Effect of pH combined with surfactant on solubility profile of weakly acidic HMG CoA enzyme reductase inhibitor- Atorvastatin Calcium

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ABSTRACT SUMMARY
This study investigated the combined effect of pH and surfactant on the solubility profile of Atorvastatin calcium, a highly permeable and an ionizable poorly water soluble drug. The equilibrium solubility of atorvastatin calcium was determined in different buffers at pH range from 2 to 7.4 and docusate sodium concentration from 0 to 10%. The maximum enhancement of solubilization is 3 fold with docusate concentration of 10% at pH of 7.4. The enhancement of invitro solubility is attributed to increase in pH and presence of docusate sodium which increases the ionization, wettability and dispersibility of Atorvastatin calcium due to micellar solubilization of ionic and unionic form of drug.

INTRODUCTION
Solubility and permeability plays an important role in formulation and development of dosage form. Solubility characteristics plays a major role in bioavailability, pharmacological action and solubility enhancement of poorly soluble drugs always pose a challenge for formulation scientist. Factors affecting solubility are particle size, shape, surface area and physicochemical characteristics of drugs, solvents, pH of medium, temperature and use of surfactants. Drugs belonging to BCS class II (low solubility and high permeability), dissolution and dose are the most important factors affecting the rate and extent of oral absorption which are dependent on solubility characteristics of drug. Any drug to be absorbed must be present in solution form at the site of absorption. Apart from this pH, pKa, and presence of surfactant plays a significant role in drug absorption. The effect of pH combined with surfactant on solubility and dissolution of drugs have been investigated by many researchers.

Atorvastatin Calcium (ATV) competitive inhibitor of HMG-CoA reductase. ATV belongs to Class II category and has an aqueous solubility of about 100 μg/ml exhibiting dissolution rate limited oral bioavailability

EXPERIMENTAL METHODS

Materials: Atorvastatin Calcium was obtained as gift sample from Micro Labs, Bangalore, Docusate sodium from Torrent Pharmaceuticals, Ahmedabad and all other chemicals used were of analytical grade.

Buffer used: Acetate buffer (pH 4.5), Phosphate buffer (pH 7.4) and 0.1N HCL(pH 1-2)

Surfactant used: DSS (2%, 5%, 10%)

Procedure: Solutions containing 2%, 5%, 10% of DSS was prepared in respective buffers. To 5ml of this solution drug was added in quantity to produce saturated solution. Then the solutions were taken in vials and place in incubator shaker maintained at 37°C. After 4 hr 1ml solution withdrawn, filtered through Whatmann filter paper, added 2ml Ferric Chloride, 2ml of Potassium Ferricyanide and volume made up to 10ml with respective buffer and kept for stabilization and analysed at 740nm.

RESULTS AND DISCUSSION
This study investigated the combined effect of pH and surfactant on the solubility and dissolution of ATV, an ionizable, poorly water soluble drug. The equilibrium solubility of ATV was determined in buffers at the pH range from 1.2 to 7.4 and docusate sodium (DSS) in concentrations from 0% to 10.0%. The equilibrium solubility of ATV in various buffers in pH range 1-7.4 containing 0-10% Docusate Sodium was studied and results revealed with increase in pH solubility increases and at pH below 4 it has very low solubility as depicted in graphs 1-3.

Fig 1: Comparative pH dependent solubility of ATV

Fig 2: Comparative effect of DSS concentration at same pH
According to Henderson Haselbach equation weakly acid drug gets ionized at higher pH. ATV calcium is weakly acidic in nature, solubility increases with increase in pH. This is due to decrease in hydrogen ion concentration at higher pH and ionized form of drug is more soluble. As the drug ionizes more solid drug goes into the solution to maintain saturated solution of unionized form of drug and pH effect is describes as ionization process (Higuchi 1968)

\[ K_a = \frac{[H^+]}{C_{ATV}} \]

where \([H^+]\) is hydrogen ion concentration, \(K_a\) is dissociation constant of ATV. \(C_{ATV}\) and \(C_{ATV}^{-}\) ionized and unionized form of atorvastatin. The surfactant exerts its micellar impact not only on unionized drug molecules but also on the ionized drug molecules. The total solubility of ATV can be expressed as sum of solubility of unionized drug and ionized drug in free solute and micelle solubilized form.

\[ C_{Total} = C_{ATV} + C_{ATV}^{-} + C_{(ATV)micelle} + C_{ATV-micelle} \]

The total solubility of ATV increases reciprocally with \([H^+]\) concentration and thus exhibits a positive relationship with pH. The solubility of ionized drug rather than unionized drug is component influenced by pH effect as shown in Fig. 5.20. For ATV MMT in oral cavity presents ATV at pH 6.8, which is greater than pKa (4.46) of ATV? Hence, it is depicted that total solubility increases proportionally with DSS concentration for any given pH range. At given concentration of DSS with increase in pH, solubility increases. However, it is observed that higher concentration of DSS would lead to greater sensitivity of the total solubility relative to pH changes. This is primarily due to the contribution of the micelle-solubilized ionized drug. In the presence of DSS, the combined solubilisation power of pH and surfactant might be more enhanced than just single pH effect. At pH 7.4 with 10.0% DSS, in particular, showed high solubility due to increased solubilisation of both the unionized drug and the ionized drug at a higher docusate concentration. In addition, the fractional solubility from the unionized drug and the corresponding micelles or that from the ionized drug and its micelles is pH dependant.

**CONCLUSION**

This study summarizes that with increase in pH and concentration of surfactant the solubility of Atorvastatin calcium increases up to 3 folds with 10% Docusate sodium at pH of 7.4 and the effect is more predominant with surfactant concentration as compared to pH.

**REFERENCES**


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