Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE LORNOXICAM BY LIQUISOLID TECHNIQUE

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ABSTRACT

The aim of the present work is to formulate a sustained release dosage form by powder solution technique (or) liquisolid technique to prolong the drug dissolution rate of Lornoxicam. There is a necessity to formulate Lornoxicam as a sustained release dosage form due to its shorter half-life (4 hrs) and its limited solubility in acidic pH, thereby improving the efficacy and patient compliance. To achieve this, Lornoxicam was dispersed in Polysorbate 80 (liquid vehicle), followed by addition of the polymer. A carrier (Avicel PH-102) was added to the liquid vehicle under continuous mixing to attain a dry powder. Coating agent (silica amorphous) was then added to enhance the flow property of the prepared powder. The release rate of Lornoxicam from liquisolid compacts were compared to the release of lornoxicam from the formulated direct compressible conventional matrix tablets (DCCMT). It was evident from the investigation that polysorbate 80 (Tween 80) had an important role in sustaining the release of drug from liquisolid matrices when compared to other non-volatile solvents. The results also showed retardation in the release rate of the drug from the liquisolid compacts. The kinetic studies revealed that the liquisolid formulation followed zero-order.

Keywords: Lornoxicam, Liquisolid, Polysorbate 80, DCCMT, Direct Compression.

INTRODUCTION

Lornoxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class with analgesic, anti-inflammatory and antipyretic properties. The mode of action of lornoxicam is partly based on inhibition of prostaglandin synthesis (inhibition of the cyclo-oxygenase enzyme). Furthermore, it has a short elimination half-life of 4 hrs, which makes it a suitable candidate to be delivered at a controlled rate[1].

Formulation of sustained release oral dosage forms is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval[2, 3].

Liquisolid technique is a new and promising method that can change the dissolution rate of drugs. It has been used to enhance the dissolution rate of poorly water-soluble drugs[4-7]. A "liquisolid system" refers to formulations by conversion of liquid drugs, drug suspensions or drug solutions in non-volatile solvents into dry, non-adherent, free-flowing and compactible powder mixtures by blending the suspension or solution with selected carriers and coating materials. Simplicity, low cost and capability of industrial production are some of the advantages of this technique. If hydrophobic carriers such as Eudragit RL and RS are used instead of hydrophilic carries in liquisolid systems, sustained release systems can be obtained[8]. There is no systematic publication regarding the use of this method for controlling the release rate of drug from polymeric matrices. Therefore, it is suggested here that

the method has the potential to formulate sustained release systems.

MATERIALS AND METHODS

Compatibility Studies

A physical mixture (1:1) of drug and polymers was prepared and mixed with suitable quantity of IR grade potassium bromide and transparent pellets were prepared. They were scanned from 4000 to 400 cm^{-1} in a Perkin Elmer FTIR spectrophotometer.

Calculation of loading factor (L_f) for Liquisolid System

As the aim of the present study was to produce sustained release formulation, polysorbate 80 was selected as the solvent because of the low solubility of lornoxicam in this solvent. To calculate loading factor, polysorbate 80 as a non-volatile solvent was added and blended for 10 min. The composition of the powder mixture is given in table 2. The flow property of this system was measured using angle of repose. The above procedure was repeated with same amounts of non-volatile solvent until a powder with flow rate was acceptable by using the formula $L_f = W/Q$ (W: amount of liquid medication and Q: amount of carrier material), the values of loading factor were obtained and used to calculate the amount of carrier and coating materials in each formulation[7-10].

Precompression studies of the prepared liquisolid powder systems

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of tablet dies. Hence, angle of repose, Carr's index and Hausner's

ratio were determined[9-12]. For the determination of angle of repose, the fixed height cone method was adopted[11,12]. The procedure was done in triplicate and the average angle of repose was calculated for each powder. In the bulk density measurements, fixed weight of each of the liquisolid powder prepared were placed in a graduated cylinder and the volume occupied was measured and the initial bulk density DB min was noted. The cylindrical graduate was then tapped at a constant velocity till a constant volume is obtained when the powder is considered to reach the most stable arrangement, the volume of the powder was then recorded as the final bulk volume, and then the final bulk density DB max was noted.

Carr's compressibility index was calculated according to the following equation:

$$\text{Carr's index \%} = \frac{DB\ max - DB\ min \times 100}{DB\ max}$$

Hausner's ratio was calculated from the equation:

$$\text{Hausner's ratio} = \frac{DB\ max}{DB\ min}$$

Preparation of conventional matrix tablet (CMT) and liquisolid (LS) compacts

Several LS compacts (LS-1 to LS-4) and Conventional matrix release tablets were prepared. Lornoxicam was dispersed in polysorbate (polysorbate 80 was used as the liquid vehicle to prepare the liquid medication), a mixture of polymer and carrier-coating materials were added to the liquid medication under continuous mixing in a mortar until the mixture showed the desired flow property. The final mixture was compressed using the rotatory tablet compression machine (Shakti, India) to achieve tablet hardness of 4-6 kg/cm^2. DCCMT were also prepared by direct compression.

Dissolution studies

The *In vitro* dissolution tests were performed on the USP dissolution apparatus 2 (paddle method), using dissolution medium pH 5.4 and pH 6.8 with a rotation speed of 50±2 rpm. The amount of lornoxicam was 16 mg in all formulations. The dissolution tests for all tablets were run for 2h in pH 5.4 [gastric fed state (neutral phthalate buffer, pH 5.4 with 1% surfactant)] at 37±0.2∘C, and subsequently in an intestinal fluid (phosphate buffer, pH 6.8 with 1% surfactant) at 37∘C for 12h to mimic *In vivo* condition. Samples were collected at suitable time intervals (e.g. 30, 60, 90 120, 240, 300, 480, 600, and 720 min). Five ml of sample was removed from each dissolution vessel and filtered through a 0.45 µm filter (Millipore Corp., Bedford, MA, USA). The same amount of fresh dissolution fluid was added to replace the amount withdrawn. The samples were then analyzed at 376 nm by UV/visible spectrophotometer. The mean of three determinations was used to calculate the drug release from each of the formulation. The *In vitro* release profiles

of LS tablets and DCCMT were compared using similarity factors, f$_2$, as per the following equation[13].

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)\right]^{-0.5} \times 100\right\}$$

Where n is number of time points, R_t is the % dissolved of one formulation at a given time point, and T_t is the % dissolved of the formulation to be compared at the same time point. The similarity factor fits the result between 0 and 100. It is 100 when the test and reference profiles are identical and approaches 0 as the dissimilarity increases. An f$_2$ above 50 may indicate that the two profiles are similar.

RESULTS

Analysis of solubility data

Solubility studies revealed that Lornoxicam was practically insoluble in aqueous, however non - aqueous solvents showed better solubility. Polyethylene glycol (PEG 200) has shown maximum solubility, which was found to be 5.63 g/100ml. Least solubility was found in polysorbate 80 (1.73g/100ml) (table 1). On the basis of aforementioned solubility data polysorbate 80 was chosen as an ideal solvent to prepare LS formulation.

Table 1: Saturation solubility studies of Lornoxicam

S.No	Solvent	Solubility (g/100 ml)
1	Propylene glycol	3.59
2	Poly Ethylene Glycol 400	4.02
3	Poly Ethylene Glycol 200	5.63
4	Glycerine	2.08
5	Polysorbate 80	1.73

Compatibility Studies

The compatibility between the drug and the selected polymers were evaluated using FTIR peak matching method. From the results (Figures 1 to 5), it may be concluded that there was no interaction between the drug and the polymers.

Preparation of conventional matrix tablet (DCCMT) and liquisolid compacts

Compositions of the liquisolid formulations and DCCMT are shown in table 2 and table 3.

### Precompression studies of the prepared LS systems and DCCMT

The angle of repose (Ө) is a characteristic of the internal friction or cohesion of the particles, the value of the angle of repose will be high if the powder is cohesive and low if the powder is non-cohesive. LS-1, LS-2, LS-3, LS-4 and DCCMT showed (Ө) values of 29.49, 31.69, 30.86, 31.78 and 30.37 respectively (Table 3), indicating that the liquisolid systems and DCCMT had an acceptable flowability. Carr's index and Hausner's ratio indicated acceptable flow properties (table 4).
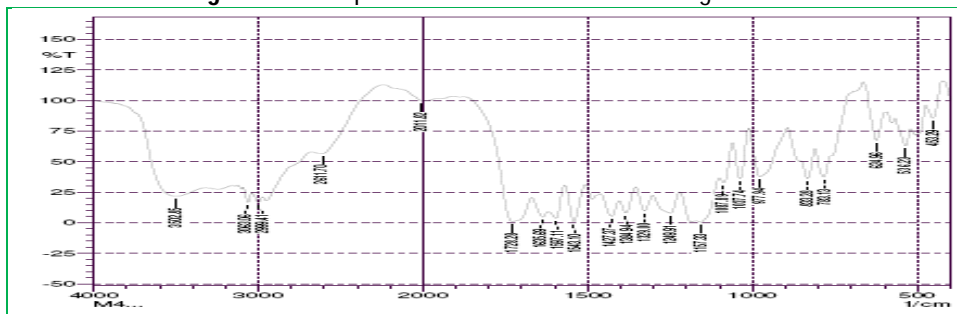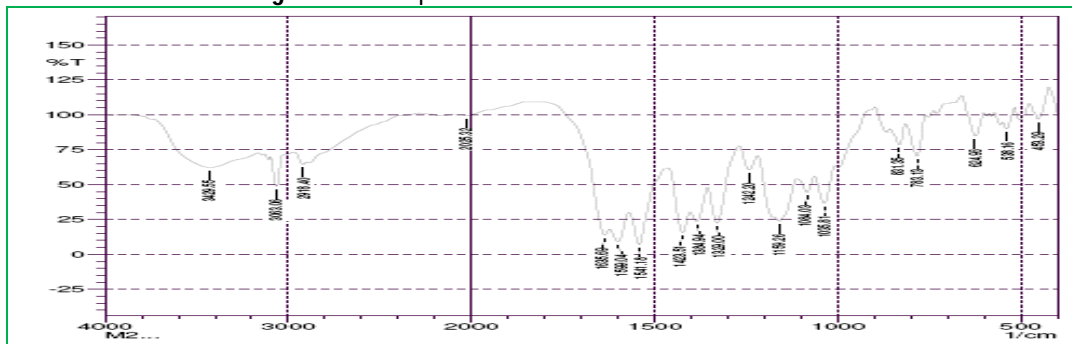
Figure 1: FTIR spectra of Lornoxicam
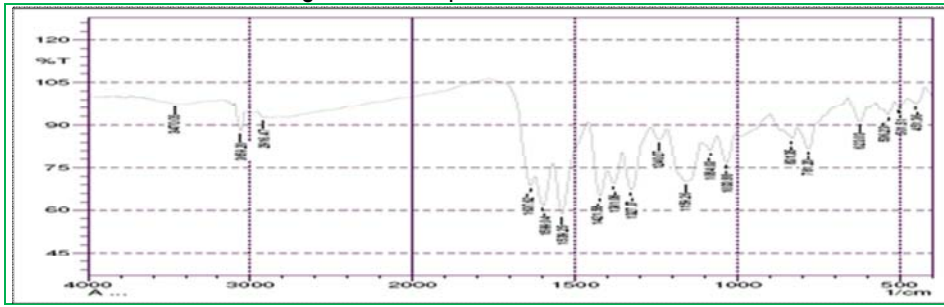
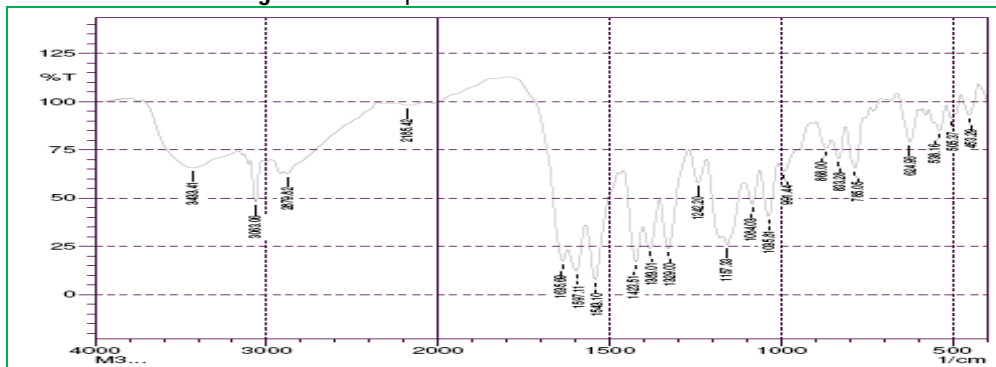**Figure 2:** FTIR spectra of Lornoxicam and Eudragit RL PO Mixture
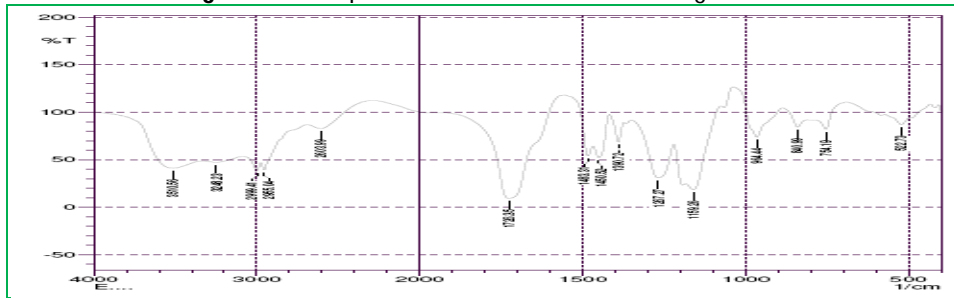
Figure 3: FTIR spectra of Lornoxicam and Eudragit S 100 Mixture

Figure 4: FTIR spectra of Lornoxicam and Sodium CMC Mixture

Figure 5: FTIR spectra of Lornoxicam and Chitosan Mixture

Table 2: Key Formulation Characteristics of Prepared Lornoxicam Liquisolid Tablets

S. No.	Liquisolid system	Carrier	Polymer	Loading factor (L_f)	Ratio of carrier to coating material (R)	Unit Dose weight (mg)
1	LS – 1	MCC	Eudragit RL PO	0.20	20.16	200
2	LS – 2	MCC	Eudragit S – 100	0.20	20.16	200
3	LS – 3	MCC	Chitosan	0.20	20.16	200
4	LS – 4	MCC	Sodium CMC	0.20	20.16	200
5	DCCMT	MCC	Eudragit RL PO	-	-	200

LS – Liquisolid, DCCMT – Direct compressible conventional matrix Tablet

Table 3: Formulation Contents of Liquisolid (LS) and Direct Compressible Conventional Matrix Tablets (DCCMT)

Ingredient (mg/tab)	Formulations				
	LS 1	LS 2	LS 3	LS 4	DCCMT
Lornoxicam	16	16	16	16	16
Polysorbate 80	25	25	25	25	-
Eudragit RL PO	32	-	-	-	32
Eudragit S – 100	-	32	-	-	-
Chitosan	-	-	32	-	-
Sodium CMC	-	-	-	32	-
MCC PH 101	121	121	121	121	150
Colloidal silicon Dioxide	6	6	6	6	2
Total weight (mg)	200	200	200	200	200

LS – Liquisolid, DCCMT – Direct compressible control matrix Tablet

Table 4: Precompression Studies of the prepared LS system and DCCMT

S.No	Liquisolid formulations	Average Θ	Average Carr's index (%)	Average Hausner's ratio
1	LS – 1	29.49	30.41	1.03
2	LS – 2	31.69	32.51	1.05
3	LS – 3	30.86	31.76	1.06
4	LS – 4	31.78	31.70	1.07
5	DCCMT	30.37	30.45	1.04

LS – Liquisolid, DCCMT – Direct compressible control matrix Tablet

Table 5: Evaluation of Liquisolid and Direct Compressible Conventional Matrix (DCCMT) tablets

Formulations	Average weight of tablet (mg)	Content uniformity (%)	% Friability	Hardness (Kg/Cm^2)
LS – 1	100.053	100.01	0.45	5.1
LS – 2	100.015	100.01	0.76	4.7
LS – 3	100.049	99.98	0.59	4.9
LS – 4	100.035	99.56	0.36	4.8
DCCMT	100.039	100.03	0.83	4.9

Table 6: Release Kinetics of liquisolid (LS) and direct compressible conventional matrix tablets (DCCMT)

Formulation code	Zero order (r^2) ± SD	First order (r^2) ± SD	Higuchi kinetics (r^2) ± SD	Peppa's Equation	
				(n)	(r^2) ± SD
LS 1	0.9819	0.9713	0.9505	0.7868	0.9693
LS 2	0.9630	0.9295	0.9215	0.611	0.9089
LS 3	0.9690	0.9266	0.9050	0.5438	0.9111
LS 4	0.9682	0.9226	0.9101	0.6821	0.9107
DCCMT	0.9621	0.9804	0.9734	0.6039	0.9848

Evaluation of LS and DCCMT

The collective data concerning Lornoxicam content in the tablet formulations, content uniformity, friability and hardness are presented in table 5.

A fundamental quality attribute for all pharmaceutical preparations is the requirement for a constant dose of drug between individual tablets, and it was found constant for all formulations. Average weights of tablets were within the limits. The selected formulations complied with the test for content uniformity as per the official pharmacopoeias by having an average Lornoxicam content of 100.01, 100.01, 99.98, 99.56 and 100.03 respectively. This may be attributed to the higher concentrations of Avicel PH-102 (Carrier) leading to more uniform distribution of the drug by their adsorption onto or absorption into the carrier, therefore having more homogeneous distribution throughout the batch.

All the selected Lornoxicam LS tablets had acceptable friability as none of the tested formulae had exceeded 1% loss in weights. Also, none of the formulated tablets were cracked, split or broken. Since all the above mentioned formulations met the standard friability criteria, they were expected to show acceptable durability and withstand abrasion in handling, packaging and shipment.

The mean hardness of formulations proved that all the LS tablets had acceptable hardness. The hydrogen bonds between hydrogen groups on adjacent cellulose molecules in Avicel PH-102 may be the reason for the strength and cohesiveness of compacts[14].

Dissolution profiles of LS compacts and DCCMT were estimated and it's *In vitro* release profile were shown in Figure 6. It is evident from the figure that the tablets prepared by LS technique (LS-1 to LS-4) showed greater retardation properties when comparison to DCCMT. The results showed that the percentage of drug released from LS matrices containing chitosan and sodium CMC is greater than LS matrices containing the same amount of Eudragit RL PO and Eudragit S 100. This could be attributed to the difference in water permeability of the polymers.

The mechanism of release prolongation is likely to be due to the efficient encapsulation of drug particles by the hydrophobic polymers. However, a major difference between DCCMT and LS formulations may be the presence of polysorbate 80 in LS. An interesting property of polysorbate 80 is the plasticizer effect by which it can reduce the glass transition temperature of polymers and impart flexibility[15].

Figure 6: *In vitro* dissolution studies
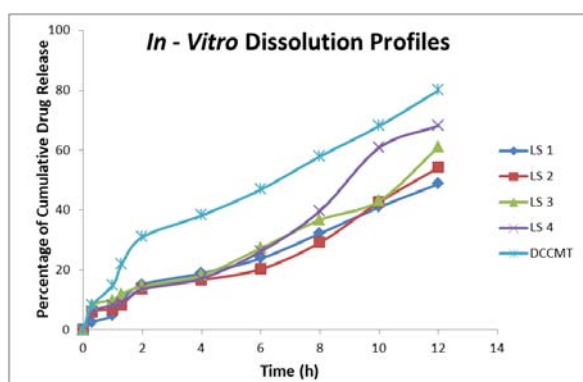
CONCLUSION

The present work showed that LS technique can be optimized for the production of sustained release matrices of poorly soluble drugs. Polysorbate 80 may be used as effective liquid vehicle. The release of drug from these formulations followed zero-order release kinetics. This investigation provided evidence that polysorbate 80 (Tween 80) has important role in sustaining the release of drug from LS matrices. The proposed new technique can be used in the preparation of sustained release formulations of poorly soluble drugs such as Lornoxicam.

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