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ORIGINAL ARTICLE

Development, Internal and External Validation of Naproxen Sodium Sustained Release Formulation: an Level A *In Vitro-In Vivo* Correlation

Naproksen Sodyum Süreli Serbest Formülasyonun Geliştirilmesi, İç ve Dış Olarak Doğrulaması: Bir Düzey A *İn Vitro-İn Vivo* Korelasyon

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ABSTRACT

Objectives: The aim of the present study was to develop and validate an *in vitro-in vivo* correlation (IVIVC) for naproxen sodium-sustained release tablets and to compare their plasma concentrations over time with the immediate-release tablets.

Materials and Methods: *In vitro* release rate data were obtained for each tablet by using the USP Apparatus II, paddle stirrer at 50 rpm in pH 7.4 phosphate buffer. A four-way crossover study was conducted in 6 healthy subjects by administering naproxen sodium sustained release 375 mg and 500 mg of immediate release tablets. Series of blood samples were collected over 24 hours and estimated by using the validated liquid chromatography tandem-mass spectrometry method.

Results: The similarity factor was calculated and it was found that values between, 50 and 100 indicates similarity of the profiles. Assessment of predicted and observed bioavailability was performed and prediction errors (PE) % calculated, as per the Food Drug Administration guidelines, the average absolute PE% of C_{max} and AUC of individual formulation was found below 15% for establishment of IVIVC, based on internal prediction strongly suggesting that the naproxen sodium IVIVC models are valid. During external validation the predicted curve for the naproxen sodium sustained-release tablets was found to be identical to immediate release tablets and considered as valid.

Conclusion: IVIVC can serve as a surrogate for *in vivo* bioavailability study and supports biowaivers, supports and validates the dissolution methods and specification settings and assists in quality control during scale-up and post-approval changes. It may be used to predict the variation in site change, process changes and to predict the absorption performance of naproxen sodium products with different release rates.

Key words: IVIVC, naproxen sodium, sustained release, dissolution, *in vivo* bioavailability study, internal and external predictability

ÖZ

Amaç: Bu çalışmanın amacı, naproksen sodyumun sürekli salım tableti için *in vitro-in vivo* korelasyon (IVIVC) geliştirmek, doğrulamak ve zamana bağlı plazma konsantrasyonlarını derhal salınan tabletle karşılaştırmaktır.

Gereç ve Yöntemler: *İn vitro* salım hızı verileri, pH 7.4 fosfat tampon içinde 50 dev/dakikada, USP Apparatus II, palet karıştırıcısı kullanılarak her bir tablet için elde edilmiştir. Naproksen sodium 375 mg sürekli salım ve 500 mg derhal salım tabletleri 6 sağlıklı kişiye uygulanarak dört yönlü bir çaprazlama çalışması gerçekleştirilmiştir. Yirmi dört saat boyunca toplanan kan örnekleri valide edilmiş sıvı kromatografisi tandem-kütle spektrometresi yöntemi kullanılarak tayin edilmiştir.

Bulgular: Hesaplanan ve 50-100 arasında bulunan değerler benzerlik faktörlerini göstermektedir. C_{max} ve AUC ortalama değerlerine yakın bulunmuştur. Tahmin edilen ve gözlemlenen biyoyararlanım değerlendirmesi yapıldı ve Gıda İlaç İdaresi yönetmeliklerine göre % tahmin hataları (PE) hesaplandı; iç tahmin ile IVIVC'nin oluşturulması için C_{max}'ın ortalama mutlak %PE'si ve formülasyonun bireysel formülasyonun AUC'si %15'in altında bulundu, naproksen sodyumun IVIVC modelleri geçerlidir. Dış validasyon sırasında, naproksen sodyumun sürekli salım tableti için öngörülen eğri, derhal salım tableti ile aynı bulunması geçerli olduğunu göstermektedir.

Sonuç: Bu IVIVC, *in vivo* biyoyararlanım araştırması için vekil olarak hizmet edebilir ve biyolojik yönlendiricileri destekler, çözünme yöntemlerini ve spesifikasyon ayarlarını destekler ve onaylar, ölçek büyütme ve onay sonrası değişiklikler sırasında kalite kontrolünde yardımcı olur. Yer değişikliği, proses değişiklikleri ve farklı emisyon oranlarına sahip naproksen sodyum ürünlerinin emme performansını tahmin etmek için kullanılabilir.

Anahtar kelimeler: IVIVC, naproksen sodyum, sürekli salım, çözünme, *in vivo* biyoyararlanım çalışması, iç ve dış öngörülebilirlik

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INTRODUCTION

In vitro-in vivo correction is a predictive mathematical model relating the relationship between an *in vitro* property of a dosage form and an *in vivo* response.[5] *In vitro-in viv*o correlation (IVIVC) is most widely established by using formulations with different release rates i.e. slow, medium and fast, data on the *in vitro* release rates and *in vivo* plasma concentration-time profiles of developed formulations, and by using deconvolution techniques to confirm the link between dissolution rate and fraction absorbed. The Food Drug Administration (FDA) guidelines has discussed the three categories of IVIVC models: namely, level A, B, and C models. Level A is a linear is most widely used as it is developed point to point correlation and stands for *in vitro* and *in vivo* absorption rate of the drug. Level A can be developed on both deconvolution and convolution-based methods. Level B compares the mean *in vitro* dissolution time to the mean *in vivo* residence time or the mean *in vivo* dissolution time. Level C is a single point comparison of dissolution time point to one pharmacokinetic parameter [e.g. C_{max}, area under the curve (AUC), and T_{max} time of the maximum plasma concentration]. Level D is a rank order analysis.[5] The development and validation of IVIVC is vital for optimization of sustained release dosage form as it predicts the *in vivo* release profile of the sustained release (SR) dosage form based on *in vitro* data.[9]

Various IVIVC studies have been published for a number of formulations, including Busprion, propranolol, nevirapine, metoprolol and other drugs.[6-17] The concepts and methods used in establishing the IVIVC are reviewed elsewhere.[4,5] According to BCS classification naproxen sodium comes under class 2 drug and in addition naproxen is relatively having a short life suggest suitable applicant for modified release formulation.[1,2] The present work is intended to formulate naproxen sodium sustained release tablet, develop and validate the internal and external predictability of level A IVIVC models. *In vitro* dissolution study was performed to check the release profile and bioavailability study conducted to check the rate and extent of absorption of developed naproxen sodium sustained release and marketed immediate release tablet. Further established and validated IVIVC models can be used as a surrogate for the bioequivalence study, minimize the time and cost for manufacturers, a quality control tool to measure the product performance, a waiver for human studies when the minor changes are done as specified in the scale-up and post-approval changes (SUPAC)- immediate release and SUPAC-modified release guidance.

MATERIALS AND METHODS

Chemicals and reagents

Naproxen sodium, HPMC K100M supplied as a gift sample by Strides Arcolab Limited, Bangalore and Colorcon Asia Pvt. Limited, Goa, India. All other materials like talc, magnesium stearate, ethyl cellulose were procured from local dealer.

In vitro dissolution study and data analysis

The drug release profiles were examined by using by using the United States Pharmacopeia (USP) dissolution apparatus (type 2, paddle) pH 1.2, 4.5, 5.5, 6.8 and 7.4 at 50 & 75 rpm (rotation per min). The dissolution studies were performed on six tablet of naproxen sodium 375 mg SR tablets (i.e. slow, medium and fast) and naproxen sodium 500 mg tablet (marketed immediate release). Samples were drawn at 0.0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0 and 24.0 hours and analyzed by using UV spectroscopy at a wavelength of 332 nm. The percentage fraction dissolved and percentage release at various time points were determined. The similarity of dissolution profiles were evaluated for fast versus slow, slow versus medium and medium versus fast by using the similarity factor (f2).

In vivo bioavailability study and data analysis

This was an single center, randomized, single-dose, open-label, 4-way crossover, bioavailability study to compare the rate and extent of absorption of a naproxen sodium 375 mg SR tablets (i.e. slow, medium and fast) and naproxen sodium 500 mg tablet (marketed immediate release), in six healthy male subjects under fasting conditions. Samples were collected at 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 hours post dose sample. A washout period of 7 days between the dosing of four periods. The study was approved by ethics committee and informed consent were provided by subjects prior enrolled into the study and. Validation of the method was carried out after the development of the liquid chromatography mass spectrometry (LCMS) methods. Validation performed as per the USFDA guidelines i.e. specificity/selectivity, carry over, linearity, precision and accuracy, recovery, dilution integrity, ruggedness, stabilities like freeze thaw stability, bench top stability, long term stability, stock solution stability. A simple and sensitive validated LCMS/MS method used for estimation of plasma sample by using protein precipitate extraction. The calibration curves were linear in the range of 1.167 µg/mL to 163.729 µg/mL for naproxen sodium. Bioavailability study evaluated through plasma concentration data by using pharmacokinetic parameters like C_{max}, AUC, T_{max}, half lifeand estimation performed by using Phoenix 6.4.0 version software.

IVIVC model development

Linear regression analysis was used to study the relationship between the drug dissolved and the drug absorbed in percentage. A correlation was established for naproxen sodium 375 mg SR tablets (i.e. slow, medium and fast) formulations (M/F, S/F, and S/M). A linear regression done by using a least squares method to estimate the regression parameters. Determination coefficient (r^2) was evaluated. The deconvolution procedure was used to obtain *in vivo* input profiles of naproxen sodium from the sustained release dosage forms. The percent of dissolved is plotted against the dissolution sampling points of target formulation to check whether developed IVIVC model is valid.

IVIVC validation

The objective is to predict the outcome of *in vivo* profile with a given model and target formulation of *in vitro* profile. Internal validation provides basis for the acceptability of the model and

external validation is superior and gives the self-confidence in the model. As per the FDA guidance on IVIVC for level A criteria as follows: for internal validation the mean absolute percent prediction error i.e. for C_{max} and AUC should not exceed 10%, and for individual formulation should not exceed 15%. For external validation the prediction errors i.e. C_{max} and AUC, for the formulation should not exceed 10%, 10% to 20% indicates in conclusive predictability and demonstrate the requirement for further study. The percent prediction errors (PE) for C_{max} and AUC were calculated as follows:

$$\%PE_{C_{max}} = \left(\frac{C_{max}\,(observed) - C_{max}\,(prediction)}{C_{max}\,(observed)} \right) x\ 100 \quad (1)$$

$$\%PE_{AUC} = \left(\frac{AUC\,(observed) - AUC\,(prediction)}{AUC\,(observed)} \right) x\ 100 \quad (2)$$

RESULT AND DISCUSSION

In vitro dissolution study

The *in vitro* dissolution studies were performed at different pH conditions (namely pH 1.2, 4.5, 5.5, 6.8, 7.4) to select appropriate pH condition. The results of dissolution studies at different pH conditions with 50 rpm, at pH 1.2 and 50 rpm, drug release was partial and utmost 11% released from the formulations (F1-F6; SR tablets composition are mentioned in Table 1) within 3 hours as shown in the Figure 1. At pH 4.5, the drug release was very slow till 24 hours. The release was incomplete for all the formulations (F1-F6; SR tablets) as shown in the Figure 2. At pH 5.5 homogeneous and slow release of drug from all the 6 formulations (F1-F6; SR tablets) over the period of 24 h, 80.59-99.86% of drug was released as shown in the Figure 3. At pH 6.8 and 7.4 about 86.79-97.32% as shown in the Figure 4 and 86.95-95.81% release of drug was observed as shown in the Figure 5. Hence pH 5.5 selected for *in vitro* dissolution studies for naproxen sodium. There is no significant changes observed in drug release when performed with 75 rpm. The *in vitro* drug release studies performed as per the USP method i.e. pH 7.4 pH condition at 50 rpm for naproxen sodium SR tablets (i.e. F2 slow, F5 medium and F4 fast). The *in vitro* release characteristics of the fast, medium, and slow sustained release tablet of naproxen sodium were determined and presented in Figure 6. The similarity factor (r^2) was calculated fast versus slow 52.52, fast versus medium 69.87 and medium versus slow 64.08 respectively.[4]

The percentage fraction dissolved for naproxen sodium are in the rank order of marketed immediate release, fast, medium and slow sustained release tablets and are presented in the Figure 6.

In vivo bioavailability study and data analysis

The mean pharmacokinetic profile for all formulations are presented in Table 2. The rank order release in the dissolution testing was obvious in the plasma concentration profile of

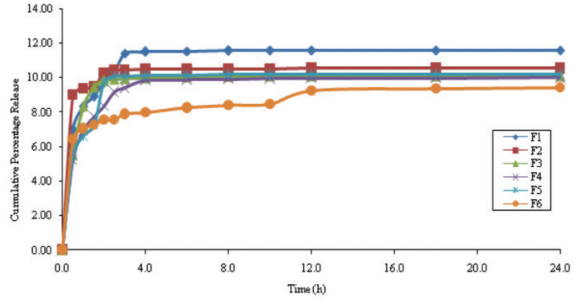

Figure 1. Percentage cumulative release profiles of naproxen sodium sustained release formulations (F1-F6) at pH 1.2 and 50 rpm

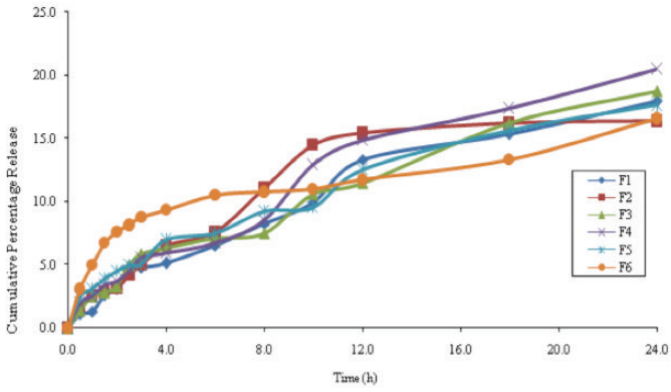

Figure 2. Percentage cumulative release profiles of naproxen sodium sustained release formulations (F1-F6) at pH 4.5 and 50 rpm

Table 1. Composition of naproxen sodium formulation (F1-F6)

Formulation	Naproxen sodium	HPMC K100M	Talc (1.5%)	Magnesium stearate (1.5%)	Talc (1%)	Magnesium stearate (1%)	Ethyl cellulose
F1	375	75 mg	-	-	4.50 mg	4.50 mg	-
F2	375	150 mg	-	-	5.25 mg	6.00 mg	-
F3	375	225 mg	-	-	5.25 mg	6.00 mg	-
F4	375	37.5 mg	6.75 mg	6.75 mg	-	-	37.5 mg
F5	375	37.5 mg	7.87 mg	7.87 mg	-	-	37.5 mg
F6	375	37.5 mg	9.00 mg	9.00 mg	-	-	37.5 mg

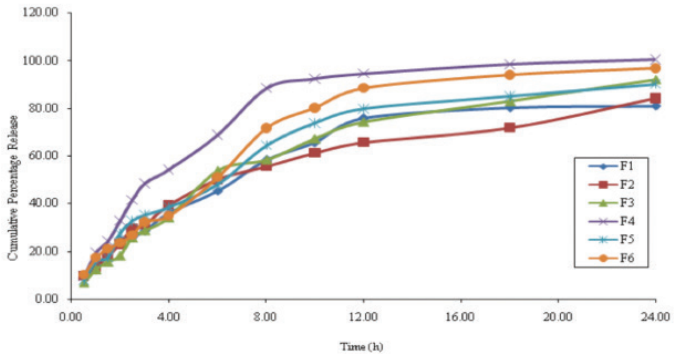

Figure 3. Percentage cumulative release profiles of naproxen sodium sustained release formulations (F1-F6) at pH 5.5 and 50 rpm

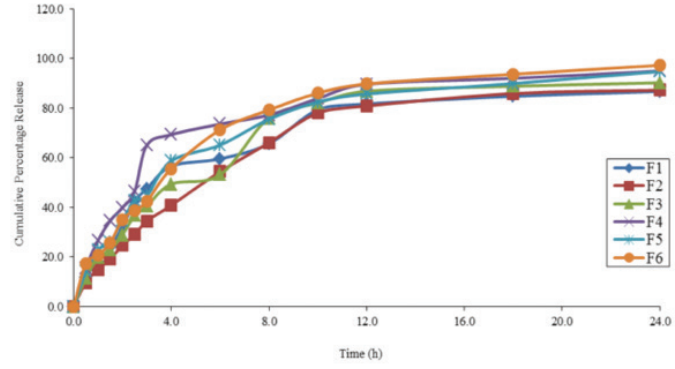

Figure 4. Percentage cumulative release profiles of naproxen sodium sustained release formulations (F1-F6) at pH 6.8 and 50 rpm

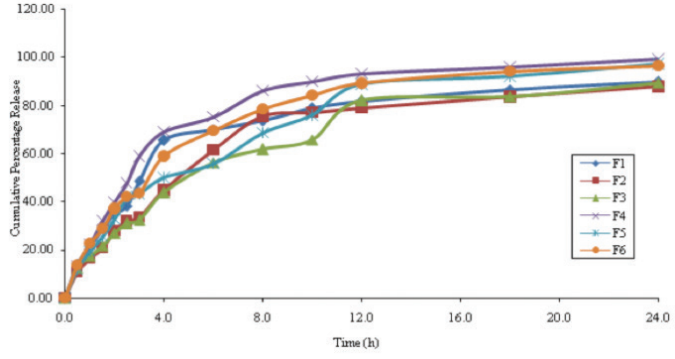

Figure 5. Percentage cumulative release profiles of naproxen sodium sustained release formulations (F1-F6) at pH 7.4 and 50 rpm

naproxen sodium as in the Figure 7. AUC of naproxen slow release and medium release tablet was significantly higher compare to immediate release and fast release tablet. There is significant difference observed in naproxen slow and medium sustained release tablet compare to marketed immediate release and fast sustained tablet. AUC of naproxen sustained release tablets was much higher than immediate release tablet, may due to change in location of naproxen sodium absorption in gastrointestinal tract.

In vitro-in vivo correlation development

Level A *in vitro* and *in vivo* correlation was developed by comparing percent dissolved versus the percent absorbed of naproxen sodium fast, medium and slow sustained release and marketed immediate release tablets. The IVIVC plot was constructed using percentage of drug dissolved at pH 7.4

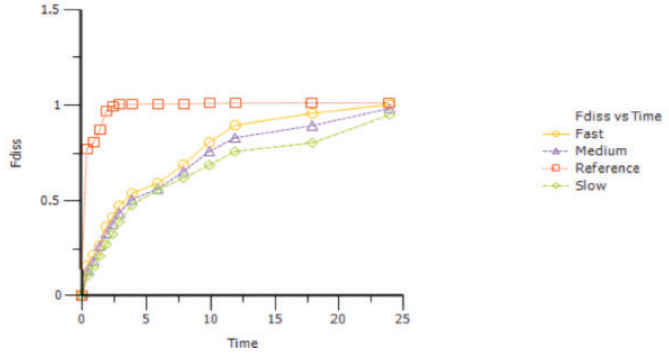

Figure 6. Percentage fraction dissolved versus time for naproxen sodium IR tablet and SR tablets (i.e. F2 slow, F5 medium and F4 fast)

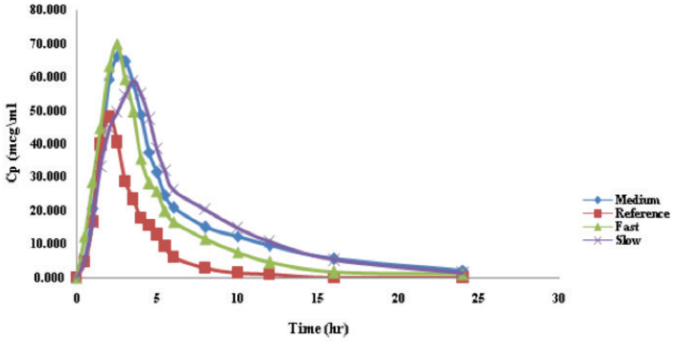

Figure 7. Mean plasma concentrations versus time of naproxen sodium for marketed immediate release and sustained release tablet (fast, medium and slow)

Table 2. Mean pharmacokinetic parameter of naproxen sodium for marketed immediate release and sustained release tablet (fast, medium and slow)

Formulation	T_{max} (hr)	C_{max} (ug/mL)	AUC (hr*ug/mL)
Immediate release tablet	1.833±0.258	54.209±10.685	147.483±36.265
Fast sustained release tablet	2.167±0.258	73.767±4.889	307.561±7.775
Medium sustained release tablet	2.667±0.258	68.879±4.562	391.273±82.259
Slow sustained release tablet	3.583±0.376	63.199±3.141	391.499±69.217

AUC: Area under the curve

buffer dissolution media at 50 rpm versus the percentage of drug absorbed. The slope of the best-fit line was examined using linear regression analysis and coefficient of correlation (r^2). IVIVC model linear regression of percentage dissolved and percentage absorbed for naproxen sodium sustained release tablet presented in the Figure 8-10. The correlation coefficient (r^2) for naproxen sodium SR tablets medium versus slow was 0.987, fast versus medium was 0.948, and naproxen sodium SR tablets fast versus medium was 0.96 respectively. Good linear regression relationship observed between all the three test formulation. Edington et al.[9] described the dissolution methodology which discriminates between the formulation and mimics the *in vivo* release profile in development of IVIVC.

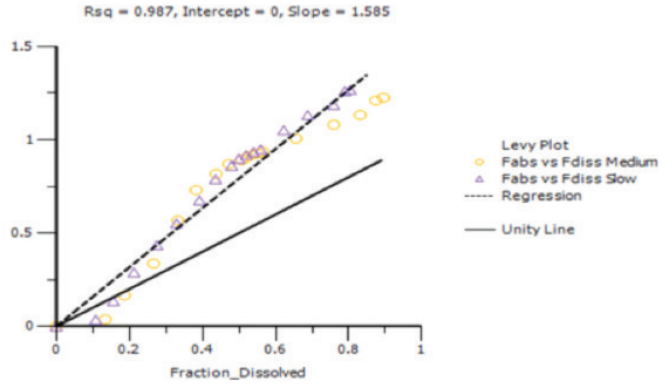

Figure 8. *In vitro-in vivo* correlation model linear regression percentage dissolved and percentage absorbed for naproxen sodium medium and slow sustained release tablet

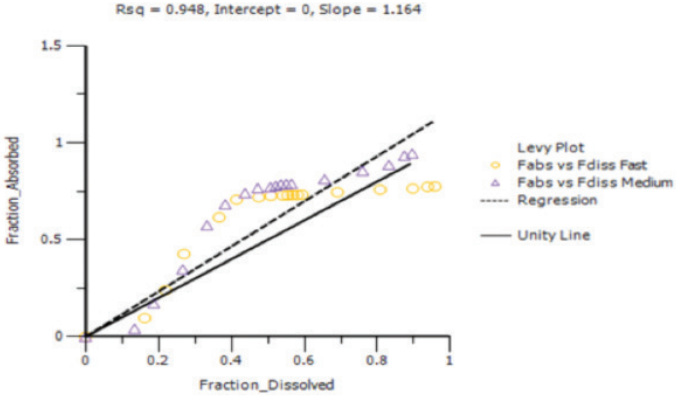

Figure 9. *In vitro-in vivo* correlation model linear regression percentage dissolved and percentage absorbed for naproxen sodium fast and medium sustained release tablet

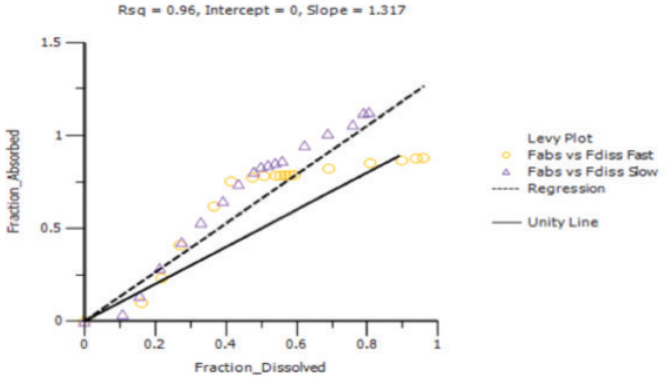

Figure 10. *In vitro-in vivo* correlation model linear regression percentage dissolved and percentage absorbed for naproxen sodium fast and slow sustained release tablet

IVIVC validation

The internal validation of the IVIVC was examined by using the mean *in vitro* dissolution data and mean *in vivo* pharmacokinetics of the naproxen sodium sustained release tablets (i.e. slow, medium fast) corresponds to fast/medium/slow SR tablets. Each of IVIVC model predicted naproxen sodium plasma concentration versus time profiles were compared to the experimental data using prediction error metrics. The observed plasma concentration of naproxen sodium sustained release tablets (i.e. slow, medium and fast) are presented in the Figure 11-13, good correlation found between the observed and predicted plasma concentration.

Internal validation

The validity of correlation assessed by determining how well the IVIVC model predict the rate and extent of naproxen sodium as characterized by C_{max} (maximum plasma concentration) and AUC (area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration). The prediction error estimated by using naproxen sodium slow SR tablets as a target formulation refer the Table 3. C_{max} and AUC were found close to the mean values. The prediction error estimated by using naproxen sodium fast sustained release tablets as a target formulation refer the Table 4. C_{max} and AUC were found close to the mean values. The prediction error estimated by using naproxen sodium medium sustained release tablets as a target formulation refer the Table 5. C_{mavx} and AUC were found close to the mean values. As per the FDA for IVIVC the average absolute prediction error should be 10% and in addition individual formulation should not exceed 15%. In the present study relatively low prediction error for C_{max} and AUC observed strongly suggest that the naproxen sodium IVIVC models are valid. Cross validation between the naproxen sodium sustained release tablets showed well within

Table 3. Prediction errors (%) associated with C_{max} and AUC for naproxen sodium fast vs. slow sustained release tablets

Formulation	Parameter	PE%
Fast	AUC	4.852
Fast	C_{max}	-21.187
Medium	AUC	0.794
Medium	C_{max}	-26.879
Slow	AUC	-5.643
Slow	C_{max}	-33.069

AUC: Area under the curve, PE: Prediction errors

the acceptance limits and provides the self confidence to next stage of validation.

External validation

IVIVC for naproxen sodium immediate release tablet was used as a target formulation to predict the plasma concentration of naproxen sodium sustained release tablets (i.e. slow, medium and fast). Figure 14-16 shows the plasma concentration versus time of predicted formulation (immediate release tablet) with naproxen sodium fast, medium and slow SR tablet. The predicted curve for the naproxen sodium SR tablets (i.e. slow, medium and fast) are identical to immediate release tablet and considered model is valid.

Table 4. Prediction errors (%) associated with C_{max} and AUC for naproxen sodium fast vs. medium sustained release tablets

Formulation	Parameter	PE%
Fast	AUC	-18.760
Fast	C_{max}	-35.896
Medium	AUC	14.180
Medium	C_{max}	-40.250
Slow	AUC	6.8779
Slow	C_{max}	-44.696

AUC: Area under the curve, PE: Prediction errors

Table 5. Prediction errors (%) associated with C_{max} and AUC for naproxen sodium medium vs. slow sustained release tablets

Formulation	Parameter	PE%
Fast	AUC	-5.852
Fast	C_{max}	-31.281
Medium	AUC	-9.495
Medium	C_{max}	-35.501
Slow	AUC	-15.271
Slow	C_{max}	-39.791

AUC: Area under the curve, PE: Prediction errors

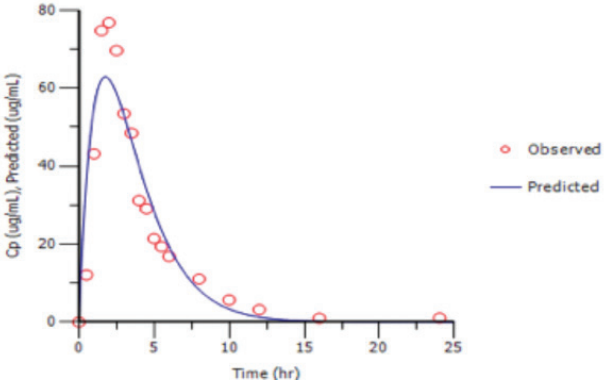

Figure 11. Observed and predicted plasma concentration for naproxen sodium fast sustained release tablet

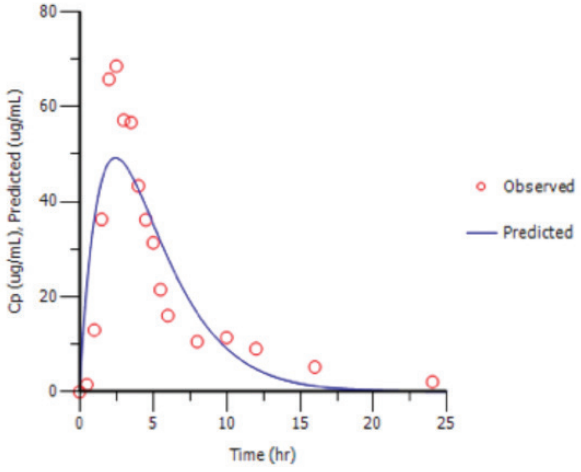

Figure 12. Observed and predicted plasma concentration for naproxen sodium medium sustained release tablet

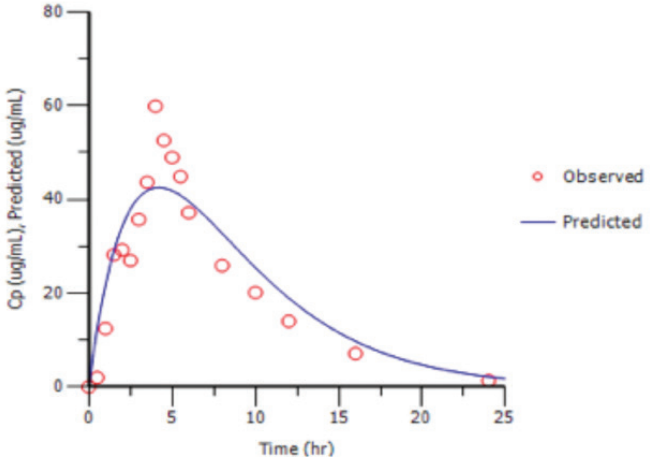

Figure 13. Observed and predicted plasma concentration for naproxen sodium slow sustained release tablet

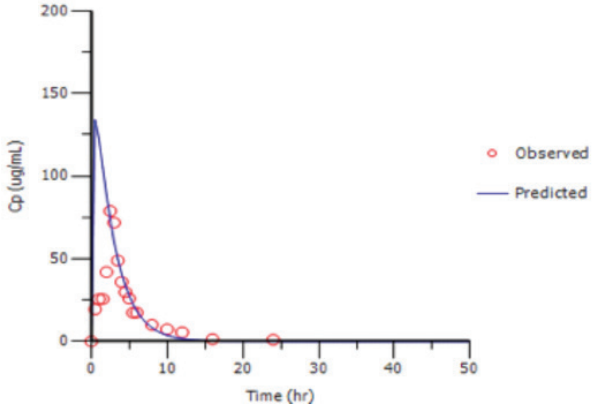

Figure 14. Plot of plasma concentration versus time of predicted formulation with naproxen sodium fast sustained release tablet

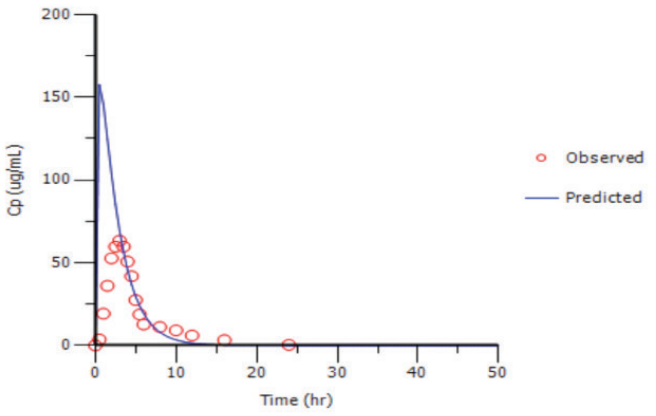

Figure 15. Plot of plasma concentration versus time of predicted formulation with naproxen sodium slow sustained release tablet

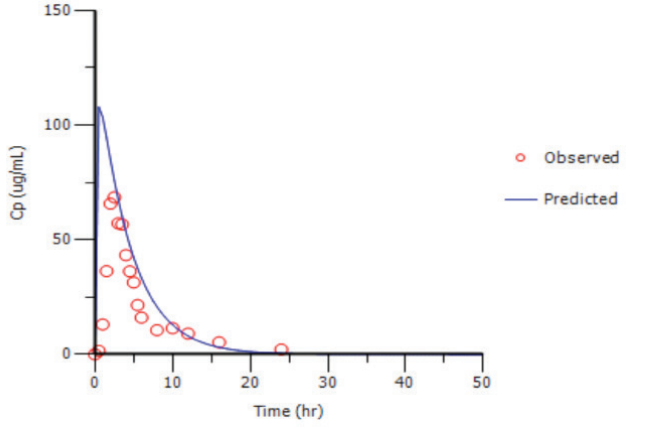

Figure 16. Plot of plasma concentration versus time of predicted formulation with naproxen sodium medium sustained release tablet

CONCLUSION

This study established and validated the internal and external predictability of an IVIVC relationship for naproxen sodium formulation. Meaningful relationship was observed between the *in vitro* and *in vivo* parameters, thus indicates an exceptional IVIVC model for naproxen sodium SR tablets (i.e. slow, medium and fast). The resulted prediction errors are within the acceptance limit as per the USFDA guidelines for both C_{max} and AUC. It can support dissolution data to predict the *in vivo* absorption, act as a biowaiver for bioequivalence and bioavailability studies and serve as a model for evaluating the naproxen sodium sustained release formulation. It can supports and validates the use of dissolution methods and specification settings, assisting in quality control which will be supportive for SUPAC.

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Conflict of Interest: No conflict of interest was declared by the authors.

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