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RESEARCH ARTICLE

Evaluation of *in vitro* Dissolution Characteristics of Flurbiprofen, a BCS Class IIa Drug

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SUMMARY

The purpose of this study is to compare the dissolution behaviors of reference (RF) and six generic (GE) products, containing 100 mg flurbibuprofen, available on the Turkish Drug Market. The in vitro dissolution from the dosage form and dissolution in biological fluids are the most important parameters affecting the absorption and bioavailability of the drug and also the in vitro dissolution determines the quality and performance of the dosage form. The in vitro dissolution tests were performed using the USP Apparatus II (paddle) method for compendial (pH 4.5 and pH 6.8) and biorelevant (FaSSIF and FeSSIF) media for all. Dissolution samples were analyzed with UV and HPLC methods. Dissolution profiles were compared with RF. Similarity factor (f_2) was used as a model independent methods, which is recommended by the FDA for comparison with dissolution profiles of solid oral dosage forms. It was observed that the dissolution profiles of all GE products were found to be similar to the RF product in pH 6.8. The RF vs the GE3 gave similar dissolution curves with f_2> 50 for FaSSIF and FeSSIF. Model-dependent dissolution behaviors were investigated in terms of kinetic models with DDSolver®. The dissolution kinetics of flurbiprofen products were mainly fit to Gombertz Model for FaSSIF and Logistic Model for FeSSIF.

Key Words: *Flurbiprofen, BCS Class IIa, NSAIDs, in vitro dissolution, dissolution kinetics.*

BCS Sınıf IIa İlaç Flurbiprofenin in vitro Çözünme Özelliklerinin Değerlendirilmesi

ÖZET

Bu çalışmada Türk ilaç pazarında bulunan 100 mg flurbibuprofen içeren referans (RF) ve altı jenerik (GE) ürününün çözünme davranışlarının karşılaştırılması amaçlanmıştır. Dozaj formundan in vitro çözünme ve biyolojik sıvılardaki çözünme, ilacın absorpsiyonunu ve biyoyararlanımını etkileyen en önemli parametrelerdir ve aynı zamanda in vitro çözünme dozaj formunun kalitesini ve performansını belirlemektedir. İn vitro çözünme testleri klasik (pH 4.5 ve pH 6.8) ve biyouyumlu (FaSSIF ve FeSSIF) ortamlarda USP Aparat II (palet) yöntemi kullanılarak gerçekleştirilmiştir. Çözünme örnekleri UV ve HPLC yöntemleri kullanılarak analiz edilmiş ve çözünme profilleri referans ürün ile karşılaştırılmıştır. Katı oral dozaj formlarının çözünme profillerinin karşılaştırılmasında FDA tarafından önerilen modelden bağımsız benzerlik faktörü (f_2) kullanılmıştır. Sonuçlar doğrultusunda tüm GE ürünlerin çözünme profillerinin, pH 6.8'de RF ürününe benzer olduğu, RF ürüne karşı GE3'ün FaSSIF ve FeSSIF için f_2> 50 olan benzer çözünme profilleri verdiği bulunmuştur. Model bağımlı çözünme davranışları DDSolver® ile kinetik modeller açısından araştırılmıştır. Flurbiprofen ürünlerinin çözünme kinetiklerinin FaSSIF için Gombertz modeline ve FeSSIF için Lojistik modeline uygun olduğu görülmüştür.

Anahtar Kelimeler: *Flurbiprofen, BCS Sınıf IIa, NSAİİ, in vitro çözünme hızı, çözünme hızı kinetikleri.*

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INTRODUCTION

In vitro dissolution rate tests are the most important measures of the performance and quality of the drug product is used to define the bioavailability effect of the formulation factors in the drug development process (FDA, 1997; Lobenberg & Amidon, 2000; Shah, 2005).

The main goal of in vitro dissolution rate studies is to estimate the performance of the most intense dosage form. Estimation of in vivo behavior sometimes requires the use of in vitro dissolution media that best reflect in vivo gastrointestinal conditions. Physiologically based biorelevant dissolution media such as Fasted State Simulating Intestinal Fluid (FaSSIF) and Fed State Simulating Intestinal Fluid (FeSSIF) are proposed for this aimed.

There are many factors that affect the in vivo performance of an oral dosage form, and it is crucial to develop drug products in order to accurately predict this in vivo performance. The main aim is to reduce the costly and ethically controversial animal and human experiments by various approaches and to form biowaiver evaluations with these new approaches. In recent years, in vivo estimates have become very important with computer and simulation programs applied in the field of pharmacy for this purpose (Dokoumetzidis et al., 2007; Jones et al., 2009).

DDSolver® is the first computer-based program written in Visual Basic for Microsoft Excel that provides free and easy-to-use advantages for the comparison of dissolution rate profiles, simplification of modeling and calculations (Zhang et al., 2010). The program is aimed to facilitate the evaluation of similarity between dissolution rate data, to create a model data library that meets dissolution rate data using nonlinear optimization method, and to compare dissolution rate profiles. Many of dissolution rate models have been assembled to create an easy access.

Different physical phenomena are involved in the process of drug product dissolution in an aqueous body fluid, eg. the wetting of the particle's surface, breakdown of solid state bonds, solvation and diffusion. Suitable mathematical equations can be used to quantify these mass transport steps, and more or less complex theories can be developed to characterize the resulting drug dissolution kinetics (Siepmanna & Siepmanna, 2013). Therefore, in vitro dissolution profiles can be divided into three groups: 1. Statistical methods (ANOVA), 2. Model-independent methods (f_1, f_2), 3. Model-dependent methods (Higuchi, Weibull, Logistic) (Mauger et al., 1986; Podczeck, 1993; Sathe et al., 1996; Moore & Flanner, 1996; Polli et al., 1997; Shah et al., 1997;Shah et al., 1998; Yuksel et al., 2000; Öner & Eryol, 2005).

In our work, similarity factor (f_2) as an independent model was used, which are recommended by the FDA, for comparison of dissolution profiles of solid oral dosage forms (FDA, 1995; FDA, 1997). Values f_2 between 50 and 100 indicate equivalent dissolution profiles. In the model-dependent techniques, the measured points of the dissolution curve are fitted to functions like the Weibull, Logistic, Gompertz, Quadratic or Higuchi (Adams et al., 2001).

In order to approach the problems more rationally and to make more accurate evaluations similar to in vivo, it is necessary to use the BCS subclass evaluations and the estimated in vivo dissolution rate methods, the current biorelevent media and the computer simulation program (Yilmaz Usta & Teksin, 2015).

As known, BCS was designed by Amidon to evaluate immediate release solid oral dosage forms, which are grouped and developed based on the solubility and permeability properties of the active ingredients and the in vitro dissolution rate of the dosage form (Amidon et al., 1995). BCS Class II and BCS Class IV drugs from these groups were subclassified for better evaluation of efficacy due to drug properties and they were grouped dependent on the acidic (a), basic (b) or neutral (c) properties of the drug in the physiological pH (a:ibuprofen, ketoprofen, b:carvedilol, ketaconazole and c: fenofibrate and danazol) (Tsume et al., 2014). Class IIa drugs are carboxylic acids with a pK_a between 4 and 5 ($pK_a \leq 5.0$), which do not dissolve in fasting and gastric pH, but typically dissolve in intestinal pH. Many BCS Class IIa drugs such as flurbiprofen, ketoprofen, naproxen, rifampicin, and carbamazepine are known to exhibit good oral absorption despite their low solubility at pH conditions. For this reason, it is aimed to evaluate the dissolution rate, dissolution kinetic and equivalence of the dosage forms in the flurbiprofen containing market which is selected as the model active substance in our study.

Flurbiprofen (2-fluoro-alpha-methyl-4-biphenyl acetic acid) is a BCS Class IIa weak acid (pK_a:4.22, $pK_a \leq 5$), non-steroidal anti-inflammatory drug of the phenylalkanoic acid series (Tsume et al., 2014) (Figure 1). Like other members of this group, it has analgesic, anti-inflammatory, and antipyretic properties (Sultan et al., 2008). The drug is well absorbed after oral administration with peak plasma levels occurring in one hour, and apparent half life of three to four hours (Kaiser et al., 1986).

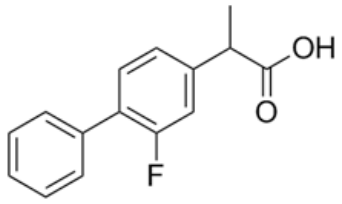

Figure 1. Flurbiprofen

MATERIALS AND METHODS

Materials

Flurbiprofen was kindly supplied from Sun Pharmaceuticals, India. RF and GEs 100 mg tablets were supplied from Turkish Drug Market. Disodium phosphate dihydrate, sodium cloride, sodium hydroxide, potassium dihydrogen phosphate sodium acetate trihydrate, monobasic sodium phosphate were purchased from Merck, Germany. Sodium taurocholate, lecithin, sodium lauril sulfate, acetic acid, triethylamine and methanol were purchased from Sigma-Aldrich, France. Batch numbers for RF and GE products are given in Table 1.

Table 1. RF and GE products batch numbers

Drug Products	Batch Numbers
RF	15262063
GE1	15A008011
GE2	11
GE3	15D849
GE4	4218003E
GE5	160831
GE6	A044875

Methods

Media Preparation

Compendial media were prepared according to USP 38. Biorelevant media prepared according to www.biorelevant.com and their compositions were shown in Table 2.

Table 2. Biorelevant media compositions

FaSSIF	FeSSIF
Sodium taurocholate 3.0mM	Sodium taurocholate 15.0mM
Lecithin 0.75mM	Lecithin 3.75mM
Sodium chloride 106mM	Sodium chloride 203mM
Monobasic sodium phosphate 28.4mM	Sodium hydroxide 101mM
Sodium hydroxide 8.7mM	Acetic acid 144mM

Dissolution Experiments

The in vitro dissolution tests were performed using the USP Apparatus II (paddle) method. Flurbiprofen does not dissolve at pH 1.2.

The stock solution for UV, was prepared at a concentration of 10 µg/mL with suitable media and appropriate dilutions were made. For the stock solution prepared for HPLC analysis approximately 11.0 mg flurbiprofen standard weighed in a 100 mL flask. 10 mL of methanol was added and the ultrasonic bath was kept for 15 minutes. After complete dissolution, the volume was supplemented with the dissolution medium.

In vitro dissolution tests were carried out with 3 tablets on Vankel/Varian (Agilent Technologies, USA) dissolution systems.

Apparatus : Type II (Paddle)
Media : pH 4.5, pH 6.8, FaSSIF, and FeSSIF
Volume : 900 mL
Temperature : 37.0 °C ± 0.5 °C
Rotation speed : 50 rpm
Sampling Points : 5, 10, 15, 20, 30, 45, and 60 min.

Samples are filtered through 0.45 µm PTFE filters (Macherey-Nagel Chromafil PRT-45/25 Polyester).

Analytical Methods

The samples in compendial dissolution media (pH 4.5 and pH 6.8) were analyzed by validated UV-spectrophotometry (Schimadzu UV-170, Japan) at 246 nm. The samples in biorelevant (FaSSIF and FeSSIF) media were analyzed by a validated HPLC system (Agilent Technologies 110, USA) with a UV detector at 247 nm to avoid the peak integration of the dissolution components and the active substance. UV and HPLC methods were developed and validated with linearity, accuracy, precision, selectivity, repeatability in dissolution parameters for all dissolution media. Validation was carried out in the direction of the ICH Q2B guideline and the analytical parameters were found within the limits (FDA 1994; FDA 1996) .

Chromatographic System

Column : Ace C8 (150 x 4.6mm , 5µm)
Detector : 247 nm, UV
Flow rate : 1.5 mL/min
Injection volume : 10 µL
Column oven °C : 30 °C
Auto sampler °C : 25 °C
Mobile phase : Buffer solution + Methanol (35% : 65%)

Buffer solution : 8.25 g of $NaH_2PO_4.H_2O$, 3.75 g of SLS and 7.5 mL triethylamine were dissolved in 1000 mL of distilled water. pH of the solution was adjusted to 2.40.

Evaluation of Dissolution Data

The dissolution data were assessed by model-independent and model dependent methods with kinetic program DDSolver®. The f_2, which is defined by Equation 1, used for model-independent method analysis. The model dependent methods, shown in Table 3, were fitted to individual dissolution data (Zhang et al., 2010).

$$f_2 = 50.\log\left\{\left[1+\left(1/n\right)\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right]^{-0.5}.100\right\}$$

Eq 1. Similarity factor

where n is the number of dissolution sample times, and R_t and T_t are the individual or mean percent dissolved at each time point, t, for the reference and test dissolution profiles (Moore & Flanner, 1996).

Table 3. Applied models for to the dissolution data of flurbiprofen tablets with DDSolver®

Module	Model	Equation	Parameters
# 328 [p, q]	Weibull 1	$F = 100.\left(1 - e^{-\frac{(t-Ti)^{\beta}}{\alpha}}\right)$	α, β, Ti
# 329 [p]	Weibull 2	$F = 100.\left(1 - e^{-\frac{t^{\beta}}{\alpha}}\right)$	α, β
# 330 [f, p]	Weibull 3	$F = F_{max}.\left(1 - e^{-\frac{t^{\beta}}{\alpha}}\right)$	α, β,Fmax
# 331 [f, p, q]	Weibull 4	$F = F_{max}.\left(1 - e^{-\frac{(t-Ti)^{\beta}}{\alpha}}\right)$	α, β, Ti, Fmax
# 332 [r]	Logistic 1	$F = 100.\frac{e^{\alpha+\beta.log(t)}}{1+e^{\alpha+\beta.log(t)}}$	α, β
# 332 [f,r]	Logistic 2	$F = F_{max}.\frac{e^{\alpha+\beta.log(t)}}{1+e^{\alpha+\beta.log(t)}}$	α, β,Fmax
# 332 [w]	Probit 1	$F= 100.\Phi\ [\alpha+\beta.\ log(t)]$	α, β
# 332 [f,w]	Probit 2	$F= F_{max}.\Phi\ [\alpha+\beta.\ log(t)]$	α, β, Fmax
# 324 [n]	Peppas–Sahlin 2	$F= k_1 . t^{0.5} + k_2 . t$	k1, k2
# 336 [f, t]	Gompertz 2	$F = F_{max} e^{-\alpha.e^{-\beta log(t)}}$	α, β, Fmax

α In all models, F is the fraction(%) of drug released in time t

[f] F_{max} is the maximum fraction of the drug released at infinite time

[n] k_1 is the constant denoting the relative contribution of t 0.5-dependent drug diffusion to drug release; k_2 is the constant denoting the relative contribution of t-dependent polymer relaxation to drug release

[p] α is the scale parameter which defines the time scale of the process; β is the shape parameter which characterizes the curve as either exponential (β=1; case 1), sigmoid, S-shaped, with upward curvature followed by a turning point (β>1; case 2), or parabolic, with a higher initial slope and after that consistent with the exponential (β<1; case 3)

[q] *Ti* is the location parameter which represents the lag time before the onset of the dissolution or release process and in most cases will be near zero

[r] α is the scale factor in Logistic 1 and 2 models; β is the shape factor in Logistic 1 and 2 models

[t] α is the scale factor in Gompertz 2 model; β is the shape factor in Gompertz 2 model

[w] Φ is the standard normal distribution; α is the scale factor in Probit model; β is the shape factor in Probit model

RESULTS AND DISCUSSION

In vitro dissolution study

The in vitro dissolution studies were performed at different pH conditions (pH 4.5 and pH 6.8) and biorelevant media (FaSSIF and FeSSIF) for RF and GE products.

The first set of data in Figure 2a shows that all products dissolved rapidly in pH 4.5, but not dissolved 85% in 15 minutes and at the end of an hour it reached 60%. It shows that the solubility of flurbiprofen is dependent on the pH and is less soluble in the low pH to high pH ratios. In pH 6.8 (Figure 2b), some of GE products (GE2, GE3, GE4, GE5) and RF dissolved very rapidly (i.e., >85% in 15 min).

In Vitro Dissolution Profiles in Compendial Media

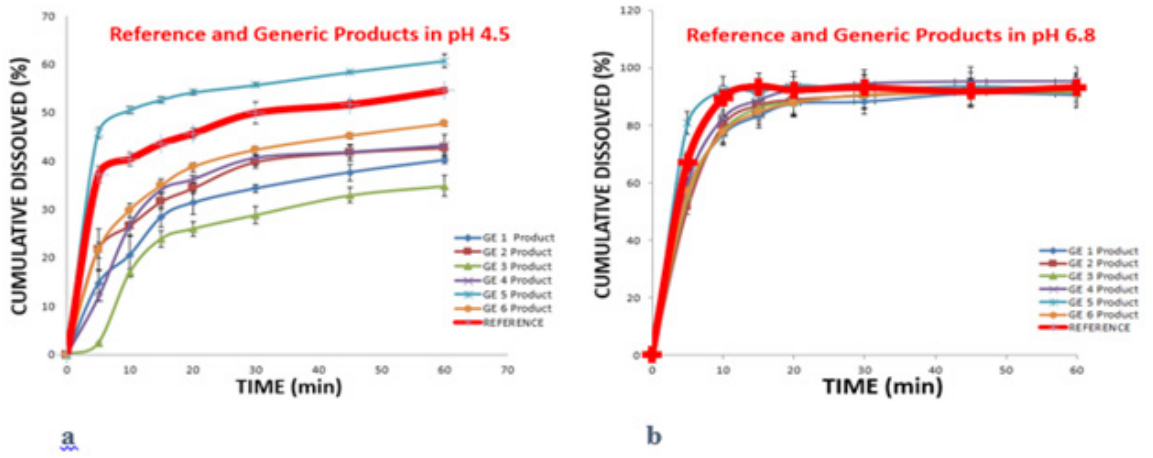

Figure 2. In vitro dissolution profiles in compendial media (a: pH 4.5, b: pH: 6.8)

The second set of data shown in Figure 3a and 3b. For the FaSSIF and FeSSIF media, the GE3 was similar to the RF and all these results were evaluated with f_2 (Table 4).

In Vitro Dissolution Profiles in Biorelevant Media

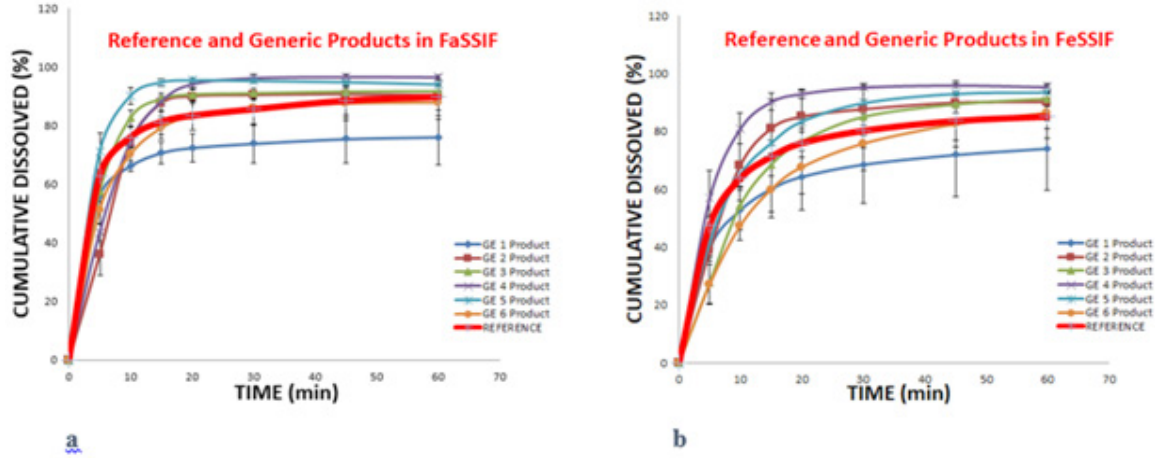

Figure 3. In vitro dissolution profiles in biorelevant media (a: FaSSIF, b: FeSSIF)

Table 4. Evaluation of model independent method with f_2

	pH 4.5	pH 6.8	FaSSIF	FeSSIF
RF vs GE1	39	57	48	48
RF vs GE2	46	57	48	56
RF vs GE3	32	58	62	52
RF vs GE4	43	69	49	42
RF vs GE5	55	64	49	57
RF vs GE6	51	58	64	47

Dissolution kinetics were evaluated by using model dependent methods (Weibull, Gompertz, Logistic, Probit, Peppas-Sahlin models) with DDSolver®. DDSolver® uses a number of statistical approaches to model suitability. These are correlation coefficient ($R_{\_obs\text{-}pre}$), the coefficient of determination (R_{sqr}, R^2 or COD), the corrected determination coefficient (R_{sqr_adj}, $R^2_{adjusted}$), the mean square error (MSE), the standard deviation of the residuals (MSE_root or Sy.x), the sum of the deviation squares (SS, SKT), sum of weighted deviation squares (WSS, ASKT), Model Selection Criteria (MSC), and Akaike Information Criteria (AIC, AKAIKE). Among these criteria, $R^2_{adjusted}$, MSC and AIC are the most commonly used parameters (Sarısaltık D., 2010).

For release models with the same number of parameters, R^2 can be used to select the most suitable model. However, when comparing models with different numbers of parameters, $R^2_{adjusted}$ should be used. The reason is because R^2 will always rise as more parameters are included, whereas $R^2_{adjusted}$ may reduce when over-fitting has occurred (Costa & Sousa Lobo, 2001). The AIC is a parameter which is dependent on the magnitude of the data as well as the number of data points. If two models have different number of parameters, it can be said that the model with lower AIC value is better (Zhang et al., 2010). The MSC is a criterion for selecting a statistical model. The MSC is modified from the AIC and has been normalized so that it is independent of the scaling of the data points. Among different models, the model with the highest MSC value is the most suitable criterion. It is quite easy to understand how well the model reflects the MSC value and generally a MSC value of more than two to three indicates a good fit (Mayer et al., 1999).

After all model dependent methods have been tested individually, evaluation has been done according to $R^2_{adjusted}$, MSC and AIC. For each drug product, the most appropriate model, with $R^2_{adjusted}$ value the highest MSC value, the lowest AIC value, were determined and given in Table 5. It was seen that the products were suitable for mostly Gombertz Model for FaSSIF, Logistic Model for FeSSIF, when dissolution kinetics results were variable for compendial media.

Table 5. Evaluation of model dependent method by DDsolver®

	GE 1	GE 2	GE 3	GE 4	GE 5	GE 6	RF
pH 4.5	WEIBULL 3	PEPPAS-SAHLIN 2	GOMPERTZ 2	GOMPERTZ 2	PROBIT 1	WEIBULL 3	WEIBULL 2
r^2_{adj}	0,993	0,998	0,987	0,999	0,999	0,999	0,999
AIC	20,7	12	25,8	9,1	3,9	4,5	10,6
MSC	3,81	4,73	3,48	5,62	5,66	5,92	4,82
pH 6.8	WEIBULL 4	PEPPAS-SAHLIN 2	LOGISTIC 2	LOGISTIC 1	PROBIT 1	GOMPERTZ 2	WEIBULL 1
r^2_{adj}	0,999	0,978	0,989	0,993	0,992	0,995	0,976
AIC	37,2	43,5	38,3	34,3	35,6	31,1	45,7
MSC	4,16	3,46	4,07	4,64	4,45	4,97	3,32
FaSSIF	GOMPERTZ 2	GOMPERTZ 2	PEPPAS-SAHLIN 2	LOGISTIC 1	WEIBULL 1	GOMPERTZ 2	GOMPERTZ 2
r^2_{adj}	0,999	0,943	0,981	0,994	0,985	0,997	0,999
AIC	18,1	52,2	42,3	34,2	41,5	26,5	11,1
MSC	4,46	1,52	2,16	3,76	2,03	4,14	5,73
FeSSIF	PROBIT 2	LOGISTIC 2	LOGISTIC 2	LOGISTIC 1	LOGISTIC 2	PROBIT 2	LOGISTIC 2
r^2_{adj}	0,999	0,988	0,999	0,991	0,999	0,999	0,999
AIC	-3	39,3	14	36,9	18	8,6	-5,8
MSC	7,55	3	6,45	3	5,68	6,96	8,12

CONCLUSION

In this study, the comparison and evaluation of GE products drawn from the market with the in vitro dissolution rate test, which is expected to reflect product performance and quality according to the RF, has been carried out.

It was observed that the dissolution profiles of all GE products were found to be similar to the RF product in pH 6.8. The RF *vs* the GE3 gave similar dissolution curves with f_2>50 for FaSSIF and FeSSIF. Biorelevant media consists of sodium taurocholate and lecithin. It was determined that, flurbiprofen solubility was affected by pH value and also concentrations of sodium taurocholate and lecithin. Dissolution kinetics were evaluated with DDSolver® and they mainly fit to Gombertz Model for FaSSIF and Logistic Model for FeSSIF. DDSolver® is capable of performing the most existing techniques for comparing drug release data, including exploratory data analysis, ratio test procedures, f_1, f_2, the multivariate statistical distance method, the model-dependent method. Sample runs of the program demonstrated that the results were satisfactory, and DDSolver® could be served as a useful tool for dissolution data analysis.

BCS Class IIa weak acid drug dissolves rapidly and acts like BCS Class I drugs in the small intestine, although it exhibits low solubility at gastric pH. Therefore, in vitro dissolution rate studies in FaSSIF

and FeSSIF besides compendial media are more useful to predict the gastrointestinal behavior of drug products.

Model-dependent and model-independent methods for the comparison of dissolution profiles are applicable and functional. However, these methods have given different results on the similarity of dissolution profiles for RF and GE products randomly selected from the market and containing the same active ingredient and similar dosage forms.

In general, it is observed that model-dependent methods are more precise and discriminative than f_2 because different methods and different parameters are decisive. Nonetheless, model-independent method f_2 for application and explanation is much simpler; only one value is obtained and used to define the similarity of the two dissolution profiles. Furthermore, the authorities are requesting an assessment by factor f_2 for the registration of solid IR dosage forms.

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