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Effect of Biopharmaceutical Classification System on Pharmacokinetic and Mechanism of Drug Release In vitro

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Abstract

The study aimed to monitor the pharmacokinetic and mechanism of drug release in vitro based on Biopharmaceutical Classification System (BCS). Two pharmaceutical products were used (original and generic) with different classes according to BCS : Paracetamol (Class I), Diclofenac Sodium (Class II), Ranitidine (Class III), and Azithromycin (Class IV). Dissolution tests were conducted using United State Pharmacopeia (USP) monograph and the release profiles were compared using difference (f1) and similarity (f2) factors as criteria in different classes. The results have shown that the f1 and f2 were influenced by BCS namely poorly soluble drugs, namely Diclofenac Sodium (Class II) and Azithromycin (Class IV) , while these factors were not affected by high-solubility drugs namely Paracetamol (Class I) and Ranitidine (Class III). On the other hand , the mechanism of drug release is not affected by this classification ..

Keywords: *Dissolution profile ,Similarity Factor , Difference Factor , Mechanism , Drug Release , BCS*

1. Introduction

Biopharmaceutical classification has provided the scientific basis for the correlation of in vitro drug product dissolution and in vivo bioavailability and has been adopted by Food and Drug Administration (FDA) as the guidance for the waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms [1,2]. The introduction of the Biopharmaceutics Classification System (BCS) in 1995 was the result of continuous efforts on mathematical analysis for the elucidation of the kinetics and dynamics of the drug process in the gastrointestinal (GI) tract [3,4]. The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability (Table 1) [5-6].

Table 1 : Biopharmaceutical Classification System

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

This paper aimed to monitor the in-vitro kinetic and mechanism of drug based on Biopharmaceutical Classification System (BCS) .

2. Materials and Methods

2.1. Chemical and standard

The standards namely Paracetamol (98.2 %), Diclofenac sodium (98.2 %), Ranitidine (99.8 %), and Azithromycin (98.99 %) were obtained from National Drugs Quality Control of Rabat. The reagents were used in this work namely methanol and acetonitrile of HPLC grade (Sigma-Aldrich , Germany). Sodium hydroxide, hydrochloric acid, and phosphoric acid (Merck KGaA, Germany). Potassium phosphate monobasic (Sigma-Aldrich ,Germany). Sodium phosphate tribasic, sodium phosphate dibasic, sodium phosphate monobasic, and ammonium phosphate monobasic (Riedel–de Haeri, Germany). 1- Octansulfonic acid sodium salt monohydrate Scharla (chemic S.A., Spain).

2.2. Apparatus

The High Performance Liquid Chromatography (HPLC) of Waters 2695 pump, an auto sampler, and Waters 2998 photodiode-array detector (PDA). Data obtained were performed by the Empower Software. Dissolution tests were performed (Hanson SR8-Plus™ ,USA), a UV–Vis spectrometer (Perkin ,USA), and a pH meter (Schott ,Germany).

2.3. Samples collection

The pharmaceutical products included Paracetamol 500 mg, Diclofenac Sodium 50 mg, Ranitidine 150 mg, and Azithromycin 500 mg products were collected from different countries and manufacturers.

2.4. Pharmacokinetic in vitro procedure (dissolution test)

Table 2 : Pharmacokinetic in vitro procedure (dissolution test) based on USP monograph

BCS	Apparatus	Dissolution medium	Technique Used
Class I Paracetamol Tablet (500 mg)	USP Apparatus 2 - 50 rpm	At 37 ± 0.5 ° C. The dissolution medium - 900 ml of buffer (pH 5.8). 27.22 g potassium phosphate monobasic in one litter and adjusted pH with hydroxide sodium 0.2 M.	5-mL sample aliquots were withdrawn at 10, 20 and 30 min using a glass syringe and filtered through 0.45-µm membrane filters. Released percentages of the active ingredient were assayed using UV –Vis spectrophotometer at 243 nm.
Class II Diclofenac Sodium Tablet (50 mg)	USP Apparatus - 50 rpm	At 37° C - 900 ml of the dissolution medium. phosphate buffer composed of sodium phosphate tribasic (76 g in litter) and hydrochloric acid (0.1 N). 250 ml and 750 ml were mixed, and the pH was adjusted to 6.8 ± 0.05 by hydrochloric acid (2 N). 5-mL sample were withdrawn at 10, 20, 30 and 45 minutes using a glass syringe and filtered through 0.45-µm membrane filters.	The method to determine the amount of dissolved drugs was carried out at wavelength of maximum absorbance at 276 nm. .
Class III Ranitidine Tablet (150 mg)	USP Apparatus - 100 rpm	At 37 ± 0.5 °C. The dissolution medium - 900 ml of distilled water. -5 mL sample aliquots were withdrawn at 10, 20 , 30 and 45 min using a glass syringe and filtered through 0.45-µm membrane filters .	The method to determine the amount of dissolved drugs was carried out at wavelength of maximum absorbance at about 314 nm.
Class IV Azithromycin Tablet (500 mg)	USP apparatus 2 - 75 rpm	At 37 ± 0.5° C. 900 ml of dissolution medium namely USP buffer (pH 6.0) composed of 27.22 g potassium phosphate monobasic in one liter of water and adjusted pH with hydroxide sodium 0.2 M. 2 ml were removed after 10, 20 and 30 min using a glass syringe and, immediately filtered through 0.45-µm membrane filters.	The assays of dissolution of two conditions were measured according to HPLC / UV, in comparison with a standard solution having a known concentration. The chromatographic system and conditions were as follows: XTerra C18-5µm 4.6 mm ×15cm column. Mobile phase was buffer (4.4 mg/ml of dibasic potassium phosphate and 0.5 mg/ml of sodium 1-octanesulfonate adjust with phosphoric acid to pH= 8.20 ± 0.05), acetonitril and methanol in ratio of (8:9:3), respectively. The mobile phase was filtered through a 0.45-µm Millipore TM Durapore filter and degassed by vacuum prior to use. The flow rate was 1.5 ml/min and the injection volume was 50 µl with temperature of 50 °C. The wavelength of the detector was set at 210 nm.

Note : If necessary, suitable dilution with dissolution medium was used in all tests [8 -11] , This work was carried out in laboratoire national de contrôle des medicaments with accredited ISO 17025 [12]

2.5. Data analysis

2.5.1. Similarity and difference factors dissolution procedure

Difference (f_1) and similarity (f_2) factors were tested to the dissolution data. The f 1 is proportional to the average difference between the two profiles, whereas the f_2 is inversely proportional to the average squared difference between the two profiles with emphasis on the larger difference among all the time points (n) [**6,7**] **.** The acceptance criteria of f_1 is (0 – 15) and the f_2 (50 – 100) of generic drugs (T_t) versus reference (original) (R_t) at number of time point (n) that are calculated by the following :

$$f_1 = \frac{\sum_{i=1}^{n} |R_t - T_t|}{\sum_{i=1}^{n} R_t} .100 \qquad \textbf{Eq. (1)}$$

$$f_2 = 50.log\left\{[1 + \left(\frac{1}{n}\right)\sum_{i=1}^{n} (R_t + T_t)^2]^{-5}.100\right\} \qquad \textbf{Eq. (2)}$$

2.5.2 Mechanism of drugs release

To study the drug release mechanism from pharmaceutical formulations, The data obtained are fitted to Korsmeyer's (log cumulative percentage of drug released versus log time) using the following equations :

$$M_t / M_\infty = at^n \qquad \textbf{Eq. (3)}$$

where M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time (total drug in a dosage form), a is the Korsmeyer's dissolution rate constant and n is the release exponent [8-11].

3. Results and Discussion

3.1. Paracetamol (Class I) [13-16].

The pharmacokinetic in vitro of Paracetamol original (reference) tablets were 76.00%, 93.65%, and 97.42% for the time points of (10, 20, and 30) min, respectively. However, the pharmacokinetic in vitro of generic Paracetamol tablet were 74.15%. 90.69%. and 94.99%. Both results of original and generic products were within normal rang of the USP criteria (Not less than 80% at 30 min). (**Table 3 and Figure 1**). On other hand, the results of f1 and f2 of generic Paracetamol versus reference Paracetamol were 2.71 and 78.82, respectively [**13**]. The similarity and difference factors were within normal values of FDA ($0 \leq f_1 \leq 15$ and $50 \leq f_2 \leq 100$) and these factors aren't affected in this Class I. Therefore, dissolution profiles of the generic product were similar to those of the reference product in USP condition. The release mechanism of Paracetamol from the reference and generic tablets was determined based on a Korsmeyer - Peppas model , and the diffusional exponents were 0.2341 and 0.2325 , respectively (**Table 4**).These (n) values results from erosion mechanisms [9]. The mechanism of Class I drug release (Paracetamol) had the same n value (0.45 > n) , due to the mechanism release of drug Class I was not effected by BCS.

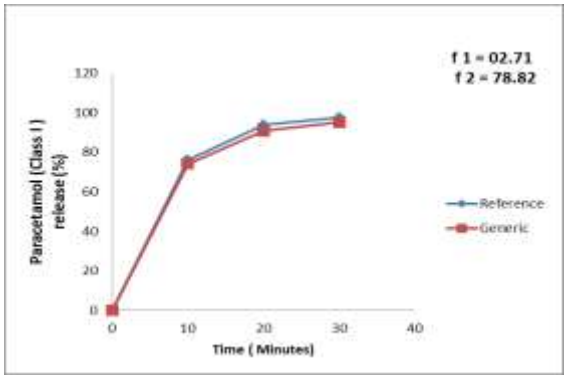

Figure 1 : Pharmacokinetic In vitro of original (reference) and generics pharmaceutical products (Class I)

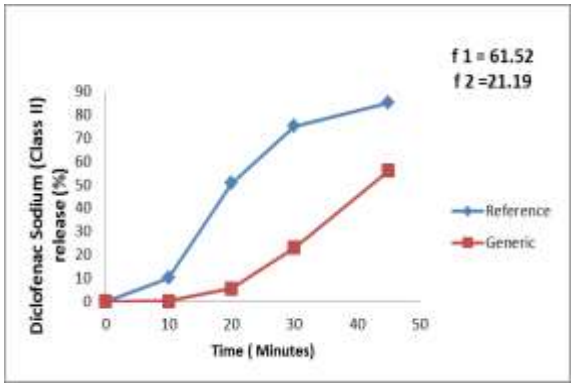

Figure 2 : Pharmacokinetic In vitro of original (reference) and generics pharmaceutical products (Class II)

3.1. Diclofenac Sodium (Class II) [13-16].

The pharmacokinetic in vitro of the original (reference) Diclofenac Sodium tablets form were 10%, 50.5%, 75 %, and 85 % at (10, 20, 30, and 45) minutes, respectively. While, the pharmacokinetic in vitro of generic Diclofenac Sodium tablets were 0.20 %, 5.44%, 22.96%, and 56.04% . This generic did not within normal value of USP monograph (Not less than 75% at 45 minutes). The original product dissolved faster than the generic product **(Table 3 and Figure 2)**. This different due to different excipients within manufacturing process. The results of f_1 and f_2 of the generic product versus original product were 61.52 and 21.19, respectively. These results were out the acceptable values due to the bioequivalence in vitro wasn't available , due to these factors were affected by poor solubility drug namely Class II . On the other hand , the results showed the comparison of the in vitro release mechanism of Diclofenac Sodium from pharmaceutical form using Korsmeyer - Peppas model . The diffusional exponents of original and generic in USP conditions were 1.4569, 3.8181 , respectively. These (n) values appear to indicate Super case-II transport (0.89 < n) (**Table 4**) [8-11]. The results showed that the mechanism of drugs Class II release was not effect by BCS.

3.4. Azithromycin (Class IV) [13-16].

The pharmacokinetic in vitro of the original (reference) products at (10, 20, and 30) minutes were 54.06%, 78.53%, and 97.34%, respectively. However, the pharmacokinetic in vitro of generic tablets were 32.20%, 46.40%, and 70.92 %, respectively (**Table 3 and Figure 4**). The results showed that generic tablets had a slower release at 30 minutes compared with the original product. The pharmacokinetic in vitro of generic product did not accept with normal value of USP (Not less than 80% at 30 minutes), due to different excipients and differences in the manufacturing processes. The results of f_1 and f_2 of the generic versus original were 61.52 and 21.19, respectively. Both results were out the acceptable values due to the bioequivalence in vitro wasn't available , due to these factors were affected by poor solubility drug namely Class IV. The diffusional exponent of original and generic products were 0.5357 and 0.543, respectively indicates non-Fickian type of mechanism release (0.45 < n < 0.89) (**Table 4**) [**7,8**]. In brief, the mechanism of drugs Class IV release was not affected by BCS .

3.3. Ranitidine (Class III) [13-16].

The pharmacokinetic in vitro of original tablets (reference) were 25.82%, 49.54%, 76.43%, 98.73 % and 102.55% for the time points of (10, 20, 30 and 45) minutes, respectively, whereas the pharmacokinetic in vitro of generic tablets were 22.63 %, 53.25 %, 86.53 % and 97.57 % (**Table 3 and Figure 3**). Both products were dissolving, more than 80% at 45 minutes and that due to the acceptance criteria in USP condition (Not less than 80% at 45 minutes). On the other mean, Both products were rapidly dissolving at 30 minutes (76.43 % compared with 86.53 %, respectively), due to no difference between pharmacokinetic in vitro of both products. The results of f_1 and f_2 of the generic versus original were 1.61 and 63.34, respectively. These values were within the normal range (0 - 15) and (50 - 100)**,** respectively. Therefore, the pharmacokinetic in vitro of the generic product was similar to the original product (available bioequivalence) . Therefore the f_1 and f_2 of generic versus original weren't affected by high solubility Class III drug. On the other hand, the release mechanism of Ranitidine from the tablets was studied based on Korsmeyer - Peppas model . The diffusional exponents of original and generic tablets in USP condition were 0.9116, 1.013 , respectively (**Table 4**).These (n) values appear to indicate super case II transport (0.89 < n) for both products [**7,8**]. The results showed that the mechanism of drugs Class III release was not effect by BCS.

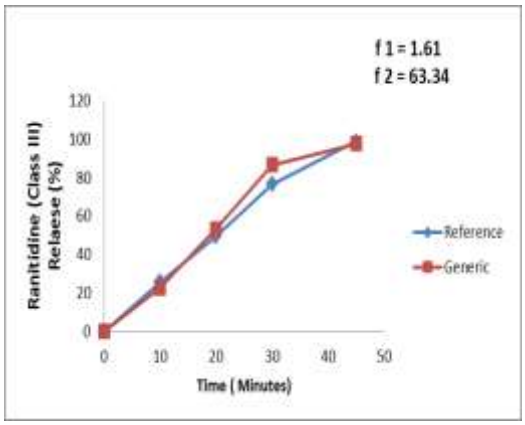

Figure 3 : Pharmacokinetic In vitro of original (reference) and generics pharmaceutical products (Class III)

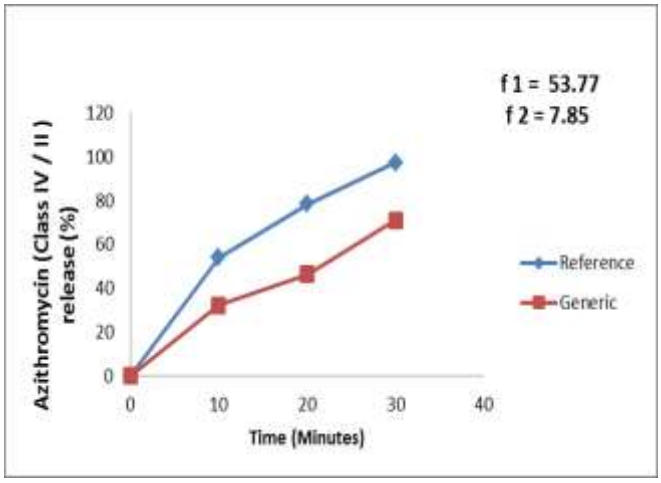

Figure 4 : Pharmacokinetic In vitro of original (reference) and generics pharmaceutical products (Class IV)

Table 3 : Results pharmacokinetic in vitro of reference versus generic of pharmaceutical products based on USP

Pharmaceutical Products	Paracetamol			Diclofenac Sodium				Ranitidine				Azithromycin		
	10 min	20 min	30 min	10 min	20 min	30 min	45 min	10 min	20 min	30 min	45 min	10 min	20 min	30 min
Reference USP .	76.00	93.65	97.42	10	50.5	75	85	25.82	49.54	76.43	98.73	54.06	78.53	97.34
Mean (%)	7.5	2.5	3.2	20	7.3	3.7	2.41	34.4	16.9	17.07	8.9	10.54	1.27	2.15
RSD (%)														
Generic USP .														
Mean (%)	74.15	90.69	94.99	0.20	5.44	22.96	56.04	22.63	53.25	86.53	97.57	32.20	46.40	70.92
RSD (%)	12.2	4.3	3.3	100	55.6	25.6	10.17	7.07	9.9	7.7	2.1	13.66	14.00	20.72
To allow use of mean data, the percent relative standard deviation (RSD %) at the earlier time points (e.g., 10 minutes) should be ≤ 20% and at other time points should be ≤ 10 %.														

Table 4 : Analysis of mechanism of drugs release in vitro

Products	Korsmeyer-Peppas Model		Difference - Similarity Factors	
	r^2	Slope (n)	f_1	f_2
Paracetamol (Class I)				
Reference USP	0.9502	0.2341	02.71	78.82
Generic USP	0.9618	0.2325		
Diclofenac Sodium (Class II)				
Reference USP	0.8942	1.4569	61.52	21.19
Generic USP	0.9737	3.8181		
Ranitidine (Class III)				
Reference USP	0.9933	0.911	1.61	63.34
Generic USP	0.9591	1.013		
Azithromycin (Class IV/II)				
Reference USP	1.00	0.536	53.77	07.85
Generic USP	0.9632	0.534		
Erosion diffusion (0.45 > n) that is represents the loss of material from a matrix due to disintegration and determines the release rate of the drug, Fickian diffusion (n = 0.45) that is defined release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient, Non -Fickian diffusion anomalous diffusion " (0.45 < n < 0.89) i.e., drug release is by coupling of Fickian diffusion and case II transport - so-called anomalous diffusion , Case II relaxation release transport (n = 0.89) that is defined release that is the drug transport mechanism associated with stresses which swell in dissolution medium. Super case II transport (0.89 < n) that is represented release curve that is linear for an exponential function of the release versus time. [**7,8**]				

4. Conclusion

In conclusion, the pharmacokinetic in vitro was affected by poorly soluble drugs. Poor pharmacokinetic in vitro for Diclofenac Sodium (Class II) and Azithromycin (Class IV). While good of pharmacokinetic in vitro for Paracetamol (Class I) and Ranitidine (Class III) that were not affected based on BCS . On the other mean , the generic drug versus reference drug can be significantly affected by the BCS. On other hand, the mechanism release of drug for pharmaceutical products was not affected based on BCS

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conficts of interest.

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