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Original Article

EFFECT OF pH, SELECTED CYCLODEXTRINS AND COMPLEXATION METHODS ON THE SOLUBILITY OF LORNOXICAM

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ABSTRACT

Objective: The objective of the present study is to investigate the effect of pH, selected cyclodextrins and methods of complexation on the solubility of lornoxicam.

Methods: Phase solubility studies were carried out according to Higuchi and Connors. Inclusion complexes of lornoxicam were prepared by different methods like kneading, ultrasoncation, spray drying along with the physical mixtures using β cyclodextrin and hydroxypropyl β cyclodextrins.

Results: Lornoxicam being weakly acidic drug showed extremely low solubility in the acidic medium (pH 1.2) and poor solubility in water. The solubility of the drug increased as the pH of the medium was subsequently increased up to 7.4 and a drastic increase in solubility perhaps several hundred folds was observed with the alkaline phosphate buffer (pH 10.0). Phase solubility studies revealed that, hydroxypropyl β cyclodextrin (HP β CD) up to the concentration of 20 mM showed a linear increase in solubility of lornoxicam whereas the solubility of lornoxicam was increased up to β cyclodextrin (β CD) concentration of 14 mM and beyond that the solubility of the drug reduced probably due to precipitation of the complexes. The stability constant (Ks) was found to be 378.55 M^{-1} and 867.262 M^{-1} for β CD and HP β CD respectively. Inclusion complexes of lornoxicam with cyclodextrins were prepared employing different methods and the effect of complexation methods on the dissolution of lornoxicam was studied. Dissolution studies revealed that, irrespective of the cyclodextrins used (β CD and HP β CD), highest drug release rate was observed from the spray dried products compared to those prepared by kneading and ultrasonication methods. Inclusion complexes prepared using HP β CD showed higher drug release compared to those prepared using β CD.

Conclusion: The study demonstrated the distinctive pH dependent of solubility of lornoxicam and also showed that cyclodextrins especially HP β CD can be utilized to improve the solubility of lornoxicam.

Keywords: Lornoxicam, pH, Solubility, Cyclodextrins, Complexation methods, Dissolution.

INTRODUCTION

Combinatorial chemistry and high throughput screening seem to have led to an increase in the number of poorly water-soluble drug candidates coming out from the discovery pipeline [1]. More than 90% of drugs approved since 1995 have poor solubility, poor permeability, or both [2]. Many compounds currently under development are Biopharmaceutical Classification System Class II compounds, i. e., high permeability but poor solubility [3]. Poor aqueous solubility hinders the in vivo efficacy of the drugs due to low bioavailability, abnormal pharmacokinetic profile, inter-subject, inter-species variation [4] and thus pose challenging problems in the oral formulation development process.

Lornoxicam, a congener of tenoxicam, is a new NSAID belonging to the oxicam group with extremely potent anti-inflammatory and analgesic activities. It is widely used for the symptomatic treatment of pain and inflammation in patients with rheumatoid arthritis and osteoarthritis. Lornoxicam (LRN) also showed great efficacy in various clinical trials in the management of perioperative and postoperative pain associated with gynecological, orthopedic, abdominal, and dental surgeries [5-8]. However, the drug is having very low aqueous solubility [9] resulting in dissolution rate limited absorption and thus limits its therapeutic efficacy due to hindered rate of absorption thereby delaying the onset of action.

Enhancement in the solubility and the dissolution rate of such drugs can improve the oral bioavailability, which further improves the therapeutic efficacy and patient compliance. Different techniques have been used to improve the solubility/ dissolution rate of poorly soluble drugs and in middle of the alternatives, the use of cyclodextrin complexation presented a great interest [10]. In recent years, pharmaceutical applications of cyclodextrins (CDs) as additives and drug-complexing agents have been growing rapidly. CDs are cyclic oligosaccharides composed of glucopyranose units and can be represented as a truncated cone structure with a hydrophobic cavity. The hydrophobic cavity forms inclusion complexes with a wide range of guest molecules. Inclusion complex formation will modify physico-chemical properties such as solubility, stability and bioavailability of poorly water-soluble drugs [11].

It is also a well known fact that, the pH of the medium is one of the important factors affecting the solubility of drugs [12] especially the weakly acidic or basic drugs. Hence, the present study is undertaken taken with an aim to investigate the effect of pH, selected cyclodextrins and methods of complexation on the solubility of a novel NSAID, lornoxicam. The solubility study is carried out in different media (pH 1.2 to pH 10) to identify the physiological pH where the drug is having highest solubility and also the influence of selected cyclodextrins (β cyclodextrin and Hydroxpropyl β cyclodextrin) and methods of complexation in enhancing the solubility of lornoxicam was studied.

MATERIALS AND METHODS

Lornoxicam was obtained as gift sample from Sun Pharma Ltd., Vadodhara. β cyclodextrin and Hydroxpropyl β cyclodextrin were generously supplied by M/s Gangawal Chemicals, Mumbai. All other reagents used were of analytical grade and were purchased from Sd fine chemicals, Mumbai.

Solubility Studies [13-15]

Phase solubility studies were carried out according to the method reported by Higuchi and Connors. An excess amount of LRN was added to stoppered glass vials containing 10 ml aqueous solutions of varying concentrations of β cyclodextrin and Hydroxpropyl β

cyclodextrin (0-20 mM) and the suspensions were stirred for 24 h at 37±0.5ºC using temperature controlled water bath (Remi Motors, Mumbai). After equilibrium, the samples were filtered and absorbance was recorded at 376.5 nm using UV/Vis spectrophotometer (Shimadzu UV-1700).

Phase solubility diagrams were obtained by plotting the molar concentration of solubilized lornoxicam versus the molar concentrations of the CDs used. The apparent stability constants (Ks) were estimated from the straight line of the phase solubility diagrams according to the following equation:

$$Ks = Slope/So (1- Slope)$$

Where, So is the solubility of l lornoxicam in absence of cyclodextrins.

In order to know the effect of pH on solubility of LRN, analogous solubility studies in different media (pH 1.2 - pH 10.0) were also carried out under same experimental conditions. The solubility of LRN in each buffer media was assessed using UV/Vis spectrophotometer at 372.5 nm for acidic media and 377.5 nm for all other media studied.

Preparation of inclusion complexes

With an aim to improve the solubility of LRN, inclusion complexes with β CD and HP β CD were prepared at two molar ratios (1:1 and 1:2) by kneading, ultrasonication and spray drying methods. Physical mixtures of LRN and CDs in the same molar ratios were also prepared for comparison purpose.

Physical mixture

The physical mixtures were prepared by gently mixing the accurately weighed amounts of LRN and CDs in a glass mortar over a period of 30 minutes.

Kneading method [16]

The required quantities of LRN and CDs were accurately weighed, transferred to a glass mortar and thoroughly mixed. The above mixture was triturated with small volume of solvent blend of alcohol and water (1:1 ratio). The slurry obtained was kneaded for 30 minutes and then dried at 37ºC for 48 hrs in hot air oven (Servewell Instruments and Equipments Pvt, Bangalore, India). The dried mass was pulverized and passed through sieve # 100 and stored in desiccator over fused calcium chloride for further use.

Ultrasonication [17]

The slurry of LRN and CDs was prepared as mentioned in the kneading method and it was ultrasonicated for 6h. During ultrasonication, paste like consistency was maintained using alcohol-water (1:1 ratio). After ultrasonication, the slurry was dried at 37ºC for 48 hrs in hot air oven. The dried mass was pulverized and passed through sieve # 100 and stored in desiccator over fused calcium chloride for further use.

Spray drying [10]

Spray dried product was obtained by dissolving required quantities of CDs and LRN in 100 ml of alcohol and water (1:1) and thereafter the solution was stirred vigorously using a magnetic stirrer for 24 hrs. Subsequently spray drying of solution was carried out using laboratory scale spray drier (Lab Ultima- LU 222 advanced) under the following conditions: Inlet temperature 135 ºC, outlet temperature 60 ºC, feed rate 5 ml/min, air flow rate 500 cm^3/h, automization air pressure at 2.5kg/cm^2 and aspiration set at 100%. The spray dried product thus obtained was collected, packed suitably and stored in a desiccator for further use.

Characterization of complexes

Drug content[16,18,]

The percentage drug content was determined by taking each physical mixture and inclusion complexes equivalent to 10mg of lornoxicam in a 100 ml volumetric flask containing 50 ml of azeotropic mixture of water and methanol (60:40v/v) and the volume was made up to 100 ml using the same media and stirred for 1hr using water bath shaker. The resulting solution was filtered and diluted appropriately with phosphate buffer of pH 7.4 and the absorbance was noted at 377.5 nm using UV/Vis spectrophotometer.

Infrared spectroscopy

The FT-IR spectra of pure drug, pure CDs, physical mixtures and the inclusion complexes were recorded on Shimadzu FT-IR spectrophotometer (IR Affinity 1) using KBr disk technique. The FT-IR measurements were performed in the scanning range of 4000-500 cm^{-1}.

In vitro dissolution

The dissolution studies for the pure drug, physical mixtures and inclusion complexes were carried out using USP dissolution apparatus (Type II) employing 0.1 N HCl as dissolution medium. The dissolution medium (900 ml) was stirred at 100rpm and the temperature was maintained at 37±0.5ºC. At specific time intervals aliquots were withdrawn, filtered through Whatman filter paper and suitably diluted and analyzed spectrophotometrically at 372.5 nm using the same media as blank.

Statistical analysis

The data obtained from the study was statistically analyzed by one way ANOVA (Tukey's multiple comparison test) using GraphPad Prism Software-5.03 (Trial version, Graph Pad Software, San Diego, CA). The analysis was performed to know the statistical significance of pH, cyclodextrins and complexation methods on the solubility of LRN.

RESULTS AND DISCUSSION

Phase solubility Studies

The phase solubility curve of lornoxicam in the presence of β CD and HP β CD is showed in Fig 1. From the figure it can be observed that β CD showed BS type solubility curve indicating limited solubility. The solubility of lornoxicam increased at the β CD concentration of 2-14 mM and above this, the solubility decreased probably due to precipitation of the complexes. It has been reported that, β CD shows B type of curves due to poor solubility of ligand itself. However, HP β CD showed AL type curve as the solubility of lornoxicam linearly increased with increased concentration of HP β CD without undergoing any precipitation [13, 14, 19]. The slopes were found to be 0.0305 (β CD) and 0.0732 (HP β CD) which are less than 1 indicating that a complex of 1:1 molar ratio was formed in the solution for both β CD and HP β CD.

The stability constant (Ks) was found to be 378.55 M^{-1} and 867.262 M^{-1} for β CD and HP β CD respectively. The correlation coefficient (r^2) values observed from the phase solubility diagrams are 0.8880 and 0.9824 for β CD and HP β CD respectively. The Ks values more than 100 and the high r^2 values indicate the formation of instantaneous and high order inclusion complexes between the lornoxicam and the CDs, especially HP β CD.

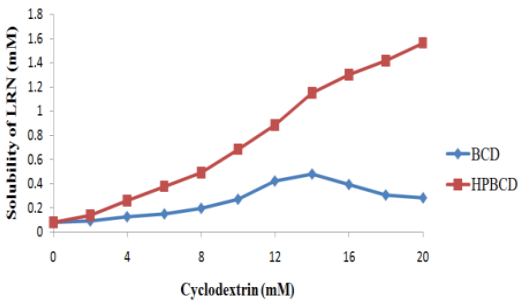

Fig. 1: Phase solubility curves of LRN in water

Solubility of lornoxicam in different media

The solubility of a weakly acidic or basic drug is often pH dependent. The solubility of LRN as a function of pH was carried out in triplicate

and is depicted in Fig 2. LRN being a weakly acidic drug with pKa value of 5.516 showed lowest solubility in the acidic medium and poor solubility in water. The solubility of the drug increased as the pH of the medium was subsequently increased up to 7.4 and a drastic increase in solubility perhaps several folds was observed with the alkaline phosphate buffer (pH 10). The pH dependent solubility could be due to existence of LRN molecules in uncharged form at lower pH media whereas at higher pH range, lornoxicam molecules are negatively charged thus showing the increased solubility [16].

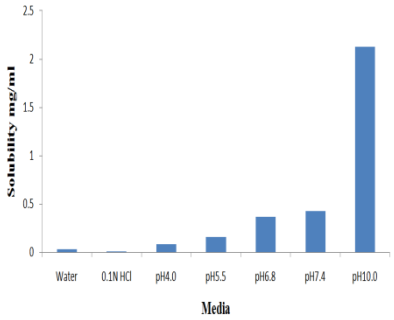

Fig. 2: Solubility of Lornoxicam in different media

FT-IR studies

In the present study, FT-IR technique is used to assess the formation of inclusion complexes that arises due to the interaction between the cyclodextrins and the drug. FT-IR spectra of pure drug lornoxicam, its physical mixture with β CD and HP β CD, the inclusion complexes prepared by different methods is given in Fig 3. The pure drug lornoxicam exhibited its characteristic absorption bands at 3099.61 cm^{-1} due to aromatic C-H stretching and at 2926.01 cm^{-1} due to C-H stretching of CH_3 group. The other prominent absorption bands appeared at 1647.21 cm^{-1} due to stretching vibrations of C=O of CONH, 1618.28 due to aromatic C=C and C=N stretching. Bending vibrations of NH group in the secondary amine were observed at 1593.20 and 1544.96 cm^{-1} whereas aromatic C=C skeleton stretching vibrations were observed at 1500.62 cm^{-1}. The peaks at 1423.47 cm^{-1} and 1327.03 cm^{-1} corresponds to O=S=O group, 790 cm^{-1} due to substituted aromatic rings, 765.74 cm^{-1} due to C-Cl stretching vibrations. The FT-IR spectra of physical mixtures of drug and cyclodextrins revealed no significant changes in absorption bands. However, the IR spectra of inclusion complexes prepared by different methods revealed that the major peaks corresponding to the LRN were affected. The changes in the characteristic bands of the drug confirm the formation of inclusion complex with both the cyclodextrins used. Thus, from the IR studies it can be concluded that the aromatic functional groups of the drug could have interacted with OH groups of the cyclodextrins through hydrogen bonding thereby forming the inclusion complexes.

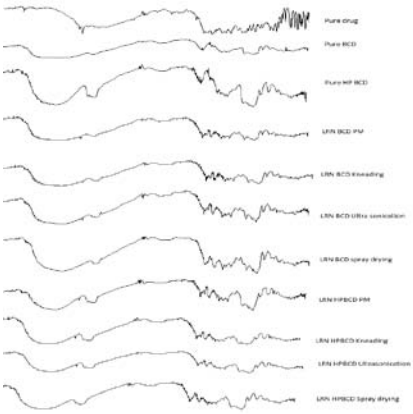

Fig. 3: FT-IR Spectra of Pure drug, Physical mixtures and inclusion complexes

Drug content

The drug content was found to be high in all the inclusion complexes prepared and it ranged from 87.38 (±1.78) to 97.94 (±1.30). The drug content was slightly reduced in case of complexes prepared with higher drug: cyclodextrin ratio irrespective of the cyclodextrin used.

Dissolution study

Dissolution rate profile for the pure drug, physical mixture and the inclusion complexes prepared by different methods utilizing β CD and HP β CD is given in Fig 4 and 5 respectively. Only about 15% of pure drug LRN was released in the acidic media (0.1N HCl) at the end of 90 min dissolution study. Slightly higher dissolution profiles of LRN were obtained from the physical mixtures and the kneaded products. Rapid dissolution is the characteristic feature of the inclusion complexes and indeed, significantly higher dissolution of LRN was observed for the inclusion complexes prepared from ultrasonication and spray drying methods compared to physical mixtures and kneaded products which is an indicative for the efficient complexation by the former methods. Among all the methods, highest dissolution was obtained for the spray dried products irrespective of the cyclodextrin utilized.

As spray drying is an energy intensive process, rapid solvent evaporation leads to amorphization of the drug as very less time is offered for crystal building process along with the inclusion of drug in cavity of the cyclodextrin and thus resulting in higher solubility[13] compared to other methods. In between the two cyclodextrins studied namely β CD and HP β CD, higher dissolution rates were obtained for both physical mixtures and inclusion complexes prepared from HP β CD. The higher dissolution of LRN from HP β CD complexes is also well supported by the phase solubility studies. From the dissolution studies it can be concluded that, HP β CD is better than β CD in enhancing the solubility and dissolution of lornoxicam.

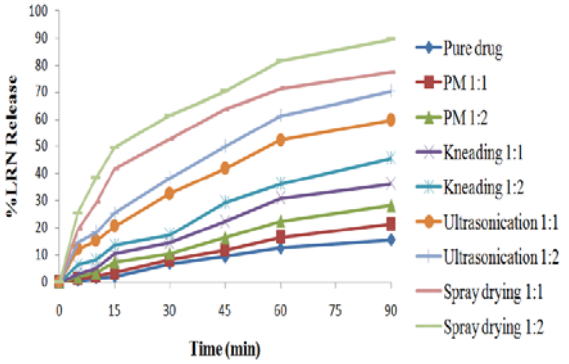

Fig. 4: Effect of complexation methods on release of LRN from BCD complexes

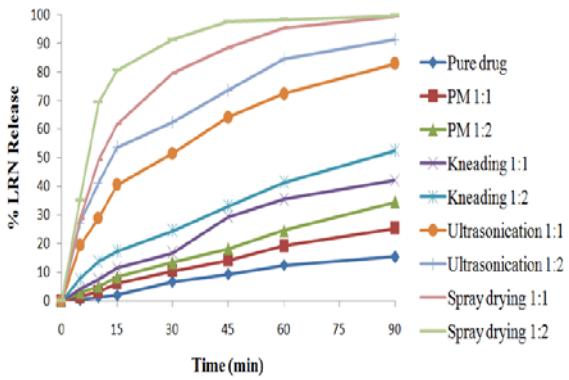

Fig. 5: Effect of complexation methods on release of LRN from HP BCD complexes

CONCLUSION

Overall, from the study it is concluded that, the solubility of lornoxicam was highly dependent on the pH of the medium as well the cyclodextrins. Solubility was found to be lowest in acidic medium which increased progressively with increase in pH of the media and a drastic increase in solubility was observed in alkaline media (pH 10.0). Phase solubility studies revealed that, presence of HP β CD can efficiently increase the solubility of LRN than the β CD with the same molar concentrations used. From the dissolution studies it is concluded that, irrespective of the cyclodextrin used, highest release rate was obtained from the spray dried products compared to the inclusion complexes obtained from other methods. Among the two cyclodextrins, inclusion complexes prepared with HP β CD showed higher dissolution rates compared to β CD. Overall, from the study it is clear that, solubility and dissolution of lornoxicam is highly dependent on the pH of the medium, type of cyclodextrin and also the method of preparation of inclusion complexes.

CONFLICT OF INTERESTS

Declared None

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