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

E. Galia,1 E. Nicolaides,2 D. Hörter,1 R. Löbenberg,1 C. Reppas,2 and J. B. Dressman1,3

Received October 24, 1997; accepted February 20, 1998

Purpose. In this paper we seek to verify the differences in dissolution behavior between class I and 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 (SIFp) and in two media simulating the small intestinal contents in the fed (FeSSIF) and fasted (FaSSIF) states, respectively.

Results. Class I powders dissolves 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 fasted state compared to the fasted state medium. The weak base ketoconazole showed complete dissolution from a tablet formulation in Simulated Gastric Fluid without pepsin (SGFp) 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.

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/SGFp) 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 II drugs and to evaluate the suitability of the two new "physiological" media, of SGFp, 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).
and high permeability (10). Our model drugs for class II were danazol, mfenamic acid and ketoconazole. The steroid danazol is a neutral, lipophilic compound (log P = 4.2 (8)) which is practically insoluble in water (aqueous solubility = 1 µg/ml (11)). Mfenamic acid, an NSAID, was chosen on the basis of its low aqueous solubility as a free acid (0.5 µg/ml (12), log P = 5.3 (8)) and the fact that changes in pH can have a profound influence on its solubility (pKa = 4.2 (8)). As an example of a poorly soluble weak base we chose the antifungal ketoconazole, the intrinsic aqueous solubility of which is 4.5 µg/ml (experimentally determined at 37°C). With pKa values of 6.5 and 2.9 (13), the dissolution of ketoconazole also varies greatly with pH in the physiological range. The log P of 4.3 (8) suggests further that ketoconazole could be solubilized by bile salts (14). The dissolution behavior of all five compounds was studied in various media including the two new "physiological" media, milk, SFGw, and in two other media commonly used to evaluate dissolution, namely SIFsp and water.

MATERIALS AND METHODS

Materials

Sodium taurocholate 98% pure lot #15H5001 was purchased from Sigma-Aldrich Chemie GmbH (Deisenhofen, Germany). Egg-phosphatidylcholine, Lipid E PC 99.1% pure, lot #12091-1, was a gift from Lipoid GmbH (Ludwigshafen, Germany). Potassium dihydrogen phosphate, sodium dihydrogen phosphate and potassium chloride, all Analytical Grade, were purchased from E. Merck (Darmstadt, Germany). The source of the long life milk, 3.5% fat, was Landesgenossenschaft Ennstal Molkerei-Betriebe (Steinach, Austria).

Panadol® tablets (500 mg acetaminophen, lot #4125) were purchased from Sterling Health (Athens, Greece). Acetaminophen powder (lot #K28457) was a gift from Stada (Bad Vilbel, Germany). Acetaminophen powder (lot #7845993P150) was purchased from Mallinkrodt (Phillipsburg, NJ, USA). Three lots of metoprolol tartrate tablets (100 mg metoprolol tartrate, lot #DF931004, lot #DF931007 and lot #DF 931011) were manufactured at the University of Maryland, Baltimore, MD, USA (15). Metoprolol tartrate powder was a gift from Ciba-Geigy, (Basel, Switzerland). Danatrol® capsules (100 mg danazol, lot #M618730) were purchased from Sanofi Winthrop GmbH (Munich, Germany). Danazol powder (lot #64H0209) was purchased from Sigma-Aldrich Chemie GmbH (Deisenhofen, Germany). Parkamed® capsules (250 mg mfenamic acid, lot #P521) were purchased from Parke-Davis (Berlin, Germany). Mfenamic Acid powder (lot #25/N) was a gift from Parke-Davis (Ann Arbor, MI, USA). Nizoral® tablets (200 mg ketoconazole, lot #95K27/995) were purchased from Janssen (Neuss, Germany). Ketoconazole powder (lot #10002924) was a gift from Janssen (Beerse, Belgium).

Methods

For all dissolution tests the USP Apparatus 2 (paddle method) was used, employing 500 ml of dissolution medium at a temperature of 37 ± 0.5°C. The dissolution behavior of the various class I and II drug substances was tested according to the conditions listed in Table I.

Samples of approximately 5 ml were withdrawn at appropriate times, using a 5 ml Fortuna Optima® syringe (Fischer Labortechnik, Frankfurt/Main, Germany) fitted with appropriate tubing to facilitate representative sampling with sample replacement. Aqueous samples were filtered through 0.45 µm filters, chosen in each case for their lack of adsorption of the compound in question. Milk samples were filtered through Whatman No 41 (8 µm) filters. In addition to the different media, different rotational speeds were used to see if there was a significant hydrodynamic effect on the rate and extent of dissolution of the drugs under consideration. All experiments were run in triplicate.

Composition of Various Media

Water. For dissolution tests in water, deionized water obtained from a Labconco "water pro. ps." system (Labconco Comp., Kansas, MO) was used. The pH of this water ranged from pH 5.9 to 7.0.

SIFsp. SIFsp was composed according to USPXXIII without pancreatin. At the time that these studies were initiated, the recommended pH for this medium was 7.5 (6).

SFGw/SIFsp. SFG, which was composed as described in USP XXIII (6) was used for the metropolol studies, whereas SFGw, i.e. without pepsin, was used for the ketoconazole studies. Both media have a pH of 1.2.

FaSSIF/FeSSIF. Fluids simulating conditions in the proximal small intestine in the fasted state (FaSSIF) and fed state (FeSSIF) were composed according to data from the literature and studies performed at the University of Michigan. Gray and Dressman (3) have summarized pH values, while Bakatselou et al. (16) have summarized data for bile salt levels in the upper jejunum for the fed and fasted state. The compositions of the two media are given in Table II.

Milk. Bovine milk, 3.5% fat, was purchased from Landesgenossenschaft Ennstal Molkerei-Betriebe Steinach/Austria. This is a homogenized milk treated with ultra high temperature (UHT) to extend the shelf-life and containing no preservatives. It is isosmotic, has a pH of about 6.5 and a buffer capacity of about 4 mEq/l/pH (17).

HPLC-Analysis

Three different HPLC/UV analytical systems were used. The first HPLC system (system 1) consisted of a Rheodyne 7161 injection valve (Rheodyne, Cotati, Ca, USA), a SP8800/8810 LC pump (Spectra Physics, San Jose, Ca, USA), a Spectra 100 UV-photometer (Spectra Physics, San Jose, Ca, USA) and a SP4400 integrator (Spectra Physics, San Jose, Ca, USA). The second HPLC system (system 2) consisted of a Bischoff Degaser Unit SDS 2000 (Bischoff, Leonberg, Germany), Bischoff 728 Autosampler (Bischoff, Leonberg, Germany). Rheodyne 7010 Injection valve (Rheodyne, Cotati, Ca, USA) mounted on a Model 732 electronic valve actuator (Micromeritics, Norcross, GA, USA), Bischoff model 2250 HPLC pump (Bischoff, Leonberg, Germany), Bischoff Lambda 1000 UV-detector (Bischoff, Leonberg, Germany) and a Shimadzu CR6A integrator (Shimadzu Europe, Duisburg, Germany). The third HPLC system (system 3) consisted of a WISP 712 autosampler...