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# EVALUATION OF VARIOUS DISSOLUTION MEDIA FOR PREDICTING THE *IN VIVO* PERFORMANCE OF BCS CLASS II DRUG

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## ABSTRACT

The *in vitro* dissolution profile of BCS class II drug in biorelevant; compendial media was compared and the potential of different media was determined in predicting *in vivo* profile. The solubility of weakly acidic drug, naproxen was determined in various media (Compendial- water, $SGF_{SP}$, $SIF_{SP}$ and Biorelevant- $SGF_{SP}$SLS, FaSSIF and FeSSIF), to calculate D/S values in different media. The dissolution of naproxen was studied using USP apparatus II in both; compendial and biorelevant media. Hixson-Crowell model was applied to determine drug release kinetics. The *in vivo* profile was predicted from *in vitro* dissolution data using modified form of model proposed by Nicolaides in 2001. Dissolution of naproxen from tablet formulation was found to be governed by pH of dissolution media. The similarity factor value indicated higher dissolution of naproxen at higher pH value ($SIF_{SP}$ and FaSSIF). The *in vivo* profiles predicted that using *in vitro* dissolution of naproxen supported delayed absorption in the presence of food. The biorelevant media are therefore better at discriminating *in vitro* release characteristics for forecasting *in vivo* performance of poorly soluble drugs.

**Key words**: Biorelevant media, FaSSIF, FeSSIF, BCS, $SGF_{SP}$SLS.

## INTRODUCTION

The goal of dissolution testing is to assure the pharmaceutical quality of the product. The use of dissolution testing of solid oral dosage forms to establish correlation between release of drug *in vitro* and absorption of drug *in vivo* from GIT avoids need for costly

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bioavailability studies; thereby, decreasing the cost of drug product development. Satisfactory IVIVC can be developed in case of BCS[1] class II drugs because these exhibit dissolution rate limited absorption. For this purpose, a dissolution test with multiple time points is required to simulate bioavailability[2]. The surfactants, pH, buffer capacity and food components can alter the solubility of drugs in GIT. The solubility and absorption of poorly water soluble drugs is influenced by physiological variation of bile salt concentration and pH during fed and fasted states[3]. The mean value of conjugated bile acids during fasting, 30 min. postprandial and 60 min. postprandial are 5 mM, 15 mM and 8 mM, respectively[4]. During fasted state, pH of duodenum is 6.1 ± 0.4 and during fed state, duodenum pH fluctuates around 5.3 ± 0.4[5]. The composition of dissolution media, volume and hydrodynamics of contents in the lumen are the main factors that affect dissolution of drug in GIT. The dissolution rate limited absorption can be accurately predicted only when these factors are adequately controlled and reproduced *in vitro*. Compendial dissolution media ($SGF_{SP}$ and $SIF_{SP}$) are best suited for quality control purpose but can not be used for IVIVC in all cases, as the composition of these can not differentiate between fed and fasted state[2]. Biorelevant dissolution media[6] (BDM) are reported to determine qualitative aspects of formulation and food effects on absorption of BCS class II drugs[7]. The *in vivo* profile from *in vitro* data can be predicted if drug exhibits dissolution rate limited absorption and absolute bioavailability of drug is known[8] .The objective of present study was to evaluate biorelevant and compendial media on the basis of D/S values and dissolution of naproxen (weakly acidic drug having $pK_a$ = 4.2 and log P =3.18) and to predict *in vivo* plasma profiles of naproxen from *in vitro* dissolution data.

## EXPERIMENTAL

### Materials and methods

Naproxen (Naprosyn Tablets – RPG Life Sci.), Lecithin (Kaushambi Enterprises, Varanasi), Sodium taurocholate (CDH, New Delhi), Potassium dihydrogen phosphate, Sodium lauryl sulfate.

### Determination of D/S value

The solubility was determined in compendial and biorelevant media having different pH values (1.2, 1.48, 5.0, 6.5 and 7.5) by adding known amounts of drug (10, 20, 30, 40 and 50 mg) in different volumes (100, 500 and 1000 mL) of dissolution media and incubated in shaker incubator at 37 ± 0.5 °C. The ionic strength of all media was adjusted to 0.15 N using

sodium chloride[9]. The D/S value for each media was obtained from solubility corresponding to second highest absorbance in the range of 0.2-0.8. These solutions also served as stock for the preparation of calibration curve. The weighted regression was used to derive coefficients (slope and intercept) of calibration curve[10].

$$b = \{\Sigma WXY-(\Sigma WX \times \Sigma WY/\Sigma W)\}/ \{\Sigma WX^2-(\Sigma WX \times \Sigma WY/\Sigma W)\} \quad ...(1)$$

$$a = Y_W - b \times X_W \quad ...(2)$$

where

$Y_W = \Sigma WY/\Sigma W$, $X_W = \Sigma WX/\Sigma W$ and Weight (W) = 1/ (Concentration)$^2$

## Dissolution test

The USP apparatus II containing 500 mL of dissolution media, maintained at 37 ± 0.5°C and stirred at 100 rpm, was used to analyze 12 units per test. The aliquots (2 mL) were withdrawn at different intervals up to 2 hrs and filtered through 0.45 µ filter. The volume of medium was replenished with an equal volume of fresh dissolution medium. The drug content was measured spectrophotometrically (Beckman, D4 640B, USA) at 229 nm. The *in vitro* dissolution profile was explained by Hixson-Crowell model, which is given by following expression: $M_o^{1/3} - M^{1/3} = Kt$ where $M_o$= original mass of drug particle, M = amount of drug release, t = time and K = dissolution rate constant[11]. Dissolution test was used to compare the discriminating ability of biorelevant and compendial media. The $f_2$ factor was calculated from the following equation[12, 13]:

$$f_2 = 50 \log [\{1 + 1/n \Sigma(T_1 - T_2)^2\}^{0.5} \times 100] \quad ...(3)$$

where, $T_1$ and $T_2$ = percent drug dissolved at each time point in two different dissolution media and n = number of observations. An $f_2$ value less than 50 indicates different dissolution profiles.

## Prediction of *in vivo* plasma profile

The plasma profiles were predicted from *in vitro* dissolution data using the model following different assumptions like negligible gastric uptake, simultaneous liquid and gastric emptying from the stomach and no intestinal permeability restrictions. The initial volume of the fluid in the stomach was assumed to be 250 mL in fasted state and 500 mL in

fed state. The average population values for gastric emptying rate were used i.e. first order gastric emptying rate in fasted state (2.8 $hr^{-1}$). The amount of drug entering the plasma was estimated from the product of drug in intestine and bioavailability. The sink conditions were assumed for dissolution in intestine[8].

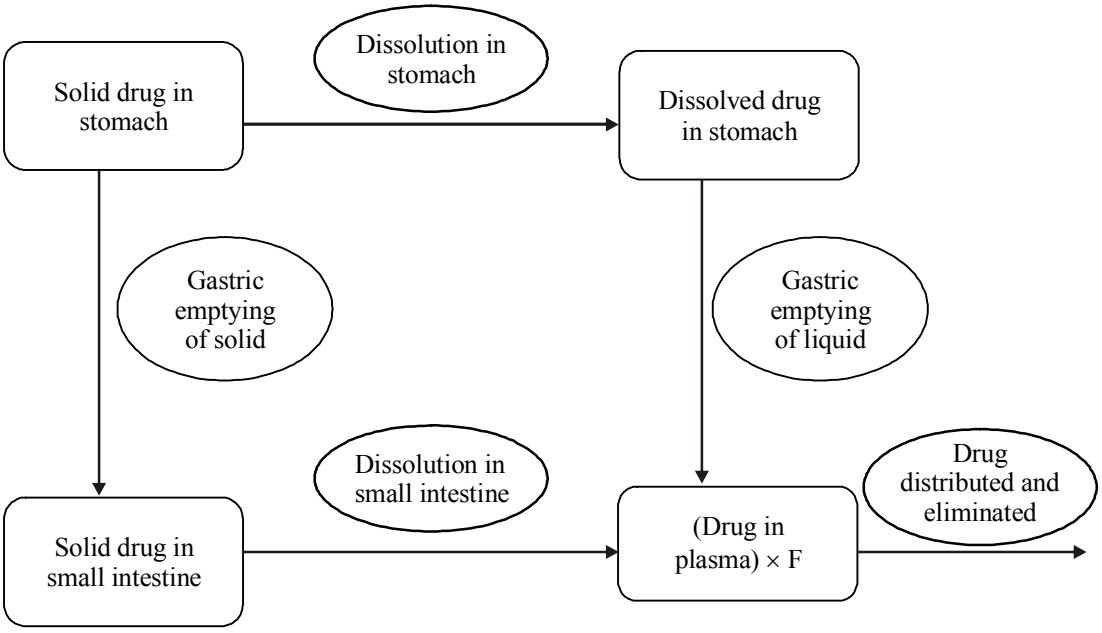



**Fig. 1: Scheme of the model used to obtain simulation profiles**[8]

## RESULTS AND DISCUSSION

The dose to solubility ratio (D/S) of naproxen in various dissolution media (Table 1) showed lowest D/S value of naproxen in dissolution media having higher pH values ($SIF_{SP}$ and FaSSIF). The dissolution of naproxen was maximum in $SIF_{SP}$ followed by FaSSIF, FeSSIF, $SGF_{SP}$SLS, water and $SGF_{SP}$ (Fig. 2). The dissolution of naproxen exhibited similarity value of less than 50 amongst compendial media except in $SGF_{SP}$ and water, where dissolution profiles were similar. The dissolution of naproxen was significantly different in biorelevant media except in $SGF_{SP}$SLS and FeSSIF, where dissolution profiles were similar (Table 2). The fasted state plasma profiles predicted from *in vitro* dissolution of naproxen in compendial media ($SGF_{SP}$ and $SIF_{SP}$) and biorelevant media ($SGF_{SP}$SLS and FaSSIF) exhibited plateau levels with in 1 hr and 4 hrs, respectively (Fig. 3a and 3b). The fed state plasma profiles predicted from *in vitro* dissolution of naproxen in biorelevant media ($SGF_{SP}$SLS and FeSSIF) achieved plateau levels in 15 hrs (Fig. 3c).

**Table 1: D/S Values of naproxen in various dissolution media**

| Dissolution media (pH) | D/S value |
|---|---|
| Distilled water | 12.5 |
| $SGF_{SP}$ (1.2) | 25.0 |
| $SIF_{SP}$ (7.5) | 0.50 |
| $SGF_{SP}$SLS (1.48) | 25.0 |
| FaSSIF (6.5) | 0.80 |
| FeSSIF (5.0) | 6.25 |

The lowest D/S in $SIF_{SP}$ and highest in $SGF_{SP}$ reflect maximum and minimum solubility of naproxen, respectively. The addition of surfactant to $SGF_{SP}$ did not improve the solubility of naproxen. The solubility of naproxen was higher in FaSSIF than FeSSIF although FaSSIF contains lower concentration of bile salts. Therefore, solubility of naproxen is dependent on pH of dissolution medium and not on surfactant. The extent of naproxen release was higher under simulated intestinal conditions than under simulated gastric conditions using both; compendial and biorelevant dissolution media. Amongst compendial media, naproxen exhibited highest release in $SIF_{SP}$ whereas amongst biorelevant dissolution media, naproxen exhibited highest release in FaSSIF. The higher pH of FaSSIF than that of FeSSIF explains higher extent of naproxen release in FaSSIF than in FeSSIF and there is no effect of surfactant concentration. The minimum extent of naproxen release in $SGF_{SP}$ confirms that extent of naproxen release is dependent upon pH of dissolution medium. The release rate of naproxen in distilled water, $SGF_{SP}$SLS and FeSSIF are comparable but no justification can be proposed. The significant difference in dissolution profile of naproxen in $SIF_{SP}$ from that in other compendial media ($f_2 < 50$) and in FaSSIF from that in other biorelevant media ($f_2 < 50$) can be attributed to higher pH (i.e. pH >5.0) value of $SIF_{SP}$ and FaSSIF. The plasma concentration of naproxen predicted using $SIF_{SP}$, FaSSIF and FeSSIF approaches plateau level within 1 hr, 4 hrs and > 15 hrs, respectively. The release of naproxen is overestimated in $SIF_{SP}$ as compared to normal physiological values as observed by Galia et al.[14] The plateau levels of naproxen predicted using FaSSIF were in agreement with literature value. The lower $C_{max}$ value in case of FeSSIF supports that in the presence of food, absorption of naproxen is delayed[15] and small intestine in fasted state is the main site for absorption of naproxen.

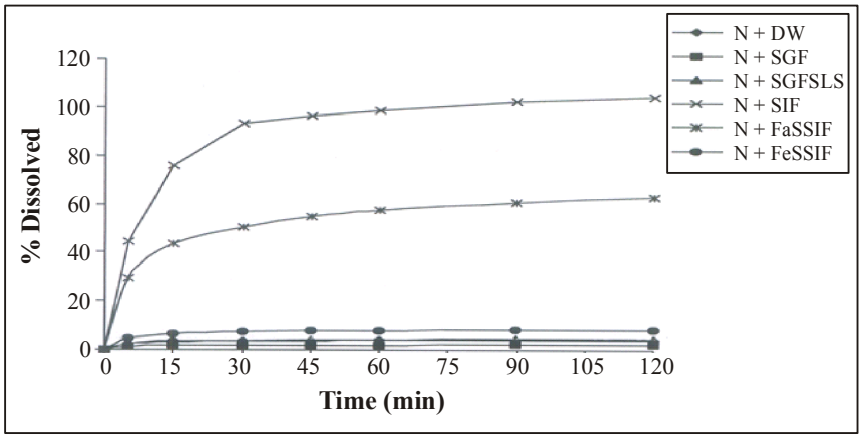
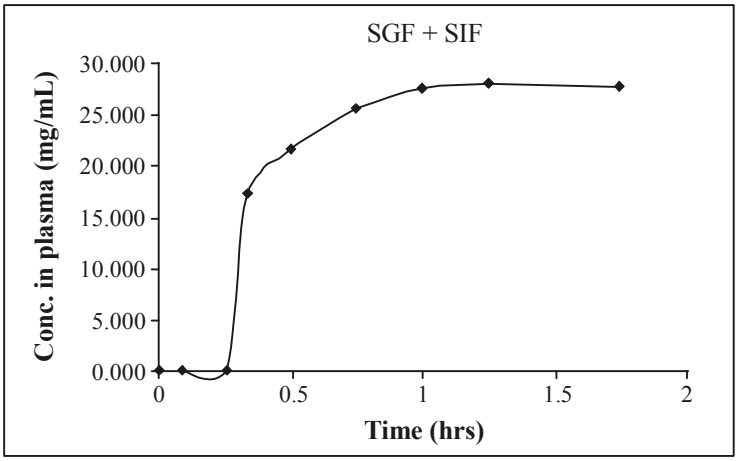



**Fig 2: Comparison of dissolution profiles of naproxen in various dissolution media**

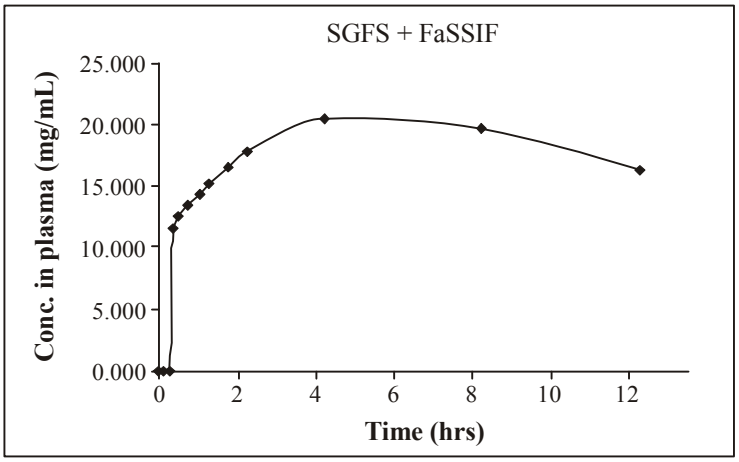
**Table 2: Similarity factor values of naproxen amongst different media**

| | **$SGF_{SP}$** | **$SIF_{SP}$** | **Distilled water** | **$SGF_{SP}SLS$** | **FaSSIF** | **FeSSIF** |
|---|---|---|---|---|---|---|
| $SGF_{SP}$ | | 2.5 | 84 | 83 | 14 | 63 |
| $SIF_{SP}$ | | | 3 | 3 | 20 | 4 |
| Distilled water | | | | 99 | 15 | 71 |
| $SGF_{SP}SLS$ | | | | | 15 | 72 |
| FaSSIF | | | | | | 17 |
| FeSSIF | | | | | | |

**(a)**



**(b)**




**(c)**

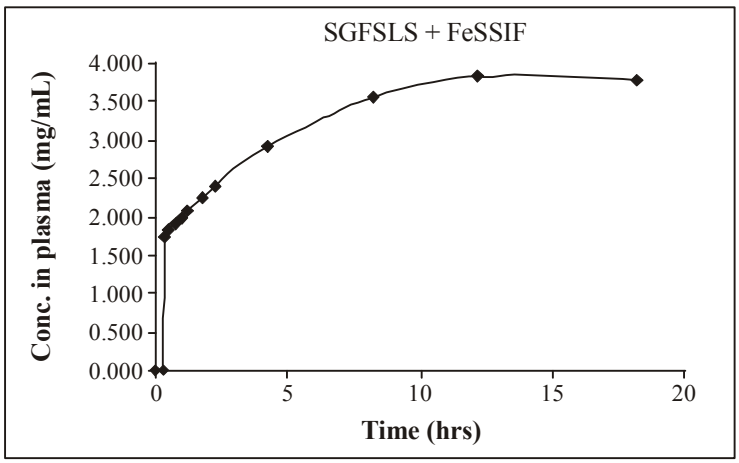



**Fig. 3: *In vivo* predicted profiles of naproxen in (a) $SGF_{SP}$ + $SIF_{SP}$ (b) $SGF_{SP}$SLS + FaSSIF and (c) $SGF_{SP}$ SLS + FeSSIF**

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