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Research Article

Formulation and evaluation of solid dispersion of lomefloxacin hydrochloride

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ABSTRACT

Lomefloxacin hydrochloride is a fluoroquinolone antibiotic used to treat bacterial infections including bronchitis and urinary tract infections. It is also used to prevent urinary tract infections prior to surgery. Although lomefloxacin is not rapidly absorbed after oral administration its half life is 8 hr., it is critical to improve the dissolution rate to enhance the bioavailability, due to its low water solubility. Solid dispersions of lomefloxacin hydrochloride with polyvinyl pyrrolidone (PVP K30) and HPMC K4M and Urea were prepared by using fusion method. The prepared solid dispersions using urea were free flowing and showed good percentage of drug content (96%w/w). The FTIR study reveals no chemical interaction between lomefloxacin hydrochloride and carriers used. The XRPD and DSC studies confirm transformation of crystalline form of lomefloxacin hydrochloride into the amorphous form. The in vitro dissolution studies of formulated solid dispersions shows the increase in solubility in order of Urea> PVP> HPMC.

Keywords: Lomefloxacin; Polyvinylpyrrolidone; Hydroxypropyl methylcellulose; Urea; Solid dispersion; Dissolution

INTRODUCTION

The therapeutic efficacy of a drug product intended to be administered by the oral route mainly depends on its absorption by the gastrointestinal tract. However, for a drug substance to be absorbed, it needs to be solubilised. Numerous works have been carried out in order to modify the dissolution kinetics of poorly soluble drugs to improve their bioavailability. Among them solid dispersion technology was most widely used (Sekiguchi, K., et al., 1961; Chiou, W.L., et al., 1971; Law, S.L., et al., 1992; Corrigan, O.I.,1985; Craig, D.Q.M., 1990; Ford, J.L., 1986). Number of insoluble drugs has shown to improve their dissolution character when converted to solid dispersion (Madhusudhan, B., et al., 2002). Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers (Delahaye, N., et al., 1997). The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water-soluble drug is increasing (Yamada, T., et al., 1999). Various hydrophilic carriers such as polyethylene glycol (Margarit, M.V., et al., 1994), polyvinyl pyrrolidone (Yagi, N., et al., 1996) and sugars (Danjo, K., et al., 1997) have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs. Polyvinylpyrrolidone (PVP) has been used for the preparation of solid dispersion as a component of binary system for various drugs (Sheu, M.T., et al., 1994).

Lomefloxacin (LM) (1-2) 1-ethyl-6,8-difluoro-7-(3-methylpiperazin-1-yl)-4-oxo-1,4 dihydro quinoline -3-carboxylic acid, HCl (Fig.1) is a fluoroquinolone antibiotic, used to treat bacterial infections including bronchitis and urinary tract infections. It is also used to prevent urinary tract infections prior to surgery. It is an INN drug and as such it has not been yet included in the BP or USP. The aim of present study was to prepare and evaluated different solid dispersion of lomefloxacin hydrochloride with PVP, HPMC and Urea so as to improve its dissolution properties (Goodman and Gilman's, 1996; Klimberg, I.W., et al., 1998).

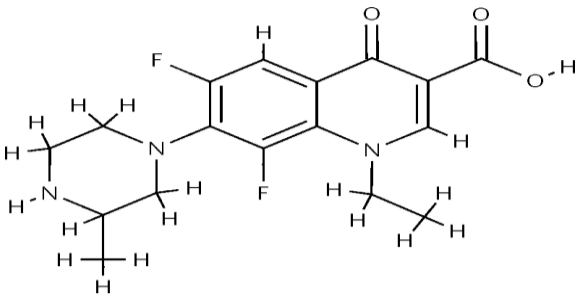

Figure 1: Chemical Structure of Lomefloxacin

MATERIALS AND METHODS

Lomefloxacin HCl was obtained as a gift sample from Dr. Reddy Hyderabad. Polyvinyl-pyrrolidone (PVP K30), Hydroxypropylmethylcellulose (HPMC K4M) and Urea

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was obtained from Merck Limited. All other chemicals were of reagent and analytical grade.

Phase Solubility Studies

Solubility requirements for lomefloxacin were carried out by a reported method (Higuchi, T., et al., 1965 ;). An excess amount of lomefloxacin (50mg) was added to the aqueous solution containing various concentrations of PVP, HPMC & Urea (0.05 to 0.25% w/v) in a series of different 25 ml stoppered conical flask. The flasks were shaken for 24 hours at room temperature (28°C) on a rotary flask shaker. After 24 hours of shaking to achieve equilibrium, 5 ml of aliquots were withdrawn, filtered (0.45 µm pore size) and spectrophotometrically analyzed for drug content at 282 nm (Shimadzu-UV 1700 spectrophotometer) (Fig. 2).

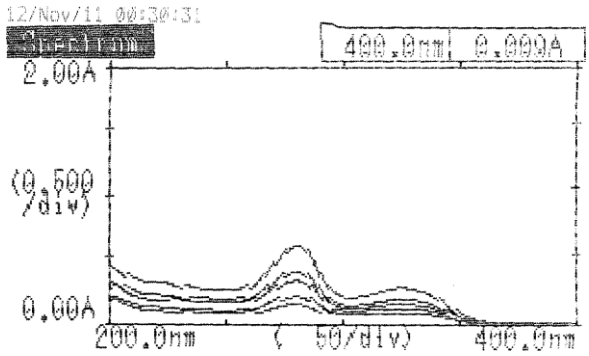


Figure 2: UV Spectra of Lomefloxacin

Estimation of Lomefloxacin

Lomefloxacin was estimated at 282 nm using UV spectrophotometer (Shimadzu-1700). Standard curve for the estimation was prepared in Phosphate buffer pH 6.8 in concentration of 10-50 µg/ml (Fig. 3). In this concentration range good linearity was observed with the correlation coefficient (r^2=0.999). The graph obeyed the Beer-Lambert's law in the selected concentration range.

Preparation of Solid Dispersion of Lomefloxacin with PVP K30 & HPMC

Solid dispersion of lomefloxacin with PVP K30 & HPMC was prepared by solvent evaporation method (Okimoto, K., et al., 1997). Each five hundred milligram of lomefloxacin was taken in two different beakers and 10 ml of ethanol was added into it to dissolve them and the PVP K-30 and HPMC were added in to it and mixed to dissolve. Ethanol was evaporated at room temperature from both beaker and resulting mass was passed through # 60. The granules were dried at room temperature for 1 hr and then dried at 85 ^{O}C for 6 hr in a hot air oven. The dried granules were stored at room temperature. The composition of various batches is shown in Table-1.

Preparation of Solid Dispersion of Lomefloxacin with UREA

Solid dispersion of lomefloxacin with urea was prepared by fusion method (Gopal Rao, M., et al., 2005). A mixture of lomefloxacine with urea in different ratios (1:1, 1:4 and 1:8 w/w) were wetted with ethanol and then heat on water bath for 1 hr. The paste formed was dried under vacuum for 24 hours. Dried powder was scrapped, crushed, pulverized and passed through sieve no 100 (ASTM-100, 150 µm) and stored in dessicator.

Characterization of solid dispersion

The prepared solid dispersions were evaluated for its various physicochemical parameters such as yield, angle of repose, bulk density, compressibility, moisture uptake, drug content and in vitro dissolution studies.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra were recorded on samples prepared by kneading method in different ratios of carriers (w/w) in a KBr pellets using Bruker Alpha FT/IR. The scanning range was 400 to 4000 $cm^{-1}$and the resolution was 4 cm^{-1}.

Differential Scanning Calorimetry (DSC)

The thermal analysis of lomefloxacin and its dispersions was performed using differential scanning calorimeter (PerkinElmer).Accurately weighed samples were placed in sealed aluminum pans and heated in a temperature range of 30-300ºC under the nitrogen flow rate of 20ml/min. The diffraction scan of solid dispersion was compared with drug and urea scans of interaction.

Table 1: Composition of Solid Dispersions of Lomefloxacin

	Quantity in Parts			
Solid Dispersions	**Lomefloxacin**	**PVP**	**HPMC**	**UREA**
SD1	1	1	-	-
SD2	1	4	-	-
SD3	1	8	-	-
SD4	1	-	1	-
SD5	1	-	4	-
SD6	1	-	8	-
SD7	1	-	-	1
SD8	1	-	-	4
SD9	1	-	-	8

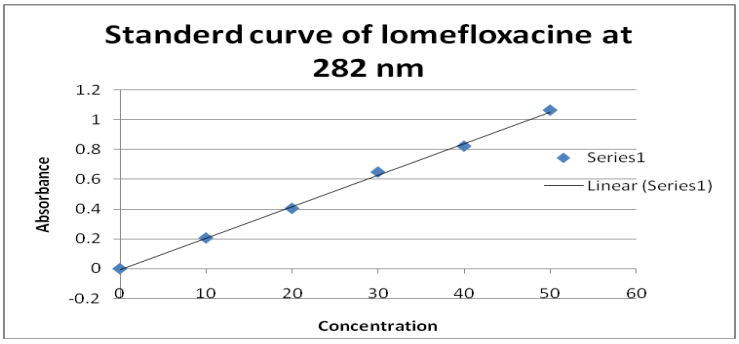


Figure 3: Standard Curve of Lomefloxacin at 282nm

Table 2: Physicochemical Evaluation of Lomefloxacin Solid Dispersion

S. No.	Batch Code	Drug Carrier	Yield	Angle of Repose	Bulk Density (g/cc)	Compressibility (%)	Moisture Uptake (%)	Drug Contain (%)
1	Pure drug	--	--	22.85±1.23	0.07	14.82±0.93	3.02±0.09	97.72±0.42
2	SD1	1:2	85.72±0.34	23.23±1.02	0.82	15.21±1.35	4.34±0.82	96.56±0.83
3	SD2	1:4	92.83±1.72	24.46±0.45	0.71	15.34±1.52	4.73±0.73	98.43±0.46
4	SD3	1:8	83.33±1.92	23.89±1.11	0.82	14.93±0.92	4.43±0.94	93.72±0.22
5	SD4	1:2	83.54±1.32	20.13±0.08	0.79	13.17±0.37	3.67±1.02	92.06±1.0
6	SD5	1:4	89.43±0.34	21.80±0.58	0.81	13.67±0.53	3.82±0.23	91.23±1.83
7	SD6	1:8	91.55±1.21	20.88±0.73	0.82	13.43±0.93	3.42±1.08	97.74±0.93
8	SD7	1:2	84.59±0.30	21.72±0.99	0.79	14.37±0.22	4.11±0.43	96.93±0.49
9	SD8	1:4	94.67±0.82	23.21±0.92	0.78	14.21±1.02	3.99±1.49	95.20±0.66
10	SD9	1:8	89.33v0.88	22.84±0.51	0.80	12.33±0.43	3.21±1.55	96.43±0.65

n=3±SD

X-Ray Diffraction

X-ray diffraction pattern of lomefloxacin and its dispersion of urea were obtained using diffractometer (Seifer 3003TT) using cu k α radiation at 30ma and 450kv. Powder X-ray diffraction pattern were traced for lomefloxacin urea and its dispersions. The position and intensities of diffraction peaks were considered for the identification and crystallinity of drug or carrier.

Dissolution Rate Studies

In vitro dissolution rate studies were performed in phosphate buffer (pH 6.8) maintained at 37± 0.5° C, using a 6 station USP XXII dissolution apparatus (Labindia, Mumbai, India) with basket rotating at 50 rpm. Solid dispersions containing 100 mg of drug were subjected to dissolution. At fixed time intervals, samples were withdrawn, filtered by 41 no. whatmen filter paper and assayed for lomefloxacin by measuring the absorbance at 282 nm (Fig 2). The concentration were calculated from stander curve method Dissolution efficacy was calculated and dissolution curve is plotted between at time't' and percentage % cumulative drug release (Modi, A., et al., 2006; Khan, K.A, 1975).

RESULTS AND DISCUSSIONS

Solubility Studies

The solubility of lomefloxacin in distilled water at 27°C was found to be 4.32 µg/mL. The influence of different carrier upon the solubility of lomefloxacin is presented in Fig.3 and shows the solubility of lomefloxacin first increases and there after a decrease was observed.

Physiochemical Parameter Study

The prepared solid dispersions were evaluated for its various physicochemical parameters such as yield, angle of repose, bulk density, compressibility, moisture uptake; drug content and result were shown in Table-2.

FTIR Study

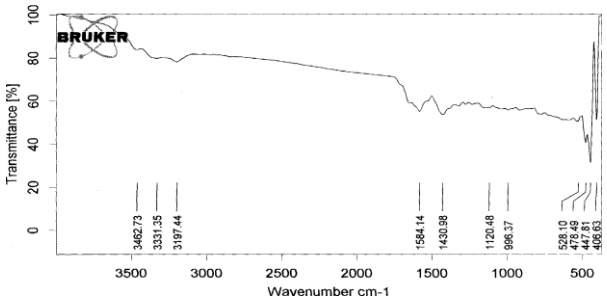
FT-IR studies were done to detect the possible interactions between the lomefloxacin and different carrier in the solid dispersion leading to crystalline state with polyvinyl pyrrolidone K30, HPMC and Urea. The characteristic peaks of lomefloxacin, Comparing the spectra of with those of solid dispersion prepared by using different methods revealed that there were no differences in the positions of the absorption bands, hence providing evidence for the absence of hydrogen bonding interactions in the solid state dispersion formulation between polyvinyl pyrrolidone K30, HPMC and Urea Fig. 4

Differential Scanning Calorimetry Study

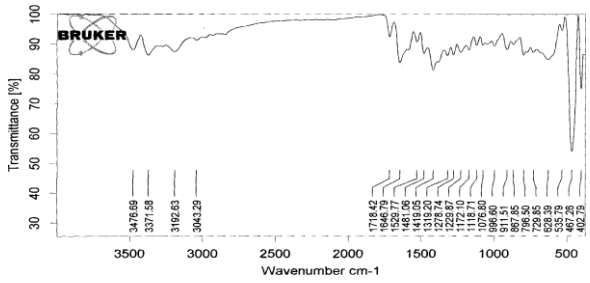
Differential scanning calorimetry shows sharp endothermic fusion peak at 239°C, which is corresponding to the melting point of lomefloxacin Fig. 5.

In Vitro Dissolution Studies of Solid Dispersions Prepared by Using Different Methods

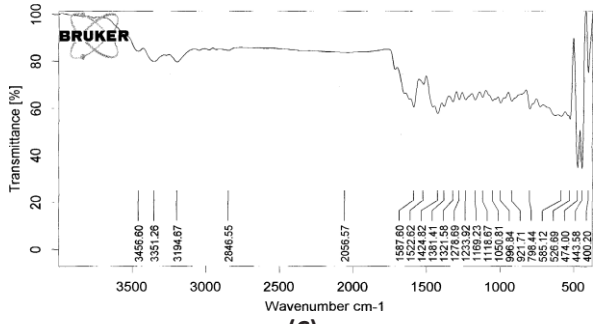
Lomefloxacin release from the solid dispersion and alone was studied in phosphate buffer (pH 6.8) up to 2 hours. Average percentage release of the pure lomefloxacin was found to be 64% in 2 hours. In the solid dispersion formulation using urea as carrier in the ratio of 1:4 (Fig. 6), the increased dissolution rate may be due several mechanisms i.e. the reduction in crystallinity, reduction in particle size to expand the surface area for dissolution enhancement of urea.



(A)



(B)



(C)

Figure 4: IR Spectra of Lomefloxacin with (A) Polyvinyl pyrrolidone K30 (B) HPMC (C) Urea

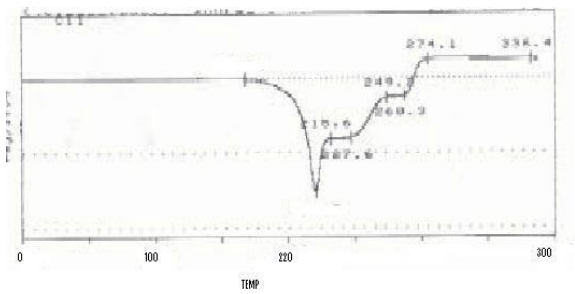


Figure 5: Differential Scanning Calorimetry of Lomefloxacin Solid Dispersion

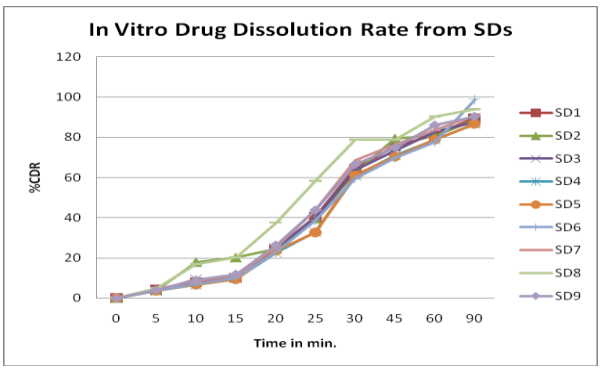


Figure 6: In vitro dissolution studies of lomefloxacin solid dispersions prepared by using different methods

CONCLUSION

The study shows that the dissolution rate of lomefloxacin can be enhanced to a great extent by solid dispersion technique using an industrially feasible method. The solid dispersion complex of drug was giving better dissolution profile as compared to pure drug. This in turn, can reduce the doses of drug reduction in dose related adverse effects and improved bioavailability.

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