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Extended Abstract
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Pharma Sci-Influence of bile salts as excipients in ranitidine, aminophylline and phenobarbital tablets on dissolution rate- Marta Pocuca- University of Novi Sad

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Abstract

Introduction:
Bile acids are amphyphilic molecules with two functionally different molecular surfaces, convex of steroid core that is hydrophobic and concave that is hydrophilic. His coexistence of non-polar and polar surfaces influences their physico-chemical properties such as formation of self-association micelles that have significant role in the physiology of the metabolism of fats, absorption of liposoluble vitamins and hydrophobic drugs. Beside their physiological role, micellar solutions of bile acids can solubilize poorly soluble organic substances. Furthermore, bile acids have a promoting effect in the transport of some polar drugs. It has also been shown that the glycosylated derivate of bile acids facilitate transport of insulin and calcitonin through cell membrane. On the other hand, it has been observed that hydrophobic cationic drugs enter the interaction with bile acid salts. Cholic acid keto derivatives prolonged the analgesic effect of lidocaine. Pharmacological studies on promotory action of keto derivatives of cholic acids, first of all of 12-monoketocholic acid indicates that keto derivatives of bile acids are of growing interest from a biomedical point of view. Bile acids have also been studied as permeability enhancers of other biological membrane such as skin, cornea and the blood-brain barrier. In pharmacological studies bile acids keto derivatives are of special interest as introduction of keto group in bile acid molecule leads to Critical Micellar Concentration (CMC) increase which results in decrease in membrane-toxic e؛ect associated with bile acids. Ranitidine hydrochloride is highly soluble in water (24.7 mg/mL) pH of water solution is. It is an acidic salt of a weak base ranitidine and has two pKa values, 2.7 (side chain) and 8.2 (dimethylamine). Per oral absorption is variable, biological availability Dier per oral dose of 150 mg is 50% (in the range from 40 to 88%), volume of distribution is 1.4 L/kg and elimination half time is 2.5 to 3 hrs. Ranitidine has an unpredictable dose-response ratio i.e., doses of 75,100 and 150 mg lead to the inhibition of hydrochloride acid overnight in the following percentage: 95,96 and 92%. According to Biopharmaceutical and lDssificDtion System (BCS) ranitidine belongs to a class III i.e., high solubility-low permeability drugs. Aminophylline, theophylline ethylenediamine, is highly soluble in water (one g dissolves in 25 mL of water to give a clear solution) pH of water solution is alkaline. It is a weak base, pKa value is 5.0. Absorption from gastrointestinal tract per oral or rectal administration is incomplete, slow and variable. Approximately 79% is converted into theophylline. Upon per oral administration of non-coated tablets peak concentration in plasma is reached in 2 hours. Mean volume of distribution is 0.5 L/kg. Elimination kinetics is highly variable, half-life of elimination is 7-9 hours in adults, non-smokers, 4-5 hours in adults, smokers, 3-5 hours in children and 20-30 hours in premature babies. According to BCS theophylline belong to a class I i.e., high solubility-high permeability drugs.

Method:
Tablets:
Cholic acid (Sigma, New Zealand, 98%) was used as the starting compound for the synthesis of its keto derivatives. 3α,7αdihydroxy-12-keto-5β-cholanoic acid (12-monoketocholic acid) and 3,7,12-triketo-5β-cholanoic acid (3,7,12-triketo-cholic acid or dehydrocholic acid)were prepared according to the procedures published earlier

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[29,30]. Investigated bile acids were transformed to sodium salts by the known procedure. Material for a preparation of ranitidine hydrochloride, aminophylline and phenobarbital tablets is presented in Tables 1-3 respectively. Formulations of control groups (Ranitidine control (RC), Aminophylline Control (AC) and phenobarbital control (PhC)) were developed according to commercial formulations, while in investigational groups magnesium stearate was replaced with an equimolar concentration of sodium cholate in the investigational group 1 (ranitidine (RIG1), aminophylline (AIG1) and phenobarbital (PhIG1); sodium 12-monoketocholate in the investigational group 2 (ranitidine (RIG2), Aminophylline (AIG2) and phenobarbital (PhIG2)) and sodium dehydrocholate in the investigational group 3 (ranitidine (RIG3), aminophylline (AIG3) and phenobarbital (PhIG3)). Adjustment of lactose or starch quantity was made in order to keep the same tablet mass for all formulations.

Dissolution test:
For dissolution testing of all formulations, ERWEKA DT 800 dissolution paddle apparatus (United States Pharmacopeia-USP 2), with fractional collector, was used. The following conditions were applied: 37 °C, 50 rotation per minute (rpm), run schedule 10, 20, 30, 40, 50, 60 min, volume of dissolution media 500 ml. Dissolution media pH was changed from 4.5 to 6.5 at 30 min and to 7.0 at 60 min. Sodium hydroxide solution (6 M) was used for pH adjustment. Obtained samples were analyzed by High Performance Liquid Chromatography (HPLC).

HPLC analysis:
All samples were analyzed using a HPLC system consisting of an Agilent Technology Series 1100 auto injector, a C18 guard column (4.6 × 15 mm, 5 µm, Zorbax), a C18 analytical column (4.6×150 mm, 5 µm, Zorbax) and Agilent series 1100 with DAD detector. Ranitidine hydrochloride samples obtained from dissolution were analyzed for ranitidine hydrochloride concentrations at 314 nm. The mobile phase was a mixture of ammonium chloride (0.1 M) and methanol (15:85 v/v), injection volume 10 µl. The flow rate was 1.5 ml/min. Under these conditions, the retention time for ranitidine was 1.18 minutes. For calibration curve concentration range was 0.01-0.1 mg/ml, R=0.9980.

Aminophylline samples obtained from dissolution were analyzed for aminophylline concentrations at 273 nm. The mobile phase was a mixture of methanol and water (45:55 v/v), injection volume 10 µl. The flow rate was 2 ml/min. Under these conditions, the retention time for aminophylline was 1.24 minutes. For calibration curve concentration range was 0.01-0.2 mg/ml, R=0.9946.

Phenobarbital samples obtained from dissolution were analyzed for phenobarbital concentrations at 235 nm. The mobile phase was a mixture of methanol and water (50:50 v/v) injection volume 10 µl. The flow rate was 1.2 ml/min. Under these conditions, the retention time for phenobarbital was 3.80 min. For calibration curve concentration range was 0.005-0.1 mg/ml, R=0.9999.

Conclusion: Bile acid salts are very promising excipients. This study confirmed their role as surfactants and lubricants.

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Biography

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