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Research Article

Studies on crystal forms of lomefloxacin hydrochloride: preparation, characterization and dissolution profile

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ABSTRACT

Crystal habit modification of lomefloxacin hydrochloride was obtained by recrystallization from various solvents based on polarity. Among the various solvents, water, methanol and ethanol can produce well defined crystal forms. The newly obtained crystals were characterized by analytical techniques viz. Optical microscopy, FT-IR spectroscopy, X-ray diffraction, Differential scanning calorimetry. In addition, the crystals were evaluated for melting point, solubility and dissolution profile. The newly developed crystals possess the different physicomechanical properties but chemically identical. The crystals obtained from water are rod shaped whereas the crystals obtained from methanol and ethanol are thin needle shape. The FT-IR spectra of newly developed crystals showed the characteristic peak as that of commercial sample. In addition, DSC spectra of newly developed crystals showed significant change in the melting endothermic compare to commercial sample and the XRD spectra revealed the slight difference in the diffraction pattern compare to commercial sample. The obtained crystals have different melting point. The crystal obtained from methanol and ethanol markedly improved solubility and dissolution profile compared to crystal obtained from water and commercial sample. Thus, the DSC and XRD indicate existence of different crystal forms of lomefloxacin.

Keywords: Crystal forms; Dissolution rate; DSC; FT-IR; Lomefloxacin; X-ray diffraction

INTRODUCTION

Many drugs are poorly soluble or insoluble in water, which results in poor bioavailability because the solubility of a drug is an important factor in determining the rate and extent of its absorption (Orienti F., et al., 2002). For class II-drugs, according to the biopharmaceutics classification system, the dissolution rate is the limiting factor for the drug absorption rate (R. Lobenberg., 2003). Numerous approaches have been employed to enhance the dissolution profile and, in turn, the absorption efficiency and bioavailability of poorly water soluble drugs. Use of water-soluble salts, polymorphic forms, water-soluble molecular complexes, solid dispersion, coprecipitation, lyophilisation, microencapsulation, and inclusion of drug solutions or liquid drugs into soft gelatine capsules are some of the major formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs (R.H. Fahmy et al., 2008; Sheth A., 1990; Javadzadeh Y., et al., 2005; Ambrogi V., et al., 2008). Many pharmaceutical substances exhibit polymorphism and pseudopolymorphism. The former is frequently defined as the ability of substance to exist in two or more crystalline phases that have different arrangement of the molecules in the crystal lattice. As a result, the polymorphic solids have different unit cells and hence display different physical properties (such as melting point, solubility, dissolution rate, physical and chemical stability, hygroscopicity, density) including those due to packing, and various thermodynamic, spectroscopic, interfacial and mechanical properties (Grant, D.J.W., 1999; Kristl A., et al., 1996). Lomefloxacin HCl is a member of fluroquinolone class of antimicrobial drug used in the treatment of wild range of gram positive and gram negative organism. Chemically Lomefloxacin is1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid. Lomefloxacin have low solubility in water showed poor dissolution rate(Harry G Brittain.1994). Thus an attempt was made investigates the different crystal forms of lomefloxacin hydrochloride using various solvents on the basis of polarity. The newly developed crystals were characterized by analytical techniques. In addition, various crystal forms were evaluated in terms of solubility and dissolution profile.

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MATERIALS AND METHODS

Material

(a)

(b)

(c)

Figure 1: Optical microscopy of (a) crystal obtained from water (Lome-I), (b) crystal obtained from methanol (Lome-II) and crystal obtained from ethanol (Lome-III)

Table 1: Melting point, DSC and FT-IR data of various crystal forms

Crystal Form obtained from	M.P (°C)	DSC data		Shape of crystals	Characteristic peaks of IR		
		Peak fusion point (°C)	Heat of fusion (J/g)		N-H Stretch (cm^{-1})	C=O Stretch (cm^{-1})	C-H Stretch (cm^{-1})
Water	295-297	318	103.4	Rod Like crystals	2700	1726.8	1380
Methanol	290-293	298.87	149.3	Thin needle like crystals	2711.10	1725.5	1365
Ethanol	291-292	299.61	142.5	Thin needle like crystals	2690	1723	1363

Lomefloxacin hydrochloride obtained as a gift sample from Ipca Laboratories, Bhopal, India. All the solvents used for recrystallization purchased from SD Finechem, Mumbai and were of analytical grade.

Preparation of crystal forms

Lomefloxacin hydrochloride was recrystallized from various organic solvents of different polarity. The lomefloxacin about 50 mg was dissolved in an appropriate amount of water, methanol and ethanol. The solution was heated to 65^0C to get the clear solution. The hot saturated solution was then filter through whatman filter paper and kept aside for 24 hrs at room temperature for crystallization. After 24 hrs well defined crystal of lomefloxacin were crystallised in the flask, filter, dried under vacuum and store in desiccators for further studies.

Characterization of Crystal forms

Optical microscopy

Photomicrographs of different crystal forms of lomefloxacin were characterized by optical microscope (Olympus, Japan). Samples were mounted on a slide and dispersed in paraffin oil and seen under the microscope at 45X and photographs were taken by camera.

FT-IR spectroscopy

All the newly developed crystals and commercial sample were scanned and recorded in the range of 4000-400 cm^{-1} by using Infrared spectrophotometer, (Shi-

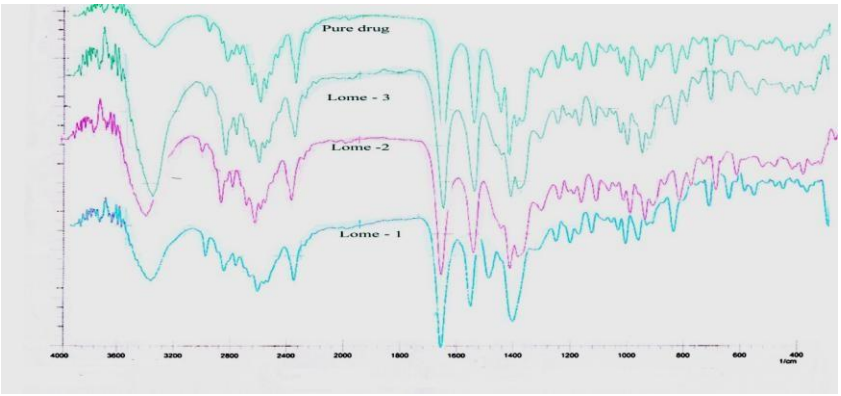

Figure 2: FT-IR spectra of pure drug, crystal obtained from ethanol (Lome-III) crystal obtained from methanol (Lome-II) and crystal obtained from water (Lome-I)

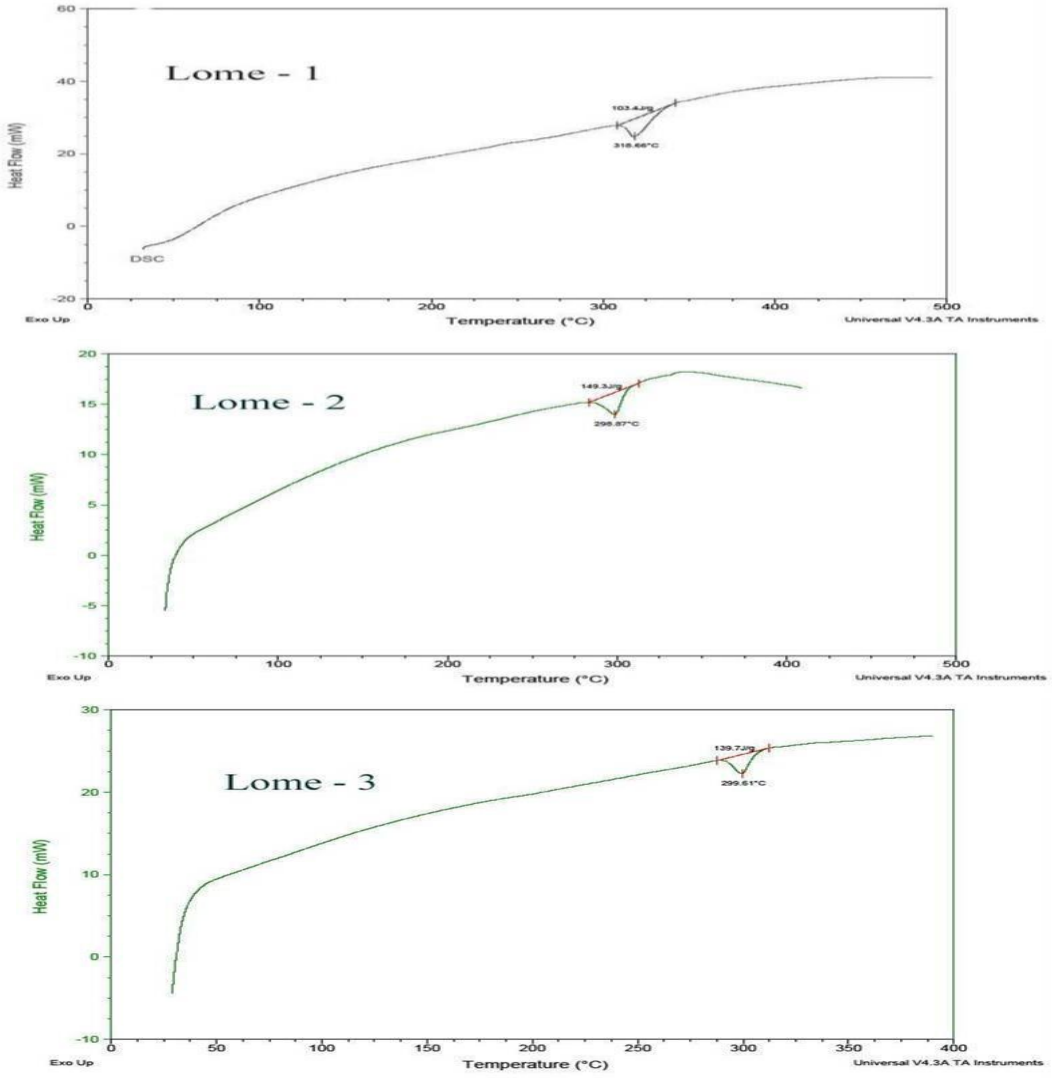

Figure 3: DSC spectra of crystal obtained from water (Lome-I), crystal obtained from methanol (Lome-II) and crystal obtained from ethanol (Lome-III) [Top-bottom]

mazdu FT-IR 8400S, Japan). The modified crystals were triturated with dried potassium bromide (KBr) using mortar and pestle. The mixture after grinding into fine powder was kept uniformly in suitable die and compressed into a pellet form by using hydraulic press. The resultant pellet was mounted in a suitable holder in the IR spectrophotometer.

Differential scanning calorimetry

After calibration, thermograms were obtained by DSC (Mettler Toledo,) heating all the crystal forms (5 mg) at a constant heating rate of 5^0C/min with chart speed of 40 ml/min under an atmosphere of nitrogen. The exact peak temperatures, melting point and heat of fusion

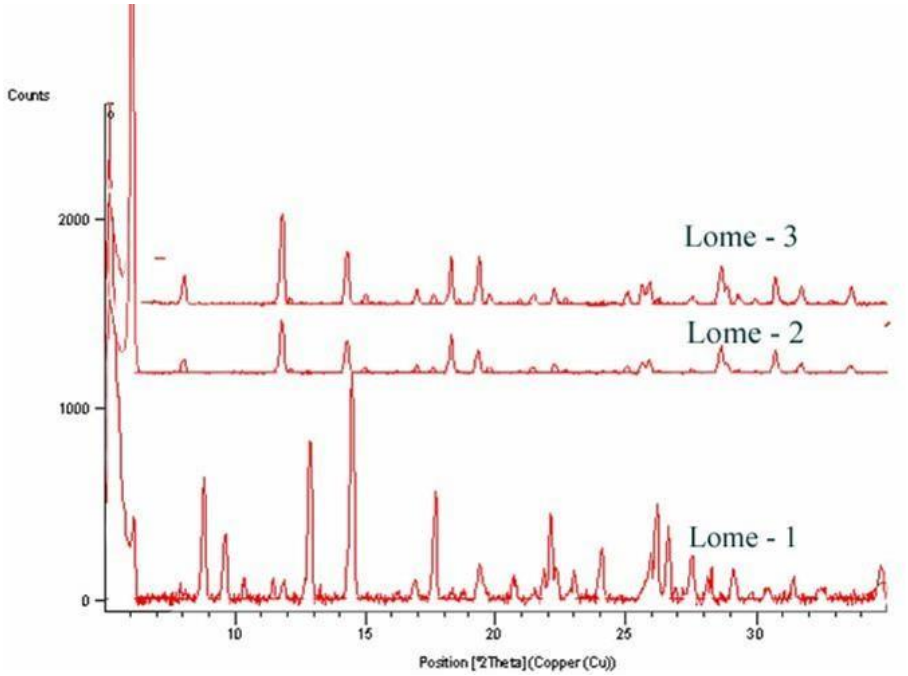

Figure 4: XRD spectra of crystal obtained from ethanol (Lome-III), crystal obtained from methanol (Lome-II) and crystal obtained from water (Lome-I)

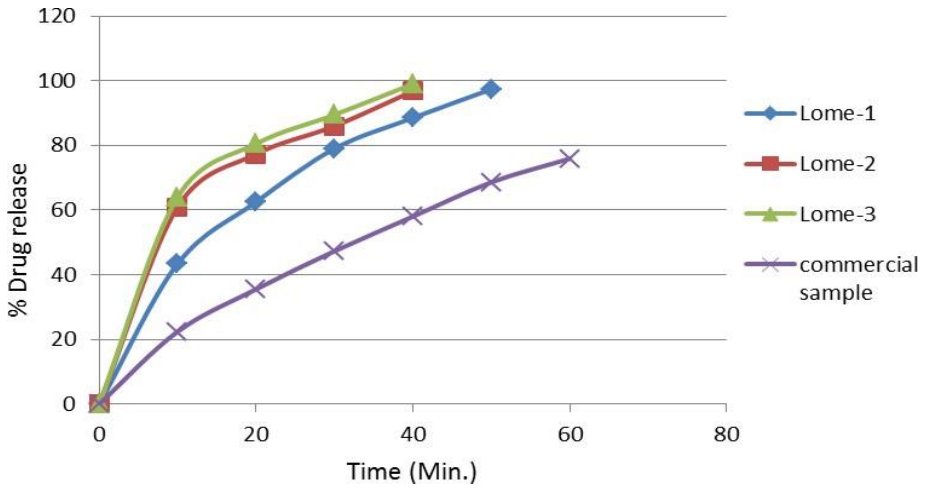

Figure 5: Percent Dissolution profile of commercial sample and various crystal forms

were automatically calculated. The temperature range for the scan was 30^0C to 400^0C for all the samples.

X-ray diffraction

X-ray diffraction pattern of crystal forms were obtained using the X-ray diffractometer (Bruker, D8 Advance, Germany) at 40 kV, 30 mA and a scanning rate of 0.02^0 /min at the diffraction angle 2 θ over the range of 5-35 using Cu (as anode) radiation of wavelength 1.5406 Å.

Solubility studies

The solubility of commercial sample and newly developed crystals were determined by adding excess solid (100 mg) to 10 ml media i.e. distilled water taken in a well stopper flask. The samples were stirred for 8 hours with the help of a magnetic stirrer at 100 rpm at 37.5^0C. The temperature was controlled using a water bath. After 8 hours of stirring, an aliquot (1 ml) of the samples were withdrawn with the help of graduated pipette, filtered through Whatmann filter paper, suitably diluted and absorbance was measured spectrophotometrically using UV visible spectrophotometer (Shimazdu, UV-1800, Japan.) at 285 nm.

Dissolution studies

The dissolution studies of commercial sample and its crystals forms were carried out using USP dissolution type-2 apparatus,(Paddle type) (Labindia, Mumbai.) after introducing of an appropriate amount of sample paddle was rotated at the speed of 75 rpm and the dissolution medium (900 ml) 0.1 *N* HCL was maintained at temperature 37 ± 0.5^0C. After specific time intervals, (5 ml) of aliquot was withdrawn and replaced with fresh and equal quantity of dissolution medium. The samples were suitably diluted and absorbance of was measured at 285 nm using U.V. spectrophotometer (Shimazdu, UV-1800, Japan.).

RESULT AND DISCUSSION

Lomefloxacin was obtained as a hydrochloride salt and not a free base from the supplier hence; it was used as such for the preparation of crystal forms. Various solvents were tried for recrystallization. Among these solvents water, methanol and ethanol to be used as solvents for crystallization in this study because salt slight appreciable solubility only in these solvents. Other solvents such as DMF, isopropanol showed too high solubility, and acetone, dichloromethane, ethyl acetate showed too low a solubility. The lomefloxacin was dissolving in particular solvent at 65^0C on water bath to get clear solution, the solution after 24 hrs of crystallization produces well defined crystals. The newly developed crystals were filter, dried and store for further studies. The photomicrographs Showed the crystals obtained from methanol and ethanol are of thin needle shaped whereas crystals obtained from water have rod shaped. (Figure.1). this could be due to the effect of solvents on the habit of crystals. Melting points of commercial sample and crystal form were evaluated by Melting point apparatus, the melting point of newly developed crystals were found to be different as that of commercial sample shown in Table.1.

FT-IR spectroscopy

IR spectra of the crystals were recorded using potassium bromide disc method and shown in Figure.2. On comparing these spectra, differences in the park pattern were observed in the region of 4000 cm^{-1} to 400 cm^{-1}. Crystals obtained from methanol and ethanol have super imposable spectra in this region while the spectrum of crystals obtained from water shown similar spectrum compare to commercial sample. Thus the FT-IR spectroscopy does not showed any difference between commercial sample and newly modified crystal forms. This indicate that the crystals have differ in crystal habit but chemically identical.

Differential scanning calorimetry

The thermal behaviour of commercial sample and its crystals are shown in Figure.3. The DSC curve revealed that the crystals obtained from methanol and ethanol showed endothermic peak at 298.87^0C and 299.61^0C respectively corresponding to its melting point. Whereas the crystals obtained from water at 318^0C corresponding to its melting point. Shift of endothermic peak towards lower temperature indicates the decrease in the melting point of drug in crystals. This decreased melting point accounts for increased solubility of drug. Thus the DSC data confirms that there polymorphic changes in the crystal forms.

X-ray diffraction

All the samples were submitted for XRD analysis. The XRD Spectra of the crystal forms obtained from methanol and ethanol showed no significant difference in peak pattern, while, a different pattern was observed in the crystals obtained from water shown in Figure.4. These obtained XRD spectra of crystal forms were different to that of commercial sample. Considering XRD analysis to be the final parameter in deciding the existence of polymorphs in a compound, it could be said that crystal forms obtained from methanol and ethanol belonged to same category. And crystal obtained from water might be a different crystal habit. The XRD studies support the existence of different crystal forms of lomefloxacin.

Solubility and dissolution studies

For finding out the dissolution rate profile and the solubility of the crystal forms, the samples were meshed through sieve No.100 and stirred at constant rate at a constant temperature of 37± 2^oC in 0.1 N HCl . Samples were withdrawn at different time intervals and analyzed by UV-spectrophotometer. Crystals obtained from methanol and ethanol showed the fastest rate of dissolution and highest solubility after 1 hrs compare to crystal obtained from water and commercial sample shown in Figure.5. The dissolution of crystal obtained from ethanol > crystal from methanol > crystal from water > commercial sample. These results favored the DSC and XRD results indicating the crystal obtained from water, methanol and ethanol to be a different crystal habit than commercial sample.

CONCLUSION

Crystallization medium has the major effect on lomefloxacin crystal modification. The crystal obtained from ethanol and methanol have needle shaped whereas crystal obtained from water has rod shaped. The crystal obtained from ethanol exhibit higher dissolution rate. The crystal modification of lomefloxacin also confirmed by DSC and XRD analysis.

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