. Due to its narrow therapeutic index, the frequency of adverse effects is dose related [8]. Considering the long therapeutic regimen of rheumatoid arthritis therapy, the administration of LX may induce adverse effects on gastro intestinal tract (GIT), central nervous system (CNS), renal & cardiac systems & on the skin. The occurrence of these adverse effects can be reduced by the use of controlled release formulations. Oral conventional dosage forms are administered 2–3 times a day to maintain adequate and effective therapeutic concentration in blood.

Spermaceti (SC) used in the current study has good pharmaceutical and biological properties [9]. SC is hard, shiny, oily to touch, slightly unctuous with faint odour and mild bland taste which makes it very useful excipient in cosmetics and pharmaceuticals. SC is non-toxic, non-irritant, non-immunogenic, biodegradable, biocompatible, gastro resistant, high carrier capacity, low production costs, reproducible properties used for drug entrapment and its release in a controlled manner. SC is used

widely used as a coating agent, stiffening agent, emollient, emulsifying agent in pharmaceuticals and cosmetics. It is included in the FDA as inactive ingredient in non-parenteral medicines licensed in the UK [10].

By employing suitable modification in the manufacturing process, controlled release formulation of LX has been developed which has several advantages over other conventional dosage forms such as reduction in the side effects & adjusting the absorption rate[11]. Recent reports showed that biocompatible, biodegradable, non-immunogenic waxes were successfully used for the encapsulating lipophilic drug and control the drug release in the intestinal tract [12]. SC is gastro resistant, but susceptible to intestinal juice [13].Without the risk of side effects, desired plasma levels can be achieved using once a day dose of controlled release preparation [14] & it is an effective route to suppress the toxicity of LX. The aim of the present study was to prepare the wax microspheres, compared the *in vitro* release of LX from wax microspheres with commercially available oral formulation Flexispaz® (8 mg capsule) and to carry out the bioavailability of two different oral LX formulation (optimized microsphere formulation and Flexispaz®8mg capsule) following single dose in healthy Albino sheep's to show the bioequivalence between both oral formulation.

Materials and Methods

Materials

Lornoxicam (LX), pure drug and Tenoxicam (TX), the internal standard were kindly donated by Micro Labs (Bangalore, India). LX is an odorless, yellow crystalline substance, practically insoluble in water and sparingly soluble in alcohol. LX has a pKa of 4.5 and is stable in neutral or slightly acidic media and decomposes in strong alkali. It has a melting point between 226 and 228 C and has molecular weight of 371.82. Spermaceti wax, Tween 80 and all other chemicals and solvents used were of analytical grade and purchased from Ranbaxy Fine chemicals (New Delhi, India). Commercially available oral capsule formulation (Flexispaz® 8mg, Glenmark, India) is used for the present study.

Preparation of microspheres

Disperse 1 part of LX (passed through sieve No. 100) in the melted 3 parts of SC and stirred to obtain a homogeneous mixture. To the mixture transferred 200 ml of Phosphate buffer solution (pH 6.3), previously maintained at a temperature higher than melting point of LX. The melted mixture was stirred for 5 min at 800 rpm by adding surfactant, Tween 80 (0.3 % w/w). Rapid cooling of the developed reaction mixture to 10^0C produces floated spherical particles. Collect the separated solid spheres by filtration and remove surfactant traces from wax spheres by washing with stream of water. Dry the free flowing microspheres at room temperature for two day. Set of five formulations were prepared presented in Table1.

Table 1. Formulations chart

Formulation Code	Drug (gm)	Spermaceti (gm)
A_1	2.8	8.8
A_2	2.9	8.9
A_3	3.0	9.0
A_4	3.1	9.1
A_5	3.2	9.2

Characterization of microsphere

Tap density, Angle of repose (h), Percent yield, & Carr's index (% I) of the prepared SC microspheres was determined.

Scanning electron microscopic studies and sphericity determination

Scanning electron microscope (SEM) photomicrographs were recorded using Joel-LV-5600 SEM, USA. Sphericity of the wax microsphere was determined using a digital camera (Sony, DSC T-4010.Cyber shot, Japan. Photomicrographs were taken) & mean Feret diameter (FD), Aspect ratio (AR) and two-dimensional shape factor (*e*R) were calculated.

Differential scanning calorimetry (DSC)

All dynamic DSC studies were carried out on DuPont thermal analyzer with 2010 DSC module & instrument was calibrated using high purity indium metal as standard. Triplicate scans were taken in nitrogen atmosphere at the heating rate of 10 C/min.

Fourier transforms infrared spectroscopy (FTIR)

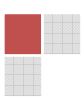
FTIR spectra of pure drug, empty microspheres and drug encapsulated microspheres were taken using FTIR spectrophotometer (Shimadzu, Model 8033, USA) in the wave number region between 4000- 400 cm^{-1}).

Estimation of drug loading

From each batch, drug loaded microspheres were selected & powdered in a mortar. Extract the drug from wax microspheres using methanol, filtered and analyzed for drug content after suitable dilution by HPLC[15].

In Vitro studies

In vitro release study of drug loaded microspheres was carried out USP XXI dissolution apparatus, type II. The prepared formulations were subjected for dissolution study in 900ml dissolution medium for 2 h in pH 1.2 hydrochloric acid buffer and 8 h in pH 7.2 phosphate buffers. 10 ml of sample solution was withdrawn periodically using guarded sample collectors at an interval of 30 min for first 4 h and at 60 min interval for the next 6 h.



In vivo studies

The study was an open, randomized complete cross over design in which 8 mg dose of LX (Flexispaz® capsule and formulation A_3) was administered to sheep's (wash out period of 2 weeks). The content uniformity of marketed product and optimized formulation has been estimated. Ten adult albino sheep's (age 5 to 7 years & weight 25 and 28 kg) employed for in vivo studies. The in vivo experimental protocol was approved by the institutional animal ethical committee, JSS Medical College Hospital and J.S.S College of Pharmacy, Mysore, Karnataka, India. The written information on the study was provided to the Veterinary Surgeon, Central Animal Facility, JSS Medical College Hospital. The drug content was determined by extracting the drug from their respective dosage forms using methanol (80%). Animals have been shifted to the clinical trial laboratory and 18 gauge (1.3X45 mm, 96ml/min) canula was inserted in to a jugular vein with heparinised saline lock for ensuing blood sample (5ml). Flexispaz® capsule and formulation A_3 (Test medications) were administered to the sheep's and blood samples were collected at 0 h (pre dose interval) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10 post dose intervals. The plasma was collected from blood samples by centrifugation (eltek-TC 4100 D centrifuge, Mnf. by Elektroshaft, Bombay, India) at 1500 rpm for 10 min. The collected plasma was stored at –20^{0}C prior to analysis. Plasma concentration of drug from the collected samples was quantified by HPLC method.

Chromatographic Studies

The HPLC system consisted of HPLC-Shimadzu (Tokyo, Japan) LC-6A model, fitted with a μ –Bondapack C_{18} (4.6 X 250 mm) column of particle size 5μm (Supelco, Bellefonte, PA). The flow rate was adjusted to 1μL/min and the drug concentration was detected using a UV/visible detector (SPD- 6Av). Tenoxicam (TX) was used as internal standard. The mobile phase consisted of 65:35 (% v/v) mixture of 5M ammonium acetate and acetonitrile with final pH adjusted to 5 with glacial acetic acid. The column was equilibrated for 30 min with mobile phase before injection and detection was carried out at wavelength of 372nm. Quantification was achieved by the measurement of the peak area ratio of the LX to the internal standard (TX). The limit of detection of LX in plasma was 100 ng/ml (500 μL of plasma injected).

Pharmacokinetics and Statistical data evaluation

The pharmacokinetic parameters were calculated using the Quick calk, computer PK calculation programme. The maximum plasma concentration (C_{max}) & time required to achieve maximum plasma concentration (T_{max}) were calculated directly from plasma level profile and the elimination rate constant (K_{el}) was calculated by the method of least square regression analysis. The area under the curve from 0 to 24h (AUC_{0-24}) was calculated using trapezoidal rule method. The drug plasma concentration and pharmacokinetic parameters were analyzed by paired t- test and analysis of variance (ANOVA) at 95% confidence limit. Difference between two related means was considered statistically significant when their P values were equal to or less than 0.05.

Results and Discussion

Waxes exhibit stable physical properties and behavior suitable to develop microspheres (biodegradable, gastro resistant, biocompatible) which sufficiently release the encapsulated drug in the intestinal lumen [17]. The present study employed the modified novel meltable dispersion emulsified cooling induced solidification method to prepared LX loaded microspheres using inert wax (SC) as carrier. The influence of various parameters on the prepared microspheres were analyzed and mentioned. The maximum drug was loaded in the microspheres at pH 4.0. If the pH was increased from 4.2 to 7.0, the percentage of LX loading was reduced from 23.22 to 4.98 %. 150 ml of aqueous phase was suitable to prepare spherical microspheres. It was observed that as the volume of aqueous phase increased, it affects the morphology and yield of the microspheres. The spherical and free flowing microspheres were produced using an optimum 1:3 w/w ratio of drug to wax (SC) (Table 1). It was also noticed that as drug to wax ratio was increased (2:3 w/w), clumps of microspheres were produced at the time cooling. SEM photographs also showed the development of drug crystal on the surface of microspheres [18].

Encapsulation of LX into SC microspheres requires the addition of surfactant (Tween 80) at an optimum concentration of 0.4% w/w for the proper distribution of lipophilic SC in hydrophilic aqueous phase. The temperature of the aqueous phase was maintained at 5^{0}C higher than the melting point of the SC in the corresponding formulations. It was observed that the resultant microspheres were free from surface irregularities, except some wrinkles. When the temperature of the aqueous phase was less than 5^{0}C than the melting point of the SC, big flakes were noticed. Average size of the produced microspheres was in the range between 309 to 317 mm presented in Table 2. Optimum Stirring speed (900 rpm) and stirring time (5 min) produces better size of the microspheres.

The micromeritic properties of the prepared microspheres are summarized in Table 2.The obtained data for angle of repose, tapped density and % Carr's indexes were well within the range, indicates good flow potential for the prepared microspheres. SEM micro photographs showed that the prepared microspheres were spherical in nature, containing inward dents and absence of drug crystals on the surface as shown in Figure.1. The microspheres were dried at room temperature for 24h, showed the sphericity value nearer to 1. However, microspheres dried for 24h at 40^{0}C exhibits the sphericity value more than 1. DSC thermograms, Figure.2 showed a sharp endothermic peak at 227.8^{0}C & 226.7^{0}C for pure LX & LX loaded formulation A_3, respectively. From the above study it was confirmed that the loaded LX was uniformly distributed on the wall of the microspheres [19].

Table 2. Micromeritic properties of the drug loaded SC microspheres

Formulation Code	Average size (µm) Mean± SD*	Yield (%) Mean ± SD*	Angle of repose (θ^0) Mean ± SD*	Carr's Index (%) Mean ± SD*	Tapped Density (g/cm^3) Mean ± SD*
A_1	309 ± 03	92.32 ± 0.8	24.12± 0.9	9.21 ± 0.6	0.39 ± 0.2
A_2	312± 06	93.43± 1.1	26.34± 1.1	10.12 ± 0.5	0.45 ± 0.4
A_3	313± 04	95.79± 0.7	27.15± 1.2	12.54 ± 0.8	0.58 ± 0.3
A_4	315± 02	91.23± 1.3	25.28± 1.0	11.89 ± 0.4	0.35 ± 0.5
A_5	317± 05	89.10± 1.1	23.14± 0.8	10.58 ± 0.3	0.32 ± 0.3

*Standard deviation n = 3

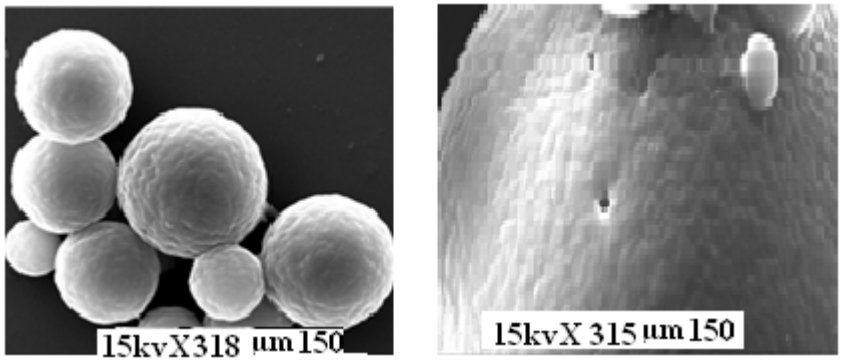
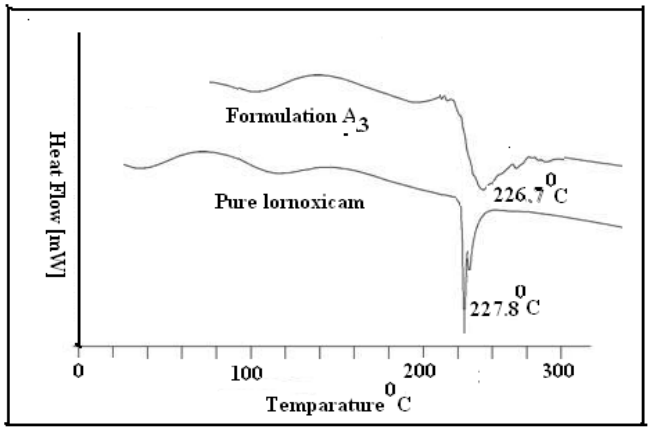


Figure. 1. SEM microphotographs of drug loaded microspheres formulation (A_3)



Fighre. 2. DSC thermograms of pure Lornoxicam and Lornoxicam loaded spermaceti microspheres (Formulation A_3)

Figuge. 3 showed the FTIR spectra of LX and compare it with the formulation A_3 at 3,090 cm^{-1} (NH stretching), 1,642 cm^{-1}(C=O stretching), 1,597 and 1,559 cm^{-1} (N–H group stretching), 1,157, 1,387, and 1,336 cm^{-1} (O=S=O group stretching), 827.94 cm 1 (–CH aromatic ring bending) and 766.8 cm^{-1} (C–Cl vibration bending). The characteristic IR absorption peaks of LX were not altered after successful encapsulation of drug, indicating no chemical interactions between the drug and used excipients [20].

The XRD pattern of LX and formulation A_3 is shown in Figure. 4. It was observed that pure drug exhibits several sharp high-intensity peaks at diffraction angles 2θ of 7.8 , 10.2 , 12.2 , 14.5 , 18.2 , 22.2 , and 24.5 suggesting that LX existed as a crystalline material. A slight decrease in LX crystalline character was observed in the diffractograms of the formulation A_3 as evidenced by the noticeable decrease in the number and intensities of peaks present in their X-ray diffractogram when compared to the corresponding pure LX [21].

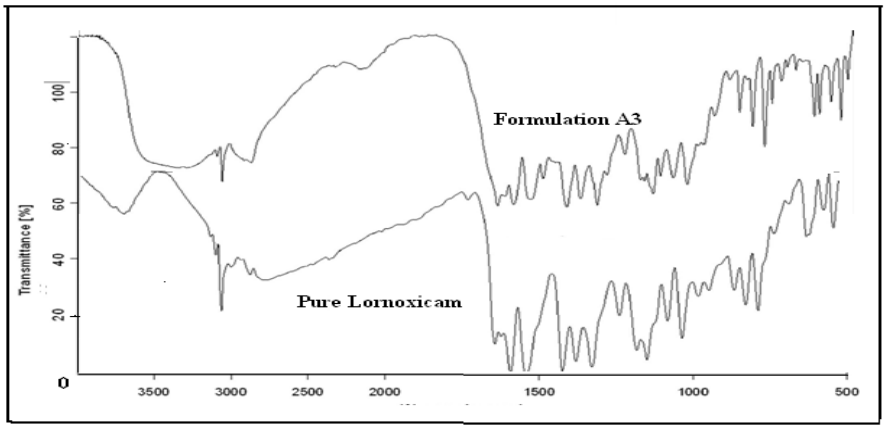


Figure-3.FTIR spectra of Lornoxicam and Lornoxicam loaded spermaceti microspheres(Formulation A_3)

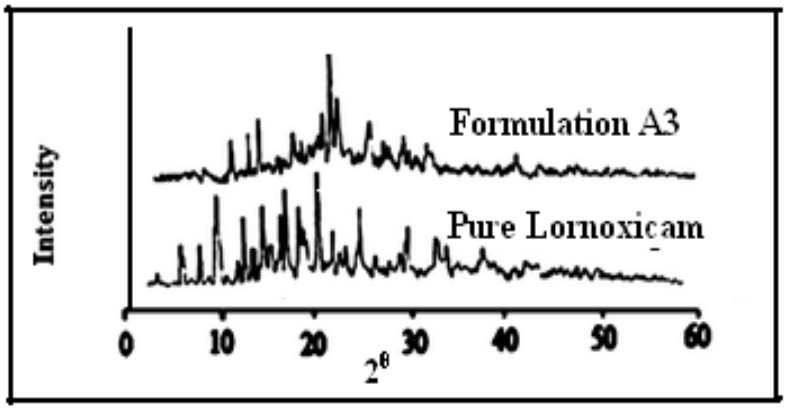


Figure. 4. XRD pattern of Lornoxicam and Lornoxicam loaded spermaceti microspheres (Formulation A_3)

The percentage of drug loading in the formulations was found to be in the range of 19.67 to 23.22 %. The drug loading capacity was maximum in the formulation A_3 (23.22) whereas minimum drug was loaded in the formulation A_4 (19.67). Drug encapsulation efficiency (%) was found to be more for formulation A_3 (95.23%) as compared to A_1 (90.32%), A_2 (92.13%), A_4 (88.23%), A_5 (89.98%).

No significant amount of drug was released from the microspheres at gastric pH, indicates spermaceti is gastro resistant in nature. The data obtained from in vitro study revealed that at the end of 12^{th} h the drug release from the optimized formulation A_3 (96.41%) was slower than Flexispaz® capsule (98.57%) in the intestinal environment. The influence of hydrophobic nature and molecular weight of spermaceti during drug release was observed.

The optimized formulation A_3 and Flexispaz® capsule were kept for stability studies at 25 ºC/ 60% RH (Relative humidity), 30 ºC/ 65% RH and 40 ºC/ 75% RH for a period of 90 days. It was observed that *in vitro* drug release from Flexispaz® capsule and formulation A_3 at the end of 90 days (12^{th} h), were 98.43 and 96.32 %, respectively. From the release studies, it was observed that, there was no significant change in *in vitro* drug release from both the products, indicates good stability for the prepared formulation. The drug content uniformity for Flexispaz®8 mg capsule and formulation A_3 was found to be 7.95 mg & 7.90 mg, respectively. The percent of drug content uniformity of Flexispaz®8 mg capsule and formulation A_3 are 99.76 and 99.49%, respectively.

The mean plasma concentration as a function of time is shown in Figure.5 and the calculated pharmacokinetic parameters of Flexispaz® and A_3 formulation are given in Table 3. After oral administration of both the products, more mean C_{max} value was observed for Flexispaz®8 mg capsule than formulation A_3 and difference in the C_{max} values obtained for both the formulations was statistically insignificant. On the basis of the therapeutic concentration range of LX, the therapeutic effects of both formulations would be probably be maintained for about 12 h following a single dose administration. In the present study, both controlled release formulations are associated with a similar onset of therapeutic response, following a single dose administration under fasting conditions [22].

Table 3. Comparison of mean values of pharmacokinetics obtained for products Flexispaz®& formulation A_3

Parameters	Flexispaz®	Formulation A_3	P value
T_{max} (h) *	2.29	2.15	< 0.05
C_{max} (ng /ml) *	914 ± 13.12	889 ± 10.30	< 0.05
$T_{1/2}$ (h^{-1}) *	4.2 ± 0.12	4.1 ± 0.10	< 0.05
U C_{0-24}*(ng/ml h^{-1})	4654 ± 56.12	4213 ± 46.30	< 0.05
AUC_{0-}*(ng/ml h^{-1})	4889 ± 65.21	4745 ± 57.38	< 0.05

*Standard deviation n = 3

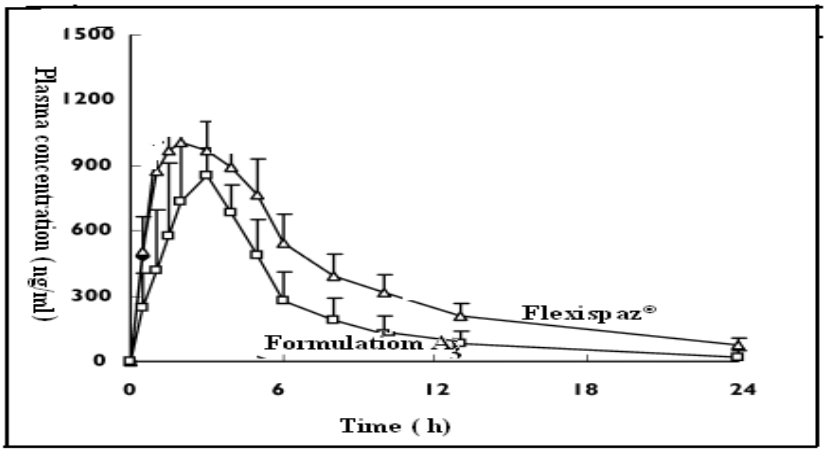


Figure. 5. Mean plasma concentrations–time profile of lornoxicam from Flexispaz® and formulation A_3.

The time taken to reach maximum plasma concentration T_{max} of LX was little higher in case of Flexispaz® compared to formulation A_3. However, no statistical significant differences were observed between two products. The calculated mean $T_{1/2}$ values for Flexispaz® and formulation A_3 were 4.2 ± 0.12 h^{1} and 4.1 ± 0.10 h^{1}, respectively & no statistical significance differences were observed between both the products[23]. From the study it was noticed that a small difference was observed between both products related to C_{max}, T_{max}, $T_{1/2,}$ and reduced fluctuations (peak to trough ratios) of the plasma concentrations.

The mean $AUC_{0–24}$ values for Flexispaz® and formulation A_3 were 4654 ± 56.12 ng/ml h^{-1} and 4213 ± 46.30 ng/ml h^{1} respectively and decreased AUC values from both products may be due to slow *in vitro* release of LX when compared with conventional dosage forms[24]. The average value of the individual and mean $AUC_{0–24}$ ratio at 95% confidence limit (0.8 – 1.24) was within acceptable limits for bioequivalent products. The observed mean AUC_{0-} values for Flexispaz® and formulation A_3 was 4889 ± 65.21 ng/ml.h^{-1} and 4745 ± 57.38 ng/ml.h^{-1} does not show any significant statistical difference between these products. In order to obtain *in vitro-in vivo* correlation, drug absorption profiles were compared for Flexispaz® and formulation A_3 using the cumulative fraction of the drug absorbed *in vivo* against cumulative fraction of the drug dissolved *in vitro* up to 12 h. Both products showed an adequate correlation & pharmacokinetic parameters clearly indicate that the parameters of formulation A_3 are in good agreement with Flexispaz®. The products Flexispaz® and formulation A_3 studied in the present study were found to be bioequivalent.

Conclusions

The objective of the present study was to prepare and evaluate wax microspheres of SC loaded with LX by optimized meltable dispersion emulsified cooling induced solidification method for controlled release. The method employed was simple, rapid, and economical and does not imply the use of toxic organic solvents. The results of the drug entrapment and micromeritic properties, exhibited fairly good spherical nature as evidenced by SEM photomicrograph. The compatible state of the drug loaded wax microspheres were evaluated by FTIR and DSC. Both the formulations were found to be bioequivalent and showed an adequate correlation between cumulative fractions dissolved in vitro and cumulative fractions absorbed in vivo. Optimized formulation A3 and marketed product Flexispaz® showed similarity in drug release profiles and in vivo bioequivalent behavior. From the present work, it can be concluded that the prepared wax microspheres demonstrate the potential use of SC for the development of controlled drug delivery systems for water insoluble or lipophilic drug..

References

[1]. Giannola LI, de Caro V, Severoino A. Carnauba wax microspheres loaded with valproic acid: preparation and evaluation of drug release. Drug Dev Ind Pharm. 1995; 21:1563–1572.

[2]. Edward JP, Terrence LB, Li S. The Chemistry of Waxes and Sterols: In: Casimir CA, David BM. Food lipids: chemistry, nutrition, and biochemistry.2nd ed. New York: Marcell Dekker; 2002.

[3]. 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):639-657.

[4]. Towart R, Graup J, Stimmeder D. Lornoxicam potentiates morphine antinociception during visceral nociception in the rat. Naunyn-Schmied Arch Pharmacol.1998; 358(1):172.

[5]. Radhofer-Welte S, Rabasseda X. Lornoxicam, a new potent NSAID with an improved tolerability profile. Drugs Today (Barc). 2000; 36(1):55-76.

[6]. Gavrilova SA, Lipina TV, Zagidullin TR, Fominykh ES, Semenov PA. Protective effect of lornoxicam on development of myocardial infarction in rats under conditions of ischemia and ischemia-reperfusion. Kardiologiia. 2008; 48(12):42-48.

[7]. Yin J, Huang Z, Xia Y, Ma F, Zhang LJ, Ma HH, et al. Lornoxicam suppresses recurrent herpetic stromal keratitis through down-regulation of nuclear factor-κB: an experimental study in mice. Mol Vis. 2009; 15:1252-1259.

[8]. Pruss TP, Stroissnig H, Radhofer-Welte S, Wendtlandt W, Mehdi N, Takacs F, et al. Overview of the pharmacological properties, pharmacokinetics and animal safety assessment of lornoxicam. Postgrad Med J. 1990; 66 (4): 18-21.

[9]. Raymond CR, Paul J S, Sian CO. Hand book of pharmaceutical excipients. 5th ed. Pharmaceutical press, Royal pharmaceutical society of Great Britain, UK: 2006.

[10]. Kibbe AH. Handbook of Pharmaceutical Excipients. 3rd ed. London, UK: American Association and The Pharmaceutical Society of Great Britain; 2000:401-406.

[11]. Hamza YES, Aburahma MH. Design and *In Vitro* Evaluation of Novel Sustained-Release Double-Layer Tablets of Lornoxicam: Utility of Cyclodextrin and Xanthan Gum Combination. AAPS PharmSciTech. 2009; 10(4):1357-1367.

[12]. Yonezawa Y, Ishida S, Sunada H. Release from or through a wax matrix system.VI. Analysis and prediction of the entire release process of the wax matrix tablet. Chem Pharm Bull (Tokyo). 2005; 53(8):915-918.

[13]. Chigwanda RTJ, Kuudzadombo A. Investigation of synthetic spermaceti wax as a potential oral sustained release drug delivery system. East Cent Afri J Pharm Sci. 2004; 7(2):24-26.

[14]. Dey NS, Majumdar S and Rao MEB. Multiparticulate drug delivery systems for controlled release. Trop J Pharm Res.2008; 7(3):1067-1075.

[15]. Aher KB, Bhavar GB, Joshi HP. Rapid RP-HPLC method for quantitative determination of lornoxicam in bulk and pharmaceutical formulations. Int J ChemTech Res. 2011; 3(3): 1220-1224.

[16]. Radhofer-Welte S, Dittrich P. Determination of the novel non-steroidal anti-inflammatory drug lornoxicam and its main metabolite in plasma and synovial fluid. J Chromatogr B Biomed Sci Appl. 1998; 707(1-2):151-159.

[17]. Chourasia MK, Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems. J Pharm Pharm Sci. 2003; 6(1):33-36.

[18]. Soppimath KS, Kulkarni AR, Aminabhavi TM. Development of hollow microspheres as floating controlled-release systems for cardiovascular drugs: preparation and release characteristics. Drug Dev Ind Pharm. 2001; 27(6):507-515.

[19]. Hamza Yel-S, Aburahma MH. Design and in vitro evaluation of novel sustained-release matrix tablets for lornoxicam based on the combination of hydrophilic matrix formers and basic pH-modifiers. Pharm Dev Technol. 2010; 15(2):139-153.

[20]. Nayak RK, Narayana Swamy VB, Senthil A, Thakkar H, Dave MK, Mahalaxmi R. Formulation and evaluation of fast dissolving tablets of Lornoxicam. Pharmacologyonline.2011; 2:278-290.

[21]. Ammar HO, Ghorab M, Mahmoud AA, Makram TS, Noshi SH. Topical liquid crystalline gel containing lornoxicam/cyclodextrin complex. J Incl Phenom Macrocycl Chem. 2012; 73:161–175.

[22]. Skjodt NM, Davies NM. Clinical pharmacokinetics of lornoxicam. A short half-life oxicam. Clin Pharmacokinet. 1998; 34(6):421-8.

[23]. Hlzenberger G, Radhofer-Welte S, Takacs F, Rosenow D. Pharmacokinetcis of lornoxicam in man. Postgrad Med J. 1990; 66:S23–S27.

[24]. Radhofer-Welte S, Rabasseda X. Lornoxicam, a new potent NSAID with an improved tolerability profile. Drugs Today (Barc).2000; 36(1):55–76.