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Evaluation of in Vitro Dissolution Profile Comparison Methods of Immediate Release Gliclazide Tablet Formulations

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Introduction

Three categories of dissolution test specifications for immediate release drug products are described in the guidance. Single point specifications are recommended as a routine quality control test for highly soluble and rapidly dissolving drug products. This comparison method can be employed in evaluating scale-up and post-approval changes such as manufacturing site changes, component and composition changes, equipment changes and process changes. Two-point specifications are suggested for characterizing the quality of drug product and for accepting product sameness under SUPAC-related changes. In the presence of certain minor changes the single point dissolution test may be adequate to ensure unchanged product quality and performance. For more major changes a dissolution profile comparison performed under identical conditions for the product before and after the changes is recommended. Dissolution profiles may be considered similar by virtue of overall profile similarity and similarity at every dissolution sample time point[1-4].

Methods used to compare dissolution data are,

- Statistical Methods (exploratory data analysis method, repeated measures design multivariate approach (MANOVA))[5, 6]
- Model Dependent Methods (zero order, first order, hixson-crowell, weibull and logistic model)[7, 8]
- Model Independent Methods (difference factor (f_1), similarity factor (f_2))[9-11].

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The aim of this study is to evaluate the methods used to compare the dissolution profiles of immediate release gliclazide tablet formulations and also to investigate the advantages and disadvantages of each method[12].

Experimental

Materials

The immediate release tablet formulation of gliclazide (lot number 8A0799) received from Servier was used as a reference product. Gliclazide (Servier, Turkey) was used as the active ingredient. The labelled amount of the drug substance is 80 mg per tablet.

Methods

Immediate release gliclazide tablet formulation was prepared by direct compression method. The tablets containing 80mg gliclazide were prepared by aerosil 200 %0.2 and magnesium stearate %0.25 as lubricants and lactose and avicel pH 101 were used as diluents in the total weight of 200 mg. Polyvinylpyrrolidone and compritol were used as disintegrants.

Dissolution Testing

Dissolution studies on test and reference immediate release tablets of gliclazide were conducted in USP Apparatus 2 (paddle method) with twelve replicates. The dissolution medium was 900 mL of phosphate buffer (pH 7.5). The paddle rotation speed was kept at 100 rpm. Samples were assayed by UV spectrophotometry at 225.8 nm (Shimadzu UV-160A, Japan). Cumulative percentages of the drug dissolved from the tablets were calculated.

Dissolution profile comparison methods

1. *Statistical Methods*

- Exploratory Data Analysis Methods

Although exploratory data analysis methods are not currently endorsed by the FDA, the method is useful in obtaining an improved understanding of the dissolution data and therefore its use is recommended. This method can be used in the first step to compare dissolution profile

data in both a graphical and numerical manner. The dissolution profile data are illustrated graphically by ploting the mean dissolution profile data for each formulation with error bars extending to two standard errors at each dissolution time point. Then the data of the dissolution profiles are summarized numerically and 95 % confidence intervals for the differences in the mean dissolution profiles at each dissolution time point are evaluated[1].

- Multivariate Approach (MANOVA)

These methods were based upon repeated measures designs where time is the repeated factor and percent dissolved is the dependent variable. For statistical methods SPSS 10.0 for Windows was employed. The calculated statistics of this method were, Pillai's Trace, Wilks' Lambda, Hotelling's Trace, Roy's Largest Root. Since the data were collected as repeated measurements over time on the same experimental unit, a repeated measures design was applied. When compared to Student's t and paired t tests, the major advantage of this design is increased precision [13].

In repeated measures ANOVA containing repeated measures factors with more than two levels, additional special assumptions enter the picture: These are compound symmetry assumption and the assumption of sphericity. Because these assumptions rarely hold, the MANOVA approach to repeated measures ANOVA has gained popularity in recent years. The compound symmetry assumption requires that the variances and covariances of the different repeated measures are homogeneous. This is a sufficient condition for the univariate F test for repeated measures to be valid. The sphericity assumption is a necessary and sufficient condition for the F test to be valid. When the compound symmetry or sphericity assumptions have been violated, the univariate ANOVA table will give erroneous results. Mauchly's test of sphericity results are used for the assumption of sphericity.

2. Model Dependent Methods

Model dependent methods are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected the dissolution profiles are evaluated depending on the derived model parameters.

In order to determine the suitable mathematical model describing the dissolution profile, the non-linear regression module of Statistica 5.0 was used. In non-linear regression analysis the Quasi-Newton and Simplex methods minimized the least squares[7, 8].

TABLE I

Mathematical models used to describe drug dissolution curves[7]

Zero Order	$Q_t = Q_0 + K_t t$
First Order	$InQ_t = InQ_0 + K_t t$
Hixson - Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_s t$
Weibull	$\log [- In(1-m)] = \beta \log(t - T_i) - \log T_d$
Higuchi	$Q_t = K_h \quad t$
Logistic	$Q_t = A / (1 + e^{-K(a-\beta)})$

3. Model Independent Methods

Model independent methods use the dissolution data in their native form. Two fit factors, the similarity factor (f_2) and the difference factor (f_1), that compare the dissolution profiles of a pair of drug products were applied to the dissolution data of the immediate release gliclazide tablet formulations[9, 10].

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} x100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum (R_t - T_t)^2 \right)^{-0.5} x100 \right\}$$

N: Number of dissolution sample times

R, T: Mean percent dissolved at each time point for the reference and test dissolution profiles

The evaluation of similarity is based on conditions of,

- A minimum of three time points (zero excluded)
- 12 individual values for every time point for each formulation
- That the standard deviation of the mean of any product should be less than 10% from second to last time point

According to the FDA's guidelines f_1 values lower than 15 (0-15) and f_2 values greater than 50 (50-100) show the similarity of the dissolution profiles. In cases where more than 85% of the drug are dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation[11].

Results and Discussion

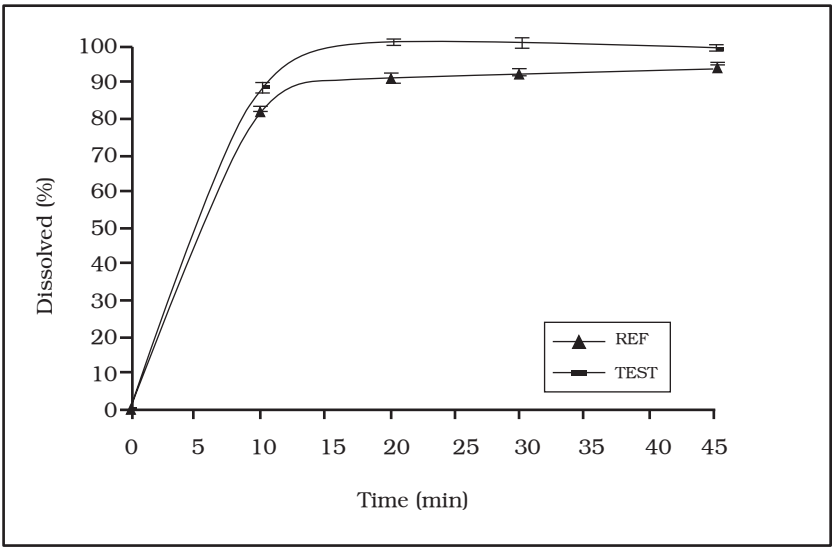

Figure 1

Mean dissolution profiles for test and reference formulations

The error bars for the formulations may overlap only at some of the time points that it may be difficult to definitively conclude that the dissolution profiles for the formulations are different or not. That's why exploratory data analysis may be useful as a first step in obtaining an improved understanding of the dissolution data. Figure 1 shows that the error bars at each dissolution time point do not overlap so the dissolution profiles can be considered to be different from each other. But the need for the evaluation with the other methods is inevitable.

TABLE II

Summary statistics for percentage released for test and reference formulations

Time (min)	Reference mean (SD)	Test Mean (SD*)	Difference (Ref-Test)	95% Confidence interval
10	81.37 (0.49*)	87.25 (1.69*)	0.897	(0.769, 4.768)
20	90.43 (1.20)	100.76 (0.49)	0.572	(-0.08, 2.466)
30	92.53 (0.81)	100.32 (1.09)	0.971	(-2.687, 1.641)
45	94.16 (0.30)	99.16 (1.06)	0.941	(-3.587, 0.607)

The calculated 95 % confidence interval for the mean differences at each dissolution time point doesn't contain zero showed differences are considered to be significantly different at the 5% significance level.

Mauchly's test of sphericity results are used for the assumption of sphericity. Sphericity assumption has been violated and MANOVA based statistical methods are evaluated (Table III).

TABLE III

Multivariate test (MANOVA) results (n=6)

Effect		Value	F	Sig.
Time	Pillai's Trace	1.000	58437.6	0.000
	Wilks' Lambda	0.000	58437.6	0.000
	Hotelling's Trace	33392.9	58437.6	0.000
	Roy's Largest Root	33392.9	58437.6	0.000
Timex Formulation	Pillai's Trace	0.734	4.819	0.035
	Wilks' Lambda	0.266	4.819	0.035
	Hotelling's Trace	2.754	4.819	0.035
	Roy's Largest Root	2.754	4.819	0.035

According to the results of MANOVA, the percents dissolved were found to be significantly different at each time point ($p<0.05$) and the effect of timexformulation interaction was also investigated and the dissolution profiles were also found significantly different ($p<0.05$).

TABLE IV

Parameters of the mathematical models for the dissolution

Model	Statistics	Reference	Test
Zero-order	r^2	0.46	0.41
	K	0.28	0.30
First-order	r^2	0.992	0.999
	K	0.15	0.21
Hixson-Crowell	r^2	0.968	0.969
	K	0.14	0.15
Higuchi	r^2	0.889	0.876
	K	17.14	18.49
Weibull	r^2	0.999	0.999
	T_d, β	2.43, 0.38	7.94, 3.12

Considering the higher determination coefficient, the preferred model which fits best to the dissolution data of reference was the Weibull distribution model.

The derived model parameters, T_d (time parameter) and β (shape factor), were compared as test against reference product using t-test and found to be significantly different ($p<0.05$).

According to the model independent methods, without any further mathematical evaluation, the profiles were found similar according to the f_2 factor. Within 15 min 87.72% of the reference and within 10 min 87.25% of the test formulation have already been dissolved that according the FDA guideline these two profiles were accepted as similar.

Conclusion

Three general approaches to compare dissolution profiles were examined; they are statistical, model dependent and model independent

approaches. This study was planned with the intent to investigate several methods, to gain familiarity with the numerical results, and to evaluate advantages and disadvantages of those methods. It is evident from the pharmaceutical literature that no single approach is widely accepted to determine if dissolution profiles are similar.

The application and evaluation of model dependent methods and statistical methods are more complicated. While the model dependent methods present an acceptable model approach to the true relationship between the dependent and independent variables the statistical methods includes post hoc procedures for the comparison of the dissolution data. The disadvantages of the model independent methods are, the values of f_1 and f_2 are sensitive to the number of dissolution time points and the basis of the criteria for deciding the difference or similarity between dissolution profiles is unclear. The limitation is that, only when the within-batch variation is less than 15%, f_2 equation should be used.

Summary

In vitro dissolution has been recognized as an important test in drug development process to find an in vitro characteristic of the formulation that reflects its in vivo performance. Immediate release solid dosage forms are routinely subjected to tests which shows the pharmaceutical quality such as content, uniformity of content, weight, hardness, friability, disintegration and dissolution test. The dissolution test is the most important one that exhibits the biopharmaceutical quality.

The immediate release gliclazide tablet formulation was prepared by direct compression method and the dissolution profile of this formulation was compared with reference formulation (Diamicron® lot no:8A0799). In this study, three general approaches to compare dissolution profiles were examined, they were statistical methods, model dependent and model independent approaches.

Key Words : Gliclazid, dissolution profile comparison methods, statistical methods, model dependent methods, model independent methods

Özet

Hemen Salım Sağlayan Gliklazid Tablet Formülasyonlarının İn Vitro Dissolüsyon Profillerini Karşılaştırma Yöntemlerinin Değerlendirilmesi

İn vitro çözünme testi, ilaç geliştirme sürecinde formülasyonun in vivo performansını yansıtacak bir in vitro özelliğinin bulunmasında önemli bir test olarak bilinmektedir. Hemen salım sağlayan dozaj şekilleri rutin olarak miktar tayini, içerik tekdüzeliği, ağırlık, sertlik, ufalanma aşınma, dağılma ve çözünme testi gibi farmasötik ürün kalitesini gösteren testlere tabi tutulmaktadırlar. Çözünme testi biyofarmasötik kaliteyi gösteren en önemli testtir.

Hemen salım sağlayan gliklazid tablet formülasyonu direkt basım yöntemi ile hazırlandı ve bu formülasyonun çözünme profili referans formülasyon ile karşılaştırıldı (Diamicron® lot no:8A0799). Çalışmada çözünme profillerinin karşılaştırılmasında kullanılan üç genel yöntem araştırıldı, bunlar istatistiksel yöntemler, modele bağımlı yöntemler ve modelden bağımsız yöntemlerdir.

Anahtar Kelimeler : Gliklazid, çözünme profili karşılaştırma yöntemleri, istatistiksel yöntemler, modele bağımlı yöntemler, modelden bağımsız yöntemler

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