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CASE STUDY

Transfer of drug dissolution testing by statistical approaches: Case study

Mohammed Amood AL-Kamarany [a,b,1], Miloud EL Karbane [a,b,1], Khadija Ridouan [a], Fars K. Alanazi [d,e,f,*], Philippe Hubert [c], Yahia Cherrah [a], Abdelaziz Bouklouze [a]

[a] *Research Team of Pharmaceutical and Toxicological Analysis, Laboratory of Pharmacology and Toxicology, Faculty of Medicine and Pharmacy, Mohammed V University, Soussi, Rabat, Morocco*
[b] *Physicochemical Service, Drugs Quality Control Laboratory, Direction of Drugs and Pharmacy, Ministry of Health, Rabat, Morocco*
[c] *Laboratory of Analytical Chemistry, Institute of Pharmacy, University of Liège, B-36, B-4000 Liège, Belgium*
[d] *Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia*
[e] *Center of Excellence in Biotechnology Research, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia*
[f] *Kayyali Chair for Pharmaceutical Industry, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia*

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Abstract The analytical transfer is a complete process that consists in transferring an analytical procedure from a sending laboratory to a receiving laboratory. After having experimentally demonstrated that also masters the procedure in order to avoid problems in the future. Method of transfers is now commonplace during the life cycle of analytical method in the pharmaceutical industry. No official guideline exists for a transfer methodology in pharmaceutical analysis and the regulatory word of transfer is more ambiguous than for validation. Therefore, in this study, Gauge repeatability and reproducibility (R&R) studies associated with other multivariate statistics appropriates were successfully applied for the transfer of the dissolution test of diclofenac sodium as a case study from a sending

* Corresponding author at: Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia. Tel.: +966 503265669; fax: +966 1 4676295.
E-mail address: afars@ksu.edu.sa (F.K. Alanazi).
[1] Equal contributor.

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laboratory A (accredited laboratory) to a receiving laboratory B. The HPLC method for the determination of the percent release of diclofenac sodium in solid pharmaceutical forms (one is the discovered product and another generic) was validated using accuracy profile (total error) in the sender laboratory A. The results showed that the receiver laboratory B masters the test dissolution process, using the same HPLC analytical procedure developed in laboratory A. In conclusion, if the sender used the total error to validate its analytical method, dissolution test can be successfully transferred without mastering the analytical method validation by receiving laboratory B and the pharmaceutical analysis method state should be maintained to ensure the same reliable results in the receiving laboratory.

1. Introduction

The transfer of analytical methods of pharmaceuticals plays important roles within the pharmaceutical industry. Transferring the methods is now a challenging step during the life cycle of the analytical method. It is considered the last step before the routine use of the method at the receiving laboratory. The receiver must therefore guarantee of their capacity to implement the method and importantly being able to obtain reliable results (Rozet et al., 2009).

An analytical transfer is a complete process that consists in transferring a validated analytical method from a sending laboratory (called sender) to a receiving laboratory (called receiver) after experimentally demonstrating the capability to master the method (Dewé et al., 2007). Verification of a test method's acceptability should be performed for all methods. When a test method is transferred to an alternative testing site requires evidence that the test procedure is functioning correctly (Stephen et al., 2002).

The transfer protocol or test plan should include suitable acceptance criteria relevant to the tests and specific dissolution profiles where dissolution is a characterization test commonly used by the pharmaceutical industry to guide formulation design. Also, it is used to control product quality and it is considered a key parameter in assessing the uniformity at the formulation stage as well as throughout the shelf-life of the product (Cohen et al., 1990).

Due to lack of formal guidance or regulatory requirements, several approaches are possible to select the experimental design, for choosing the statistical data treatment and hence for the decision process namely the dissolution test (Fontenay, 2008). The success of an analytical method transfer is tested by comparing results or their summary parameters such as the means and variances of the participating laboratories obtained after analyzing similar samples. Therefore, it is important for the researchers to search ways to validate the analytical transfer.

Several terms and statistical approaches for the transfer of analytical methods have been described and designed. The USP (2009) described the transfer of analytical procedures: A proposal for a new general information chapter 1224. Also the FDA (2006) has released an official guidance on how to conduct and document method transfer. The ISPE (The International Society for Pharmaceutical Engineering) design provides adequate probabilities to accept successful method transfers correctly only for relatively small error amounts (Schepers and Wätzig, 2005; Kaminski1 et al., 2010). Also the conventional statistical approaches generally were used in the transfer of quantitative methods namely bioanalytical applications associated with risk evaluation of this transfer (Rozet et al., 2008). On the other hand, the United States Pharmacopoeia concept (1010) was used as the equivalence test for analytical method transfer (Schepers and Wätzig, 2006) and it uses total error as a decision criterion for transfer of HPLC–UV method (Rozet et al., 2006). The best way to estimate the characteristics of dispersion of an HPLC method and a powerful tool for analytical transfers was studied (Vial and Jardy, 2001).

The objective of this work is to demonstrate the applicability of the total error approaches with certain statistical models to a more variability domain pharmaceutical namely dissolution test and in the interpretation of acceptance criteria of transfer of dissolution profiles of solid pharmaceutical form.

2. Materials and methods

2.1. Standard and placebo

The reference standard (*RF*) for diclofenac sodium (DS) (98.2%) was obtained from Drugs Quality Control Laboratory as certified by external secondary standard. The product A as originator was obtained from Novartis for pharmaceutical industries and product B as generic was obtained from Galanica for pharmaceutical industries (Morocco). The placebos used in validation of the analytical method were the fallowing: calcium phosphate tribasic, sodium starch glycolate, magnesium stearate, polyvinylpyrrolidone, microcrystalline cellulose, sucrose, purified talc, disperse red, lactose, selenium dioxide, cellulose acetophthalate, titanium dioxide, ethanol, polyethylene glycol, iron oxide red, iron oxide yellow, maize starch, silica colloidal anhydrous, silicone antifoam, sodium methyl carboxyl and polysorbate 80.

2.2. Reagents

At the sending and receiving sites, methanol was of HPLC grade from Sigma–Aldrich (Germany). Hydrochloric acid and phosphoric acid were supplied by Merck KGaA (Germany). Sodium phosphate tribasic was obtained from Riedel-de Haen (Germany).

2.3. Apparatus

At the sending site, the chromatographic system consisted of Waters 2695 pump, auto sampler and Waters 2998 photodiode-array detector (PDA). Data acquisition was performed by the Empower Software data registration TM. Dissolution test of Erweka DT 600, Frankfurt (Germany). pH meter of Concort (Belgium). Balance of Precisa (Switzerland).

At the receiving site, Dissolution test of Hanson SR8-Plus™ (USA), the chromatographic system consisted of Waters 2695 pump, auto sampler and Waters 2998 photodiode-array detector (PDA). Data acquisition was performed by the Empower

Software data registration TM. Balance of Mettler Toledo (Switzerland). pH meter of Schott (Germany).

2.4. Chromatographic conditions

At the sending and receiving sites, the chromatographic system and conditions were as follows: Waters YMC C18 −3 μm 150 cm × 4.6 mm and phenomenex C18 −3 μm 150 cm × 4.6 mm columns, respectively; eluent: buffer (pH = 2.5, 0.5 g/l phosphoric acid 1.4 g/l sodium phosphate monobasic dihydrate and /MeOH (30/70 v/v)). 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 ml/min and the injection volume was 20 μl with a temperature of 30 °C. The wavelength of the detector was set at 276 nm.

2.5. Validation of the analytical method at the sending laboratory

2.5.1. Preparation of assay validation

In order to validate the analytical method, two kinds of samples were prepared in an independent way: calibration standards and validation standards. In the calibration standards (CSs), samples were prepared in seven known concentrations with two assays as the following: dissolve an accurately weighed standard DS in diluent A (water and methanol, 30 ml:70 ml) specifically 0.5411, 1.090, 5.486, 13.54, 46.33, 54.81 and 68.38 mg/100 ml without matrix (placebo). Samples were shaken by mechanical means for 10 min and sonicated for about 10 min. Five milliliters from stock standards was transferred into a volumetric 50 ml flask and it was completed by diluent B namely medium dissolution (the dissolution medium used in the validation was prepared as follows: sodium phosphate tribasic (76 g/l) and hydrochloric acid 0.1 N (250 mg and 750 ml) were mixed and the pH was adjusted to 6.8 ± 0.05 by hydrochloric acid 2 N. Seven concentrations (0.0005411, 0.001090, 0.005486, 0.01354, 0.04633, 05481 and 0.06838 mg/ml) were obtained. Those solutions were filtered using a 0.45-μm filter. The validation standards (VSs) were prepared as the calibration standard with matrix (placebo) with three assays. The evaluation of the HPLC method specificity was performed by preparing placebo tablets containing the same excipients of the commercial products (United States Pharmacopeia, 2009; Hubert et al., 2003; International Conference, 2005; ISO/IEC, 2005).

2.5.2. Computation analysis

The data obtained were treated and computed using e-Novel software (Arlenda, Belgium). A linear regression model (through zero using the highest level only) is fitted on the back-calculated concentrations as a function of the introduced concentrations in order to obtain the following Eq. (1), where Y = back-calculated concentrations (mg/ml) and X = introduced concentration (mg/ml) (Hubert et al., 2003):

$$Y = aX + b \tag{1}$$

Trueness is expressed in terms of absolute bias (Ab) (mg/ml), % relative bias (Rb) or % recovery (R) at each concentration levels of the validation standards. Those terms were calculated based on Eqs. (2)–(4) (Miller and Miller, 2000; ISO, 1994). $\hat{\mu}$ is the mean of the introduced concentrations and $\hat{x}$ is the estimate of the mean concentration obtained from calculated concentrations then we have:

$$Ab = \hat{x} - \hat{\mu} \tag{2}$$

$$Rb\,(\%) = 100 \times \frac{\hat{x} - \hat{\mu}}{\hat{\mu}} \tag{3}$$

$$R\,(\%) = 100 \times \frac{\hat{x}}{\hat{\mu}} \tag{4}$$

An accuracy profile is obtained by linking on the one hand the lower bounds and on the other hand the upper bounds of the β-expectation tolerance intervals calculated at each concentration level (Hubert et al., 2003; Mee, 1984). The formula to compute these β-expectation tolerance intervals is

$$bias\,(\%) \pm k RSD_{IP}\,(\%) \tag{5}$$

$$RSD_{IP}\,(\%) = 100\frac{\sqrt{\hat{\sigma}_B^2 + \hat{\sigma}_W^2}}{\mu} \tag{6}$$

$$k = Q_t\left(v; \frac{1+\beta}{2}\right)\sqrt{1 + \frac{n\hat{\sigma}_B^2 + \hat{\sigma}_W^2}{pn(\hat{\sigma}_B^2 + \hat{\sigma}_W^2)}} \tag{7}$$

$$v = \frac{(R+1)^2}{\frac{\left(R+\frac{1}{n}\right)^2}{p-1} + \frac{1-\frac{1}{n}}{pn}} \tag{8}$$

where $\hat{\sigma}_B^2$ and $\hat{\sigma}_B^2$ are the estimates of the between-series and within-series variances, respectively, $Q_t(v; \frac{1+\beta}{2})$ is the β quantile of the Student's distribution with v degrees of freedom and v is the Satterthwaite's approximation of the degrees of freedom; where R is the ratio of the between-series over the within-series variance; p is the number of series and n the number of repetitions per series, then n is estimated by the average number of repetitions. On the other hand the intermediate precision standard deviation (SD) was calculated by using the following equation (Chapuzet et al., 1997; Hubert et al., 1999):

$$S_{IP} = \sqrt{\hat{\sigma}_B^2 + \hat{\sigma}_W^2} \tag{9}$$

The limit of detection is the smallest quantity of the targeted substance that can be detected based on Eq. (10). While the lower limit of quantitation (LOQ) was assayed under experimental conditions (Hubert et al., 2003):

$$LOD = \frac{LOQ}{3.3} \tag{10}$$

The risk of having measurements outside the acceptance limits is directly derived from the above Tolerance Interval, using the same estimates and t distribution in a different manner, i.e. by computing the probability to be above the upper acceptance limit plus the probability of being below the lower acceptance limit instead of computing the interval where it is expected to observe β% of the future measurements (Mee, 1988). The probability to have measurements outside the acceptance limit can be expressed as follows:

$$P\left[\left|\frac{X_i - \mu_T}{\mu_T}\right| > \lambda\right] = P\left[\frac{X_i - \mu_T}{\mu_T} < (-\lambda)\right] + P\left[\frac{X_i - \mu_T}{\mu_T} > (+\lambda)\right]$$

$$P = \left[t(v) < \frac{-\lambda(\%) - bias(\%)}{RSD_{IP}\sqrt{1 + \frac{n\sigma_B^2 + \sigma_W^2}{pn(\sigma_B^2 + \sigma_W^2)}}}\right] + P\left[t(v) > \frac{\lambda(\%) - bias(\%)}{RSD_{IP}\sqrt{1 + \frac{n\sigma_B^2 + \sigma_W^2}{pn(\sigma_B^2 + \sigma_W^2)}}}\right] \tag{11}$$

where X_i is the individual result, μ_T is the considered true value, p is the number of series and n is the number of repetitions per series, λ is the acceptance limit, v is the Satterthwaite's approximation of the degrees of freedom, RSDIP is the relative standard deviation of the intermediate precision.

2.6. Dissolution profile at the sending laboratory

The dissolution rate studies on conventional DS tablets 50 mg namely reference (product A) and generic (product B) were carried out according to USP paddle method (Apparatus 2), at a stirring rate of 50 rpm for 45 min. The dissolution medium was 900 ml of buffer solution 6.8 at 37 ± 0.05 °C (United States Pharmacopeia, 2009). The dissolution medium used in the validation was prepared as follows: sodium phosphate tribasic (76 g/l) and hydrochloric acid 0.1 N (250 mg and 750 ml) were mixed and then the pH was adjusted to 6.8 ± 0.05 by hydrochloric acid 2 N. Two milliliters of sample aliquots was withdrawn at 10, 20, 30 and 45 min using a glass syringe and filtered through 0.45-μm membrane filters. The dissolved amount was determined by a validated method namely HPLC–UV detection and it was compared with a standard solution having a known concentration.

2.7. Transfer of dissolution profile

2.7.1. Experimental design at the sending and receiving laboratories

The protocol of transfer of dissolution profiles (kinetic of DS) was designed in three days for two products namely one reference (product A) and one generic (product B). For each day, six tablets were measured. The time points used in dissolution were 10, 20, 30 and 45 min as the same time points and dissolution condition of the sender laboratory. In the protocol of dissolution test transfer was used 18 tablets (units) for the same lot of products. The protocol was applied with different apparatus and operator. The data obtained from transfer were calculated by using Microsoft Excel software and Minitab Statistical Software 15.

2.7.2. Statistical approaches for transfer of drugs dissolution testing

The dissolution test has high variability (Qureshi and Shabnam, 2001) in results, therefore certain statistical approaches were applied for transfer of drugs dissolution allowing appropriate possibility of selection of the experimental design.

Descriptive statistics was used to describe the basic features of the data in the dissolution study. These approaches provide simple summaries about the sample and the measures. The central tendency, desperation and the percent coefficient of variation (% CV) of sender and receiver labs were measured.

The confidence interval of a standard deviation ($CI\sigma$) and the confidence interval of a coefficient of variation of precision intermediate ($CI_{CV_{IP}}$) of the sender laboratory were calculated based on Eqs. (13) and (15), respectively. Also, the standard deviation (σ) and the coefficient of variation of precision intermediate (CV_{IP}) of the receiver laboratory were measured based on Eqs. (12) and (14) (Mallet et al., 2010; Pierre, 2007):

$$\sigma = \sqrt{\frac{1}{N-1}\sum_{i=1}^{n}(X_i - \bar{X})^2} \tag{12}$$

$$CI\sigma = \left[\sigma \times \sqrt{\frac{(N-1)}{x^2_{(1-\sigma/2)}}}, \sigma \times \sqrt{\frac{(N-1)}{x^2_{(\sigma/2)}}}\right] \tag{13}$$

$$CV_{IP} = 100\frac{\sqrt{\sigma^2_W - \sigma^2_B}}{\overline{\overline{x}}} \tag{14}$$

$$CI_{(CV_{IP})} = \left[CV_{IP} \times \sqrt{\frac{(N-1)}{x^2_{(1-\sigma/2)}}}, CV_{IP} \times \sqrt{\frac{(N-1)}{x^2_{(\sigma/2)}}}\right] \tag{15}$$

where $x^2_{(1-\sigma/2)}$ is the percentile of a chi-square distribution with degrees of freedom (to calculate the 95% the $CI\sigma$ and the $CI_{CV_{IP}}$, the region under the x^2 distribution that equates to 95% is found between and x^2 0.025 and x^2 0.975), $\hat{\sigma}^2_W$ is a variance inter-series (reproducibility). $\hat{\sigma}^2_B$ is a variance intra-series (repeatability), n is a number of assay in one series, N is the number of assays in three series. $\overline{\overline{x}}$ is general mean of three series .

Difference (f_1) and similarity (f_2) tests were applied to the dissolution data. The difference (f_1) factor is proportional to the average difference between the two profiles, whereas similarity (f_2) factor is inversely proportional to the average squared difference between the two profiles with emphasis on the larger difference among all the time points. The values of f_1 and f_2 factors for products of sender lab versus products of receiver lab were calculated from the means of percent dissolved at each time point. The difference factor f_1 and the similarity factor f_2 of originator drugs of the sender laboratory versus originator drugs of the receiver laboratory as well as generics drugs of sender lab versus generic drugs of receiver laboratory based on validated method were calculated by using the following equations (Food and Drug Administration, 1997):

$$f_1 = 100 \times \frac{\sum_{i=1}^{n}|P_{s-}P_r|}{\sum_{i=1}^{n}P_s} \tag{16}$$

$$f_2 = 50\log\left\{100 \times \left[1 + 1/n\sum_{i=1}^{n}(P_s - P_r)^2\right]^{0.5}\right\} \tag{17}$$

where P_s is a mean of drug release percentage of sender lab with the time point and P_r is a mean of drug release percentage of receiver lab with the time point, then n is the number of time.

For knowing the mechanism of drug release at sender and receiver labs from these formulations, the data were fitted to (Korsmeyer's log cumulative percentage of drug released versus log time) (Costa, 2001; Dash et al., 2010):

$$M_t = M_\infty = at^n \tag{18}$$

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.

The R-chart control approach was used to monitor over time the dispersion of dissolution test of sender laboratory based on Eqs. (19) and (20) and rang (R) of receiver laboratory was measured, where the R^- is the center line of the average size, upper control limit (UCL) and lower control limit (LCL) are represented. The factors $D3$ and $D4$ depend only

on n, and are tabled (Marilyn and Robert, 2007; Baillargeon, 1997):

$$LCL = D3R^{-} \quad (19)$$

$$UCL = D4R^{-} \quad (20)$$

3. Results and discussion

3.1. Validation based on total error approaches

RP–HPLC/UV method was developed and validated based on the accuracy profiles (total error) for the determination of DS release in solid pharmaceutical forms at the sending laboratory. The specificity test by HPLC/UV demonstrated that the excipients from tablets did not interfere in the drug peak and the selectivity of detection was ensured by determining the retention time of DS.

In order to find the most suitable regression model, several response functions (standard curves) were fitted namely: the weighted ($1/X^2$) quadratic regression, weighted ($1/X^2$) linear regression, weighted ($1/X$) linear regression, linear regression after square-root transformed data, weighted ($1/X$) quadratic regression, linear regression after log transformed data, quadratic regression, linear regression through zero fitted using level 1.0 only and linear regression through 0 fitted using the highest level only and the last model as a simple model ($Y = aX + b$) was selected for routine analysis. Also the validation phase was completed by the investigation of the risk profiles of various acceptable regression models in order to avoid obtaining measurements outside the acceptance limits fixed *a priori* in the sender laboratory. Therefore, the transfer of analytical method does not need revalidation at the receiving laboratory. This approach gives enough guarantee that each of the future results, generated by this method during routine use, will be close enough to the true value. Accuracy profile obtained for the validation of the HPLC–UV analytical method for the quantification of DS release is considering the linear regression through zero fitted using the highest level. The accuracy profile methodology uses only one statistical decision methodology, namely a β-expectation tolerance interval. The acceptance limits were settled to ±5% and considered the first order risk of 5%. All the response functions allowed demonstrating the capability of the method to quantify DS over the whole concentration range chosen and this is because the tolerance intervals were totally included inside the acceptance limits. The systematic errors namely trueness at each concentration level were expressed by absolute bias (mg/ml), relative bias (%) and recovery (%). Differently, the random errors were evaluated by standard deviation (SD) and relative standard deviation (% *RSD*) values for repeatability and intermediate precision at each concentration level. On other hand, the total errors namely systemic and random were expressed by accuracy parameter (Table 1 and Fig. 1).

Table 1 Results of the validation of the method dedicated to the determination of DS percent release in tablets form using the linear regression model through 0 fitted with high concentration.

Response functions	Day 1	Day 2	Day 3
Slope	4.3743E + 07	4.3776E + 07	4.3763E + 07
R^2	ND	ND	ND
RSS	5.2488E + 04	3.2527E + 06	2.4398E + 06
Trueness	Absolute bias (mg/ml)	Relative bias (*RSD* %)	Recovery (%)
0.5411×10^{-3}	0.00788×10^{-3}	1.457	101.5
1.090×10^{-3}	0.00774×10^{-3}	0.7097	100.7
5.486×10^{-3}	0.00372×10^{-3}	0.06773	100.1
13.54×10^{-3}	0.02287×10^{-3}	0.1688	100.2
46.33×10^{-3}	0.08698×10^{-3}	0.1877	100.2
54.81×10^{-3}	0.05112×10^{-3}	0.09326	100.1
68.38×10^{-3}	0.02388×10^{-3}	0.03492	
Accuracy	β-expectation confidence limits (mg/ml) (%)		Risk (%)
0.5411×10^{-3}	[0.0005423, 0.0005557]	[0.2195, 2.694]	0.009647
1.090×10^{-3}	[0.001096, 0.001099]	[0.5771, 0.8423]	0
5.486×10^{-3}	[0.005477, 0.005502]	[−0.1641, 0.2996]	0.0005163
13.54×10^{-3}	[0.01352, 0.01362]	[−0.1984, 0.5360]	0.00000020
46.33×10^{-3}	[0.04601, 0.04683]	[−0.7017, 1.077]	0.0001634
54.81×10^{-3}	[0.05481, 0.05491]	[−0.002924, 0.1894]	0
68.38×10^{-3}	[0.06833, 0.06848	[−0.07248, 0.1423]	0
Precision	Repeatability (*RSD* %)	Intermediate precision (*RSD* %)	
0.5411×10^{-3}	0.5058	0.5058	
1.090×10^{-3}	0.05420	0.05420	
5.486×10^{-3}	0.03666	0.06598	
13.54×10^{-3}	0.1501	0.1501	
46.33×10^{-3}	0.3635	0.3635	
54.81×10^{-3}	0.03879	0.03916	
68.38×10^{-3}	0.03836	0.04197	

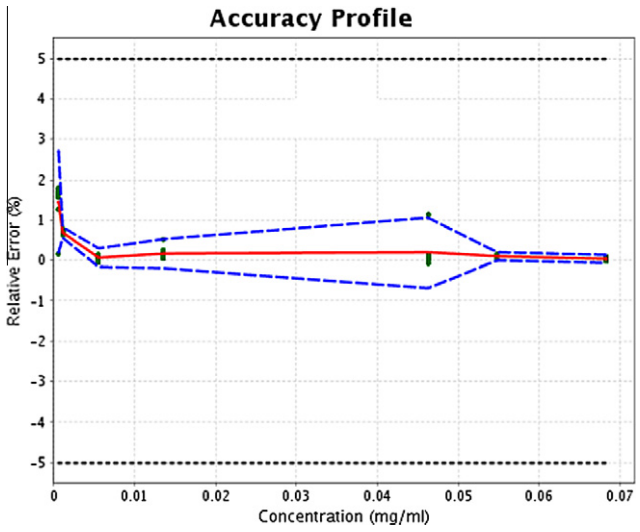

Figure 1 Accuracy profile obtained for the validation of the HPLC–UV analytical method for the quantification of DS release by considering: linear regression through 0 fitted using the highest level only. Plain line: relative bias; dashed lines: β-expectation tolerance limits; dotted curves: acceptance limits (%) and dots: relative back-calculated concentrations of the validation standards.

Seven calibration standards for DS were prepared in order to evaluate the relationship between the area under the curve and the concentration. The linearity of the relationship was evaluated in a concentration range of 0.5411×10^{-3} mg/ml–68.38×10^{-3} mg/ml, covering the normal range of concentrations obtained when analyzing release of DS in tablet with slope (1.011), intercept (0.000011), R^2 (correlation coefficient) equal 1.0 and RSS (residual sum of squares) (0.00000027) .

The limit of detection (*LOD*) of the developed method was equal to 0.08200×10^{-3} mg/ml, while the lower limit of quantitation (*LOQ*) was equal to 0.5411×10^{-3} mg/ml and the upper *LOQ* was equal to 68.38×10^{-3} mg/ml based on computation analysis.

3.2. Transfer of dissolution profile

The transfer of validated method based on accuracy profile that designated the simultaneous combination of systematic (measured by biases, i.e. method trueness) and random errors (measured by relative standard deviation ''RSD'', i.e. method precision) associated with ISO 17025 (sender accredited laboratory) gives enough guarantee for the future results. On the other meaning, the generated results using the current method during routine use will be close enough to the true value. Therefore, dissolution test can be successfully transferred without mastering the analytical method or revalidation by the receiving laboratory.

3.2.1. Descriptive approach

The dissolution results of DS as the means of percent dissolved versus time between sender and receiver laboratories are shown in Table 2 and Fig. 2. The comparison of dissolution profiles of mean three series of the two labs (each data point represents a mean of 18 measurements for each product). The results of the percent release of product A in solid form of sender laboratory are 14.55%, 61.55%, 93.56% and 103.09% for the time 10, 20, 30 and 45 min, respectively. While, the percent release of product A of receiver laboratory is 14.01%, 56.76%, 90.02% and 97.23% for time point of 10, 20, 30 and 45 min, respectively. The percent release of product B of sender lab is described at 10, 20, 30 and 45 min and was 50.8%, 95.04%, 102.72% and 103.06%, respectively. The percent release of product B of receiver method was 52.70%, 96.58%, 98.30% and 100.19%, respectively at the same time point. Results of dissolution show that products A and B of sender and receiver laboratories are rapidly dissolving and dissolution amount is greater than *Q*-value of USP namely 75% at 45 min. The transfer of the dissolution method is accepted even though using two different conditions and different apparatus as well as different operators. Also, dissolution amount is greater than 85% at 30 min in media of sender and receiver laboratories with pH 6.8, therefore the transfer is accepted based on WHO norm. Where *Q* (single point value) is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content (Carlos et al., 2004; World Organization Health, 2005).

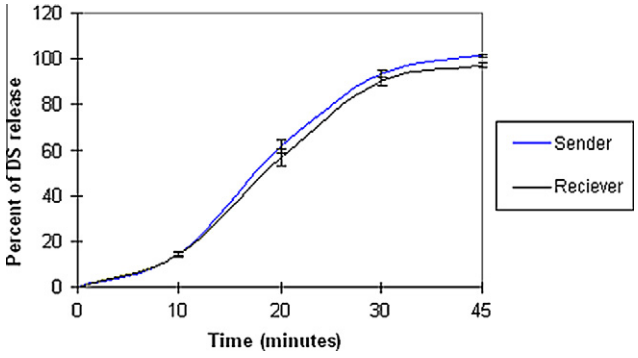

Figure 2A Dissolution profile of product A at sender and receiver laboratories.

Table 2 Descriptive criteria to accept the transfer.

Lab	Sender lab				Receiver lab				Accept criteria
Days	Day 1	Day 2	Day 3	Inter-days	Day 1	Day 2	Day 3	Inter-days	
Mean (%)									
A	101.16	99.79	102.21	101.06	96.625	99.18	97.353	97.72	*Q*-value > 75%
B	102.71	102.72	103.75	103.06	100.89	99.48	101.48	100.62	
CV (%)									
A	1.32	1.73	1.74	1.82	1.17	3.36	1.60	2.38	*CV* < 10%
B	0.81	1.29	2.09	1.49	1.49	0.92	1.29	1.44	

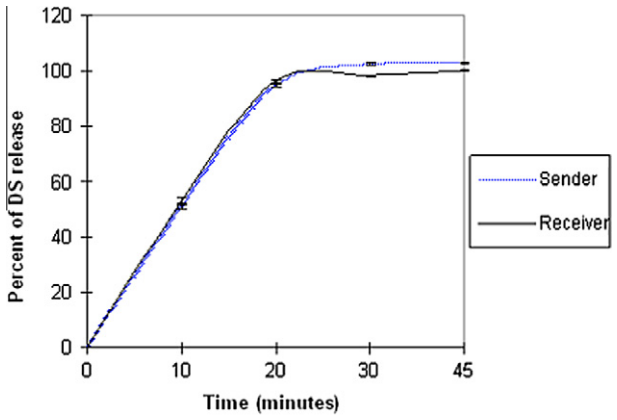

Figure 2B Dissolution profile of product B at sender and receiver laboratories.

A classic descriptive approach for transfer of dissolution test takes into account the variability of the method; therefore the % *CV* of dissolution rate associated with the time namely during 10, 20, 30 and 45 min were observed and measured in two laboratories. The % *CV* of DS releases at the beginning point (10 min) in two labs was less than 20% and the % *CV* of DS releases at the final point (45 min) in two labs was less than 10%. These results due to the transfer are accepted based on FDA (Food and Drug Administration, 1997) (Mallet et al., 2010) (Table 2).

3.2.2. Repeatability and reproducibility approach

The repeatability and precision intermediate of dissolution profile of sender laboratory as characteristic of the quality were calculated for evaluating the competence of the laboratory in performing measurements. The transfer of drugs dissolution testing is accepted because of the SD of receiver laboratory according to the limit of $CI\sigma$ of sender laboratory and the CV_{IP} of receiver laboratory according to the limit of $CI_{CV_{IP}}$ of sender laboratory (Table 3).

3.2.3. Bioequivalence in vitro approach

The results of f_1 and f_2 of product A (originator) of sender lab versus product A (originator) of receiver laboratory are 4.04 and 66.12, respectively. While the results f_1 and f_2 of product B (generic 1) of sender laboratory versus product B (generic) of receiver laboratory are 2.04 and 68.70, respectively. Both of the results are within normal range (0–15) and (50–100) (Food and Drug Administration, 1997) (Table 4). Also, it is considered normal value based on FDA (or equivalent statistical criterion). This result indicates the acceptance of the bioequivalence *in vitro* and transfer of dissolution test.

3.2.4. Drugs mechanism in vitro approach

The kinetic of DS originator release from 50 mg tablets (product A) based on USP condition and the application Korsmeyer's model are shown in Table 5. This model gives an indication of the type of drug mechanism of release *in vitro* within inter-laboratories. To confirm the diffusion mechanisms, the data were fitted into Korsmeyer's equation and the results showed good linearity of product A for sender and receiver laboratories (R^2: 0.8963 and 0.9076, respectively, with high slope value (n) of 1.334 and 1.3057, respectively). These (n) values appear to indicate super case-II transport. On other hand, the model was used to know the mechanism release of Generic (product B) of sender and receiver laboratories. In Korsmeyer's plot the R^2 values obtained are 0.8097 and 0.7761, respectively; and for that of n values are 0.4822 and 0.4563. These (n) values appear to indicate anomalous (non-Fickian) diffusion for the tablets released. It is clear that the transfer cab be accepted because the drug release in inter-laboratories has the same mechanism (Dash et al., 2010).

3.2.5. R-chart control approach

The result of R-chart control of sender lab was described in Fig. 3. However, R-chart control based on dissolution data of sender in three days for products A and B shows the variation in a measurement during the time period namely three days that the dissolution profile is observed. This approach is performing to show how the process capabilities are affected by changes to transfer of test. The upper control limits of sender laboratory for products A and B (8.40 and 7.75, respectively) are drawn above the centerline and often annotated as "UCL". While the lower control limits of sender lab for products A and B (0.00 and 0.00, respectively) are drawn below the centerline and often annotated as "LCL" (Baillargeon, 1997). On the other hand, the variation of dissolution profile of receiver laboratory was measured based on R^- (inter-days) and the result showed include R^- of receiver lab for products A and B (4.80 and 3.33, respectively) within range of UCL and LCL of R-chart of sender lab. This is due to the achievement and maintaining the stability pro-

Table 3 Repeatability and reproducibility to accept the transfer.

Lab	Sender lab $CI\sigma$	σ receiver lab				Sender lab $CI_{CV_{IP}}$	Receiver lab CV_{IP}
		Day 1	Day 2	Day 3	Inter-days		
Product							
A	$1.21 \leqslant \sigma \leqslant 2.41$	1.133	3.237	1.558	2.32	$1.42 \leqslant PI \leqslant 2.84$	2.50
B	$1.08 \leqslant \sigma \leqslant 2.16$	1.45	0.911	1.31	1.45	$1.12 \leqslant PI \leqslant 2.25$	1.5

Table 4 Bioequivalence *in vitro* to accept the transfer.

Days	Day 1		Day 2		Day 3		Inter-days	
	f_1	f_2	f_1	f_2	f_1	f_2	f_1	f_2
Product								
A	8.2	57.41	0.24	74.82	3.70	66.13	4.04	66.12
B	0.40	74.12	4.54	66.12	1.19	65.87	2.04	68.70
Accept criteria f_1 = (0–15), f_2 = (50–100)								

Table 5 Drug mechanism in *vitro* to accept the transfer.

Days	Day 1				Day 2				Day 3				Inter-days			
Lab	Sender		Receiver		Sender		Receiver		Sender		Receiver		Sender		Receiver	
	R^2	Slope (n)	R^2	Slope (n)	R^2	Slope (n)	R^2	Slope (n)	R^2	Slope (n)	R^2	Slope (n)	R^2	Slope (n)	R^2	Slope (n)
Product																
A	0.8664	1.350	0.9045	1.310	0.9347	1.2325	0.9018	1.3429	0.8878	1.4195	0.9167	1.3471	0.8963	1.334	0.9076	1.3057
B	0.8176	0.4707	0.772	0.4696	0.7971	0.4084	0.7689	0.4587	0.8146	0.5675	0.7875	0.4407	0.8097	0.4822	0.7761	0.4563

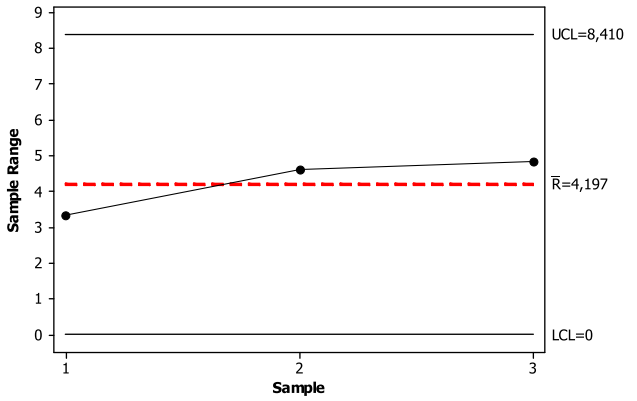

Figure 3A R-chart control of dissolution data of sender laboratory of product A.

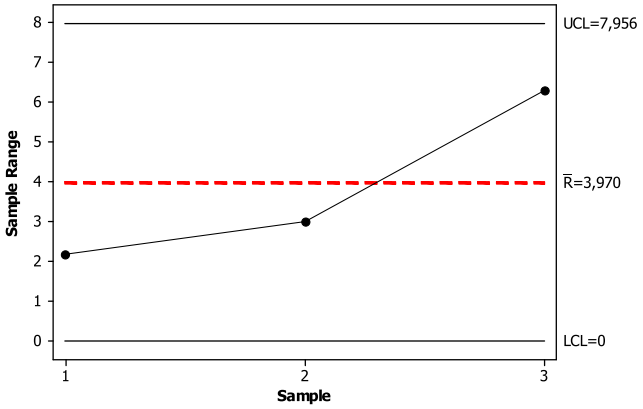

Figure 3B R-chart control of dissolution data of sender laboratory of product B.

Table 6 R-chart control to accept the transfer.

	R-chart control of sender lab		Sample rang of receiver lab inter-days			
	UCL	LCL	Day 1	Day 2	Day 3	Inter-days
Product						
A	8.40	0	3.2	7.7	3.6	4.80
B	7.95	0	3.6	2.4	3.8	3.33

cess of dissolution test data between sender and receiver laboratories. Accordingly, this approach may be led to accept the transfer of the dissolution method (Table 6).

4. Conclusion

The statistical procedure developed in this work can be used to accept transfer of dissolution test between sender and receiver labs after development of dissolution condition. These approaches could be used during analytical method development studies to compare the profiles obtained using different dissolution test of inter-laboratories to evaluate the gauge of repeatability, reproducibility bioequivalence *in vitro* and mechanism of drug release as an easy and accurate way to their calculation. Also if the sender used the total error to validate its analytical method, dissolution test can be successfully transferred without mastering the analytical method validation by receiving laboratory B.

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