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Research Paper

Evaluation of Various Dissolution Media for Predicting *In Vivo* Performance of Class I and II Drugs

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Purpose. In this paper we seek to verify the differences in dissolution behavior between class I and class II drugs and to evaluate the suitability of two new physiologically based media, of Simulated Gastric Fluid (SGF) and of milk for their ability to forecast trends in the *in vivo* performance of class II compounds and their formulations.

Methods. Dissolution behavior of two class I drugs, i.e. acetaminophen and metoprolol, and of three class II drugs, i.e. danazol, mefenamic acid and ketoconazole, was studied with USP Apparatus 2 in water, SGF, milk, Simulated Intestinal Fluid without pancreatin (SIF_{sp}) and in two media simulating the small intestinal contents in the fed (FeSSIF) and fasted (FaSSIF) states, respectively.

Results. Class I powders dissolved rapidly in all media tested. Acetaminophen dissolution in milk was slow from one tablet formulation, in all other cases dissolution was more than 85% complete in 15 minutes. The dissolution rate of metoprolol was shown to be dependent on formulation and manufacturing method, and one of the three tablet formulations did not meet compendial specifications (80%/30 minutes). Dissolution behavior of class II drugs was greatly affected by choice of medium. Dissolution from a capsule formulation of danazol proved to be dependent on the concentration of solubilizing agents, with a the 30-fold increase in percentage dissolved within 90 minutes upon changing from aqueous media without surfactants to FaSSIF. Use of FeSSIF or milk as the dissolution medium resulted in an even greater increase in percentage dissolved, 100 and 180-fold respectively. Dissolution of the weak acid mefenamic acid from a capsule formulation is dependent on both pH and bile salt concentration, which leads to an offset between increased bile salt concentration and lower pH in the fed state compared to the fasted state medium. The weak base ketoconazole showed complete dissolution from a tablet formulation in Simulated Gastric Fluid without pepsin (SGF_{sp}) within 30 minutes, 70% dissolution in 2 hours under fed state simulated upper jejunal conditions but only 6% dissolution in 2 hours under fasted state conditions.

Conclusions. As predicted, dissolution of class II drugs proved to be in general much more dependent on the medium than class I drugs. With the array of compendial and physiological media available, it should be possible to design a suitable set of tests to predict the *in vivo* dissolution of both class I and II drugs from immediate release formulations.

KEY WORDS: dissolution; physiological media; milk; compendial media; acetaminophen; metoprolol; danazol; mefenamic acid; ketoconazole.

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INTRODUCTION

The use of high throughput techniques for screening new compounds for pharmacological activity is becoming increasingly important (1). As a result, drugs being developed today exhibit an ever wider range of physicochemical characteristics. To assess whether these compounds possess not only the desired pharmacological activity but also the properties necessary for adequate bioavailability following oral administration, additional tests are required. Especially sought after are *in vitro* tests that are capable of predicting *in vivo* performance.

The recently proposed Biopharmaceutics Classification Scheme (BCS) (2) can be used as a guide to define which tests are most suitable for which drugs. According to the BCS, drugs can be divided into four classes on the basis of their aqueous solubility and their ability to permeate the mucosa in the gut from the apical to the basolateral side. Class I drugs are defined as those with high permeability which are able to dissolve readily in aqueous media over the pH range 1 to 8. Since dissolution is not rate limiting to oral absorption of these drugs, a point to point correlation between *in vitro* dissolution and absorption is not to be expected. Instead, a one point dissolution test requiring 85% dissolution within 15 minutes in a mild aqueous medium has been suggested as an indirect measure of bio(in)equivalence of two immediate release formulations of a class I compound (3).

In contrast to class I drugs, the choice of medium is expected to play a very important role in the dissolution of class II drugs. Class II drugs are defined as those with high permeability but whose solubility in aqueous media is insufficient for the whole dose to be dissolved in the gastrointestinal (GI) contents under usual conditions. Since dissolution, for these substances, is the rate limiting step to absorption and since dissolution of a class II drug can depend on a wide variety of factors such as surfactants, pH, buffer capacity, ionic strength and volume available for dissolution, the media used need to closely represent the prevailing conditions in the upper GI tract in order to achieve a meaningful *in vitro/in vivo* correlation (IVIVC) (4). Compendial media often fail for IVIVC of class II drugs because their composition does not take the above-mentioned physiological parameters into account. In an attempt to better predict *in vivo* performance of class II drug formulations, two new media representing the fed and fasted state in the upper jejunum have been developed (5). Milk, 3.5 % fat, and the USP simulated gastric fluid (6) with or without pepsin (SGF/SGF_{sp}) were additionally chosen as media to represent fed and fasted state conditions, respectively, in the stomach.

In this paper we seek to verify the differences in dissolution behavior between class I and class II drugs and to evaluate the suitability of the two new "physiological" media, of SGF_{sp}, and of milk, for their ability to forecast trends in the *in vivo* performance of class II compounds and their formulations. The class I drugs chosen for our dissolution studies were acetaminophen and metoprolol. Acetaminophen, an analgesic and antipyretic, was chosen on the basis of its high water solubility (14.5 mg/ml (7)), lack of ionization in the physiological pH range (pKa = 9.5 (8)), and favorable absorption properties. The second class I drug chosen was metoprolol, a widely used β-blocker, which has a pKa of 9.7 (8), a log P value of −0.1 (8) an aqueous solubility exceeding 1000 mg/ml (tartrate salt) (9)

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