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An alternative method to the evaluation of similarity factor in dissolution testing

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Abstract

This paper addresses an alternative method to the evaluation of similarity factor f_2 as a criterion for assessment of similarity between two in-vitro dissolution profiles as proposed in the SUPAC-IR Guidance (1995). Diltiazem hydrochloride Sustained-Release (SR) tablets were tested and the following independent-model dissolution parameters were used: $t_{10\%}$ dissolution time, $t_{25\%}$ dissolution time, $t_{50\%}$ dissolution time, mean dissolution time (MDT), dissolution efficiency (DE) at t_{120}, and at t_{360}. To compare the dissolution profiles, several release models were tested such as Higuchi, zero order, first order, Baker-Lonsdale, Hixson-Crowell, Weibull and Korsmeyer-Peppas. The similarities between two in-vitro dissolution profiles were assessed by pair-wise independent-model procedures such as difference factor (f_1), similarity factor (f_2) and Rescigno index (ξ_1 and ξ_2). The in vitro release kinetics of diltiazem hydrochloride sustained release tablets were evaluated using USP apparatus 2.

Keywords: Similarity factor; Drug release; Dissolution; Drug release models; Diltiazem hydrochloride

1. Introduction

The similarity factor (f_2) is a logarithmic transformation of the sum-squared error of differences between the test T_j and reference products R_j over all time points, m (Moore and Flanner, 1996):

$$f_2 = 50 \log\left\{\left[1 + (^1/_m)\sum_{j=1}^{m} w_j|R_j - T_j|^2\right]^{-0.5} \times 100\right\},$$

where w_j is an optional weight factor. The similarity factor fits the result between 0 and 100. It is 100 when the test and reference profiles are identical and approaches 0 as the dissimilarity increases. This method is more adequate to compare dissolution profile when more than three or four dissolution times points are available and can only be applied if the average difference between R_j and T_j is less than 100. If this difference is higher than 100 normalization of the data is required (Moore and Flanner, 1996).

This similarity factor, has been adopted by Center for Drug Evaluation and Research (FDA)

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and by Human Medicines Evaluation Unit of The European Agency for the Evaluation of Medicinal Products (EMEA), as a criterion for assessment of similarity between two in-vitro dissolution profiles and included in the "Guidance on Immediate Release Solid Oral Dosage Forms; Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing; In Vivo Bioequivalence Documentation" (CDER, 1995), commonly called SUPAC-IR, and in the "Note For Guidance on Quality of Modified Release Products: A. Oral Dosage Forms; B. Transdermal Dosage Forms; Section I (Quality)" (EMEA, 1999). The similarity factor (f_2) as defined by FDA and EMEA is a logarithmic reciprocal square root transformation of one plus the mean squared differences in percent dissolved between the test and reference products.

The FDA and EMEA suggested that two dissolution profiles were declared similar if f_2 was between 50 and 100. It should be noted that in the f_2 SUPAC-IR and EMEA Guidance R_j and T_j are defined as the percent dissolved in each sampling time point j, different from the previous definition proposed by Moore and Flanner. From the context of these guidances it was generally interpreted that f_2 should be computed from average cumulative percent dissolved. It is not clear from the guidances whether the percent dissolved is referred to as the cumulative percent dissolved up to time point t or as the incremental percent dissolved observed from the previous time point $t-1$ to the current time point t. In addition, it is not clear if R_j and T_j are the average of percents dissolved of all dosage units at time point t or refers to the percent dissolved of individual dosage units, respectively, for the test and reference drug products.

The f_2 is insensitive to the shape of the dissolution profiles and do not take into account the information of unequal spacing between sampling time points. The similarity factor f_2 is a sample statistic that cannot be used to formulate a statistical hypothesis for assessment of dissolution similarity. It is, therefore, impossible to evaluate false positive and false negative rates of decisions for approval of drug products based on f_2. Implementation of f_2 to assess dissolution similarity is, in fact, a one-sided problem rather than an interval criterion suggested by CDER and EMEA guidances. Simulation results also indicated that the similarity factor is too liberal in concluding similarity between dissolution profiles (Liu and Chow, 1996; Liu et al., 1997). For each pair of dissolution profiles using this similarity factor a characteristic f_2 value is obtained. This value use the mean percent dissolved of test and reference products, and do not reflect the dispersion associated with each dissolution profile. In general, no statistical inference can be made, by direct implementation of the criterion based on this f_2 factor, about dissolution dissimilarity from tablet sample to tablet batches population.

Another way to compute f_2 value is to use, not the mean percent dissolved of the two profiles, but all the dissolution tests, n, conducted on the individual dosage units. In this manner, a cluster of f_2 values will be obtained. These values are calculated from the combination of all the results from the reference and test products. The n^2 cluster of f_2 values should be normally distributed along the mean f_2 value. Calculating the confidence interval (CI) for the f_2 value it is possible to make inference statistics from the sample used to the tablet batch population, about the dissimilarity of the dissolution profiles.

To test this other f_2 method of calculation three dissolution profiles were examined. The diltiazem hydrochloride Sustained-Release (SR) dosage forms studied were polymeric matrix tablets. The drug release with different stirring rates (USP apparatus 2) were compared using the following dissolution parameters: $t_{10\%}$ dissolution time, $t_{25\%}$ dissolution time, $t_{50\%}$ dissolution time, mean dissolution time (MDT), dissolution efficiency (DE) (Khan and Rhodes, 1972; Khan, 1975) at t_{120}, t_{360} and t_{1440}. To compare the dissolution profiles, several release models (Table 1) were tested such as Higuchi (Higuchi, 1961, 1963; Cobby et al., 1974), zero order, first order (Gibaldi and Feldman, 1967; Wagner, 1969), Baker-Lonsdale (Baker and Lonsdale, 1974), Hixson-Crowell (Hixson and Crowell, 1931), Weibull (Langenbucher, 1972; Goldsmith et al., 1978; Romero et al., 1991; Vudathala and Rogers, 1992; Bataille et al., 1997) and Korsmeyer-Peppas (Korsmeyer et

Table 1
Release models tested

Zero order	$Q_t = Q_0 + K_0 t$
First order	$\ln Q_t = \ln Q_0 + K_1 t$
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_s t$
Weibull	$\log[-\ln(1-(Q_t/Q_\infty))] = b \log t - \log a$
Higuchi	$Q_t = K_H\sqrt{t}$
Baker-Lonsdale	$(3/2)[1-(1-(Q_t/Q_\infty))^{2/3}]-(Q_t/Q_\infty) = Kt$
Korsmeyer-Peppas	$Q_t/Q_\infty = K_k t^n$

al., 1983; Peppas, 1985; Harland et al., 1988) (Table 1).

The similarities between two in vitro dissolution profiles were also assessed by other pairwise independent-model procedures such as difference factor (f_1) (Moore and Flanner, 1996) and Rescigno index (ξ_1 and ξ_2) (Rescigno, 1992). The differences for $t_{10\%}$, $t_{25\%}$ and $t_{50\%}$ dissolution times were statistically examined by a one-way analysis of variance – ANOVA ($\alpha = 0.05$).

2. Materials and methods

Diltiazem hydrochloride (180 mg) SR tablets were commercial formulations. All chemicals were reagent grade. The dissolution testing of diltiazem hydrochloride SR tablets were performed on the USP apparatus 2 ($n = 6$) at a stirring speed of 50, 100 or 150 rpm (profile A, B and C), using 1000 ml of dissolution fluid (water) at 37 ± 0.5°C (Costa and Sousa Lobo, 2000). Dissolution samples were collected for analysis and replaced by an equal volume of fresh dissolution fluid at 30, 60, 120, 180, 240, 300, 360, 720 and 1440 min ($m = 9$).

The high-performance liquid chromatography system consisted of a pump (Varian model 9012), a 20 μl loop and a variable wavelength detector (Varian model 9050) set to 235 nm. A C8 column (LiChrospher 100 RP8 5 μm 100×4 mm) was used. The mobile phase was acetonitrile/dissodium phosphate 0.01 M solution (Na_2HPO_4) (50:50) with triethanolamine 0.01%, at a flow rate of 2.0 ml/min.

3. Results and discussion

The diltiazem matrix tablets in contact with the dissolution fluids, swelled forming a jelly mass that practically did not change for more than 4–6 h. The tablets release profile can be seen in Fig. 1.

Differences were detected between the calculated dissolution parameters in the three dissolution conditions studied, especially for A profile, at 50 rpm stirring rate (Fig. 1 and Table 2). The $t_{10\%}$, $t_{25\%}$ and $t_{50\%}$ dissolution times and the mean dissolution time decreased as stirring speed increased. The dissolution efficiencies increased as

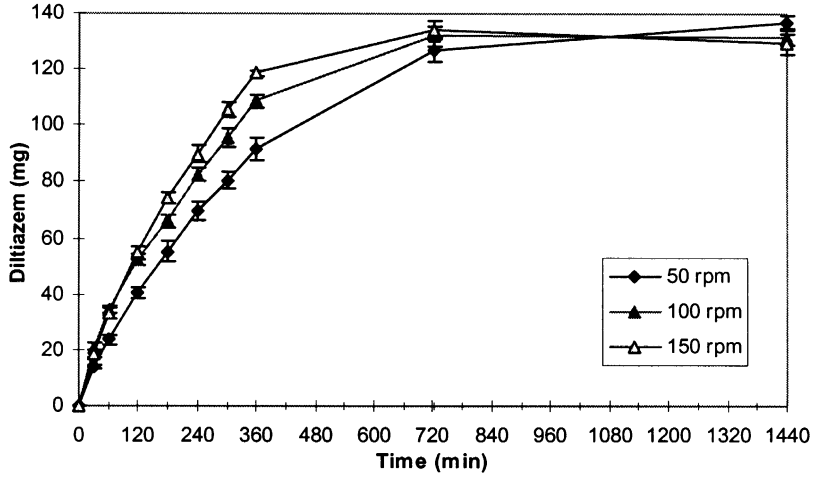

Fig. 1. Diltiazem tablets release profile.

Table 2
Comparison of the dissolution parameters

	A	B	C
$t_{10\%}$	42.8	26.9	28.7
$t_{25\%}$	139.1	97.8	90.7
$t_{50\%}$	353.0	282.8	234.7
MDT	318.2	215.6	193.7
DE t_{120}	12.5	17.0	17.4
DE t_{360}	29.3	35.2	39.3
DE t_{1440}	54.7	57.8	62.3

long stirring rates increased. Using a one-way ANOVA ($\alpha = 0.05$), statistically significant differences were found for $t_{10\%}$, $t_{25\%}$ and $t_{50\%}$ dissolution times between profile A and the other stirring conditions. Between B and C profiles, the differences were statistically significant only for $t_{50\%}$ dissolution time.

Comparing the A/B diltiazem dissolution profiles the mean f_2 value obtained with the proposed method (Fig. 2 and Table 3) was 61.4 with a standard deviation (SD) of 5.6 (variation coefficient of 9.1%). The f_2 maximum value was 74.7 and the minimum value was 50.0. The kurtosis of f_2 values distribution was 0.09 indicating a relatively small peaked distribution compared with the normal distribution. Skewness characterizes the degree of asymmetry of a distribution around its mean. The skewness of f_2 values distribution was 0.35 indicating a distribution with an asymmetric tail extending toward more positive values. All the f_2 values obtained (36) were higher than the limit value of 50, indicating a similarity between the two dissolution profiles. The 95% CI for the population f_2 mean extended from 59.6 to 63.2. The 99% CI extended from 59.9 to 63.8.

Table 3
Similarity factor f_2 evaluated by two different methods

	SUPAC-IR	Alternative method (mean ± SD)
A/B	61.8	61.4 ± 5.6
A/C	49.7	49.7 ± 2.7
B/C	65.3	64.0 ± 4.5

For the comparison of A/C diltiazem dissolution profiles the mean f_2 value (Fig. 3 and Table 3) was 49.7 with a SD of 2.7 (variation coefficient of 5.4%). The f_2 maximum value was 54.0 and the minimum value was 43.6. The kurtosis of f_2 values distribution was -0.39 indicating a relatively small flat distribution compared with the normal distribution. The skewness of f_2 values distribution was -0.50 indicating a distribution with an asymmetric tail extending toward more negative values. From the f_2 values obtained, 20 (56%) were higher than the limit value of 50 and 16 (44%) were smaller than this limit value. The 95% CI for the real f_2 mean extended from 48.8 to 50.6 and the 99% CI for the f_2 mean extended from 48.5 to 50.8.

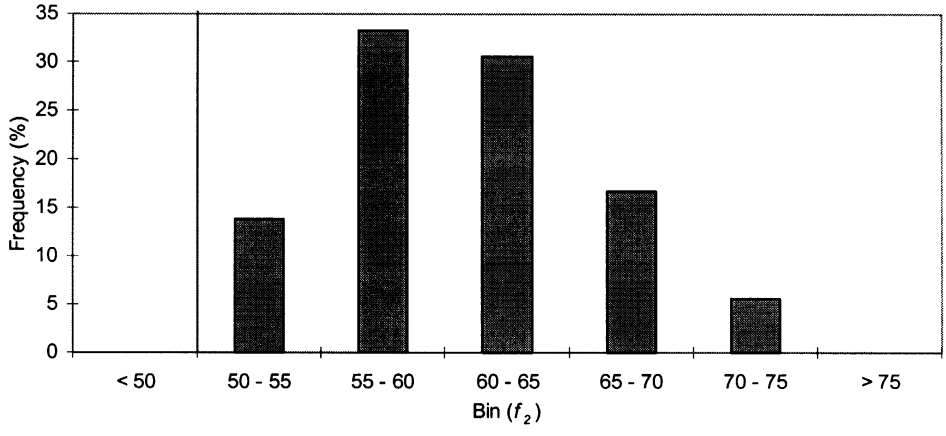

Fig. 2. f_2 histogram for A/B diltiazem dissolution profiles.

Comparing the B/C diltiazem dissolution profiles the mean f_2 value (Fig. 4 and Table 3) was 64.0 with a SD of 4.5 (variation coefficient of 7.0%). The f_2 maximum value was 72.7 and the minimum value was 55.2. The kurtosis of f_2 values distribution was -0.64 indicating a relatively small flat distribution compared with the normal distribution. The skewness of f_2 values distribution was -0.002 indicating a symmetric distribution. All the f_2 values obtained (36) were higher than the limit value of 50, indicating a similarity between the two dissolution profiles. The CI (95%) for the real f_2 mean went from 62.6 to 65.5. The CI (99%) for the real f_2 mean varied from 62.1 to 66.0.

The area (probability) in any interval can be calculated from the cumulative are under the standard normal curve using Z transformation. The area between $-\infty$ and 50 (i.e. area bellow 50 or the probability that f_2 value be lower than 50) was, in the A/B case, 2.1%, i.e. the probability that any two dissolution profiles from method A and B be considered similar was as higher as 97.9%. The area between $-\infty$ and 50 was, in the A/C case, 54.7%, i.e. the probability that any two dissolution profiles from method A and C be considered similar was 45.3%. The area between $-\infty$ and 50 was, in the B/C case, lower than 0.1%, i.e. the probability that any two dissolution profiles from method B and C be considered similar was higher than 99.9%.

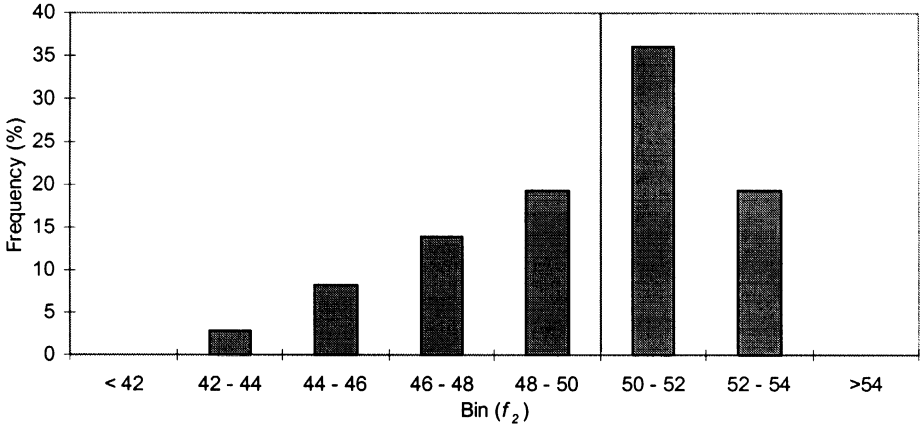

Fig. 3. f_2 histogram for A/C diltiazem dissolution profiles.

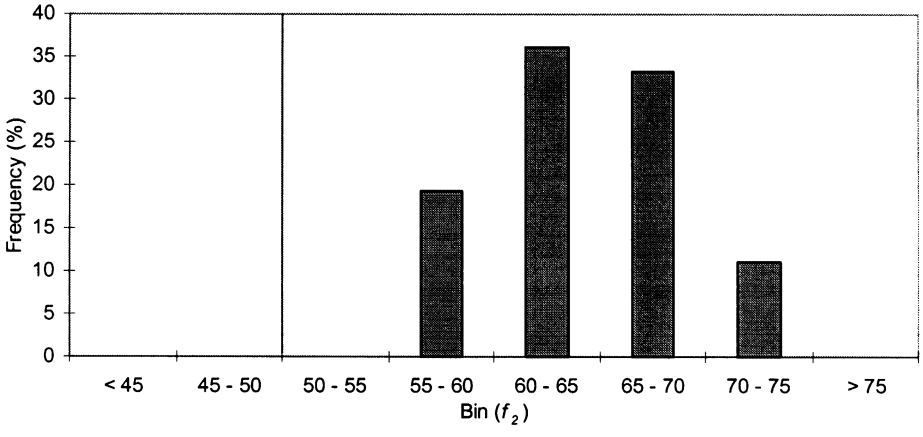

Fig. 4. f_2 histogram for B/C dissolution profiles.

Table 4
Linearization of the diltiazem release profiles (Q expressed in mg)[a]

Release models		A	B	C
Higuchi	K	5.8250	6.4435	7.4424
	R^2	**0.9954**	**0.9951**	**0.9980**
Zero order	K	0.2487	0.2603	0.2603
	R^2	0.9854	0.9910	0.9910
First order	K	0.0054	0.0046	0.0052
	R^2	0.8934	0.8980	0.8807
Baker-Lonsdale	K	0.0002	0.0002	0.0003
	R^2	0.9760	0.9707	0.9724
Hixson-Crowell	K	0.0061	0.0058	0.0065
	R^2	0.9389	0.9409	0.9294
Weibull	β	0.8837	0.8023	0.9145
	R^2	**0.9990**	**0.9955**	**0.9987**
	T_d	440.1647	376.8107	320.9218
Korsmeyer-Peppas	K	0.1519	0.1688	0.2233
	n	0.697	0.695	0.638
	R^2	**0.9994**	**0.9989**	**0.9999**

[a] K – release rate constants; n – exponent release; β – shape parameter.

Table 5
Other used similarity parameters using mean values

	A vs B	A vs C	B vs C
f_1	13.7	22.5	9.0
ξ_1	0.06	0.10	0.04
ξ_2	0.06	0.10	0.05

Table 4 summarizes the release rate constants (K) calculated by the above mentioned mathematical release models and determination coefficient (R^2) of the observed release data and the simulated profiles. The results show that the rate constant values are significantly smaller in the case of profile A. For each of the examined samples the best fit was achieved with the application of Higuchi, Weibull and Korsmeyer-Peppas ($n \approx 0.6$) model. The Weibull shape parameter, β, showed no significant variation ($\beta < 1$). The T_d (time interval necessary to dissolve or release 63.2% of the drug present in the pharmaceutical dosage form) values were tendencially smaller (fast dissolution process) when the stirring rate was increased.

Based in f_2 similarity factor, it can be concluded that the A/B and B/C dissolution profiles were similar. The A/C dissolution profiles gave a non-conclusive result. Using SUPAC-IR f_2 value (49.7) these two dissolution profiles should be considered not similar. But this value is very close to the limit value of 50 and it might be affected with analytical or sampling errors leading to wrong conclusion about similarity (Type II error; considered as different when they are really similar). Using the proposed alternative method to calculate f_2 the same value is obtained (49.7) but it is possible to calculate the probability of 45.3% that any two individual dissolution profiles from method A and C be considered similar. Because of this almost 50:50 probability in the A/C case, its possible to obtain values pointing opposite ways depending on the sampling or other random influences. The model independent parameters confirmed these results (Table 5): f_1 values lower than 15 for A/B and B/C and higher than 15 for A/C profiles; ξ_1 and ξ_2 values equal or lower than 0.06 for A/B and B/C and higher than 0.06 for A/C dissolution profiles.

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