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IN VITRO DISSOLUTION PROFILE COMPARISON: A TOOL FOR BIOWAIVERS BASED ON BCS

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ABSTRACT

Dissolution testing has been recognized as an important tool in drug development and assessment of quality of pharmaceutical products both in case of novel drug product and interchangeability drug products. *In vitro* dissolution testing is one of the primary United States Pharmacopoeia/National Formulary (USP/NF) test, which is performed to ensure that a drug product meet the USP/NF standards of identity, strength, quality, purity, stability and bioequivalence in case of interchangeable drug products. *In vitro* dissolution profile comparison of drug release can be used as a surrogate in formulation development and *in vivo* bioequivalence testing. The comparison of dissolution profiles is considered to be critical test for assessing the performance of a drug product. In the present study, *in vitro* dissolution profile of two in-house batches, containing Biopharmaceutical Classification System (BCS) class 1 API (Zidovudine) was compared with reference product (Retrovir) by model independent approach to meet the requirements for biowaiver. Batch 2 of in-house formulation is considered to be similar to reference product and could be interchangeable.

Keywords: *Biopharmaceutical classification system; biowaivers; in vitro dissolution profile comparison.*

INTRODUCTION

The dissolution test for oral solid dosage forms was first introduced in *United States Pharmacopoeia (USP)* 18 in 1969. *In vitro* dissolution has been recognized as an important tool both in drug development and quality assessment of the pharmaceutical dosage forms[1]. During the development of a medicinal product, dissolution test is utilized as a tool to identify critical formulation factors influencing the bioavailability of the drug. As soon as the composition and the manufacturing process are defined, dissolution test is used in the quality control for scale-up and to ensure both batch-to-batch consistencies. Furthermore, in certain instances a dissolution test can be used to demonstrate bioequivalence[2]. The various applications of *in vitro* dissolution have been outlined in Figure 1.

Drug absorption from solid dosage forms after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. In such situation, *in vitro* dissolution testing is act as tool used to measure drug release rates and further solubilization of drug in dissolution media. Because of the critical nature of the first two steps, *in vitro* dissolution may be relevant to the prediction of *in vivo* performance[3]. If an active substance is of BCS class 1 drug it is reasonable to expect that it will not cause any bioavailability problem (Table 1).

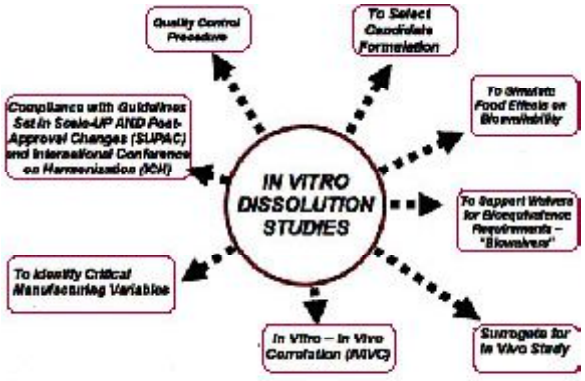

Fig 1. *Applications of in vitro dissolution studies.*

Table 1. *Biopharmaceutical Classification System of drugs*

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

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The bioequivalence study (in which the rate and extent of drug absorption in humans is evaluated) for BCS class 1 drugs may be waived based on the case history and similarity of dissolution profiles. The similarity should be justified by dissolution profile comparison by model independent method using mathematical indies to define similarity factor f2, covering at least three time points, using three different buffers[4]. Provision for waivers of *in vivo* bioavailability/ bioequivalence (BA/BE) studies (known as biowaivers) under certain conditions have been provided under FDA guidelines (21 CFR 320.22)[5]. Therefore, for the approval of generic drugs, *in vitro* dissolution testing becomes a potential surrogate for *in vivo* bioequivalence and used for achieving biowaivers, rendering BA/BE studies unnecessary[4].

Two in-house batches of solid oral dosage forms were formulated using different techniques (containing zidovudine, BCS class 1 active pharmaceutical identity (API)) along with reference formulation. In the present study, the *in vitro* dissolution profile of two in-house test formulations have been compared with the reference formulation in order to obtain a biowaiver as per FDA requirement.

Experimental

Materials

Two batches of solid dosage formulations of test product (in-house preparation) and reference formulation (Retrovir, Glaxo SmithKline, obtained directly from the manufacturers through direct representative) containing zidovudine were studied.
Methanol HPLC grade, acetic acid and hydrochloric acid were of analytical grade and were used as received. All other solvents and reagents were of analytical grade or equivalent. Deionised water was used in preparation of all test media; the three dissolution media employed were 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8. These media were selected based on the FDA Guidance for Industry and the need to meet the criteria for biowaiver [5]. Dissolution was carried out using Dissolution Apparatus, Distek 2100 series, with six vessels of 1-L capacity each.

Methods

The dissolution method under investigation employed compendia conditions with USP Apparatus II (Paddle) at a rotation speed of 75 rpm in a various medium ranging from water, 0.1N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8. The sampling time points of 10, 15, 20 and 30 were used to support all phases of clinical development and stability. Dissolution of twelve tablets was carried out (six tablets at a time) in vessels, each containing 900 mL of the dissolution media. The dissolution media was maintained at 37±0.2 ºC. The sample (10 mL) withdrawn was replaced with equal amount of fresh media. The concentration and quantity of the active pharmaceutical ingredients of each sample were determined using HPLC determination (High Performance Liquid Chromatography, Agilent 1100 and 1200 series, USA).

For data analysis, the Empower software was used to program the HPLC and to acquire and process the primary data. Excel (Microsoft Corp., USA) was used to calculate the percent dissolved of the active pharmaceutical ingredients (APIs) for twelve individual tablets, and the mean and standard deviation were obtained.
The similarity of the dissolution profiles was determined using the similarity factor, f2. The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) of dissolution between the two curves.

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

Two dissolution profiles are considered to be similar when the f2 value is greater than 50 and dissimilar when less than 50[5].

RESULT AND DISCUSSION

FDA Guidance for biowaiver for immediate-release solid oral dosage forms states that "*a product is said to be rapidly dissolving when not less than 85% of the labelled API dissolves within 30 minutes*"[5]. The API (Zidovudine) in test formulation showed almost complete dissolution in the 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer including water (with in 30 min), however it appears that pH 4.5 favoured the dissolution slightly more than the other medias (Table 2).

Table 2: *In vitro dissolution profile of batch 1.*

Time% (min)	API Release(ref)	RSD (ref)(n=12)	% API Release (test)	RSD (test)(n=12)
Media - Water				
10	80	2.0	74	3.0
15	85	4.8	76	5.2
20	92	3.2	80	2.8
30	95	2.7	83	5.2
F2 =49				
Media - 0.1N HCl				
10	83	1.2	63	2.6
15	89	3.4	76	4.0
20	95	4.5	83	2.2
30	97	1.8	86	3.0
F2 = 42				
Media - pH 4.5 acetate buffer				
10	85	1.9	76	3.0
15	91	1.4	80	2.8
20	93	2.7	83	1.9
30	99	2.9	90	3.2
F2 = 50				
Media - pH 6.8 phosphate buffer				
10	82	4.2	75	3.8
15	85	4.8	79	5.8
20	91	5.2	83	3.9
30	100	2.2	90	3.7
F2 = 55				

IN VITRO DISSOLUTION

As evidenced from Table 3, the batch 2 can be said to be rapidly dissolving. FDA Guidance on dissolution testing of immediate-release solid oral dosage forms states that for highly-soluble and rapidly dissolving drug products (BCS classes 1 and 3), more than 85% dissolution in 0.1N HCl in 15 min can ensure that the bioavailability of the drug is not limited by dissolution[3]. In such cases; the rate-limiting step for drug absorption is gastric emptying, as in the case of BCS class 1 APIs[6]. A drug product undergoing more than 85% dissolution in 15 min in 0.1 N HCl behaves like a solution and generally should not have any bioavailability problems[2]. Batch 1 released around 75% of API in the three media in 15 min; however the batch 2 of formulation release is about 90% of same API in 15 min in all media(s). A comparison of the *in vitro* dissolution profiles of the two in house batches in all different media(s), with that of reference formulation has been shown in Figures 2-3.

Table 3: *In vitro dissolution profile of batch 2.*

Time(min)	% API Release (ref)	RSD(ref) (n=12)	% API Release (test)	RSD(test) (n=12)
Media - Water				
10	89	3.5	82	2.8
15	97	4.9	88	5.3
20	100	5.9	91	3.9
30	102	4.6	94	4.7
Dissolution ≥ 85% in 15 min; F2 not required (similar dissolution profile)				
Media - 0.1N HCl				
10	91	3.8	81	2.8
15	97	5.1	89	1.8
20	101	3.9	93	4.2
30	102	2.3	95	3.7
Dissolution ≥ 85% in 15 min; F2 not required (similar dissolution profile)				
Media - pH 4.5 acetate buffer				
10	88	3.2	85	1.9
15	97	3.8	90	4.1
20	101	4.0	93	5.2
30	103	1.7	94	3.7
Dissolution ≥ 85% in 15 min; F2 not required (similar dissolution profile)				
Media - pH 6.8 phosphate buffer				
10	84	2.9	82	2.9
15	94	3.1	88	3.4
20	98	2.2	91	4.1
30	101	3.0	94	2.8
Dissolution e"85% in 15 min; F2 not required (similar dissolution profile)				

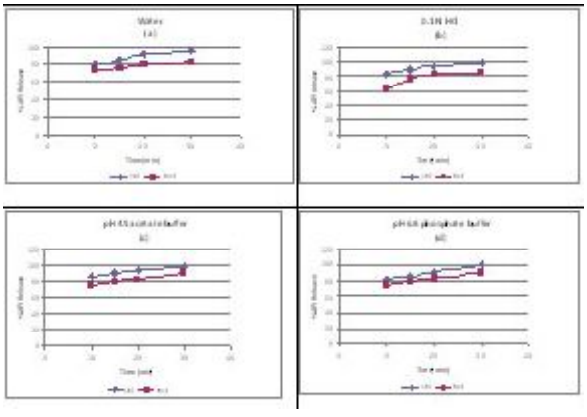

Fig. 2: *Comparative mean dissolution profile of test and reference in different dissolution media(s) (batch 1).*

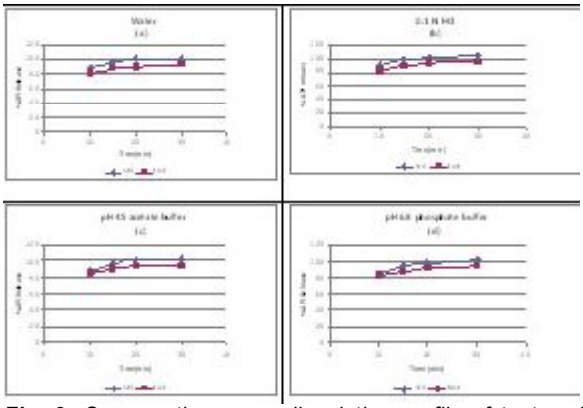

Fig. 3: *Comparative mean dissolution profile of test and reference in different dissolution media(s) (batch 2).*

In some instances, the dissolution result indicated more than 100% release, which is a reflection of the overage of APIs in the product and is in agreement with the assay result of the products from the same batches.

The f_2 was calculated to determine similarity between batch 1 of test formulation with that of reference formulation in all medias (water, 0.1N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8). Subsequently, f_2 was not determined for the comparison of products with more than 85% release of API in 15 min because they were established to be very rapidly dissolving. That's why, in case of batch 2, f_2 was not calculated. The values 49, 42, 50 and 55 were obtained, respectively, for API release, indicating lack of similarity of these products in 0.1N HCl (Table 2).

Bioequivalence indicates that the rate and extent of absorption of two or more similar dosage forms containing similar amounts of the same drug do not differ significantly. The batch 2 formulation is chemically equivalent because it contains API (Zidovudine) at the same label strength as that of reference formulation. In case of batch 1, the dissolution characteristics of test product are different from reference formulation. The batch 2 of formulation showed greater than 85% dissolution of API in 15 min in all the medias (0.1N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8) and can be classified as very rapidly dissolving products, and can be considered to have similar dissolution characteristics, and assumed to be bioequivalent to reference formulation (being BCS class 1 API). By contrast, batch 1 did not meet all the criteria for a rapidly-dissolving product, and f2 analysis showed that dissolution of the API (Zidovudine) from batch 1 is dissimilar to that from reference formulation (Retrovir).

Therefore, it can be concluded that batch 2 formulation and reference formulation may be used interchangeably; however batch 1 can not be used interchangeably.

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