In Vitro/In Vivo Correlation for Acyclovir Immediate-Release Tablet Formulations Based on Computational Simulation Program

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Abstract:

Purpose: The purpose of this study was to stimulate the drug release and absorption *in vivo* using a novel *in vitro* system which mimics the gastro-intestinal tract in man and establish a level A *in vitro/in vivo* correlation (IVIVC) and develop drug-specific absorption model to predict the bioavailability of acyclovir 800mg immediate release formulation. **Methods:** The *in vitro* dissolution behaviors and *in vivo* absorption characteristics in different dissolution and artificial digestive system media were used to estimate the availability of acyclovir raw materials, commercially available products, three different formulations and reference products. *In silico* prediction for the correlation of immediate release formulation and IVIVC analysis was evaluated for overall absorption kinetics of acyclovir. **Results:** The results of this study clearly revealed that a dissolution specification for acyclovir, a BCS Class III compound, of 85% drug release in 30 minutes under BCS-conform conditions would result in comparable pharmacokinetic parameters, indicating bioequivalency of these products and permeability-limited absorption. **Conclusion:** The acyclovir 800mg formulation from IVIVC criteria and dissolution profile applied to BCS Class III drugs with similar absorption pattern, provided that any influence of excipients and/or the manufacturing process on the permeability could be excluded. Therefore extension of biowaiver concepts to immediate release drug products containing acyclovir thus seems to be feasible and appropriate, assuming that product selection of excipients is made.

Key Words: Acyclovir, Immediate Release, In vitro-in vivo correlation (IVIVC), BCS

Introduction

The first regulatory guidance for studying bioavailability and bioequivalency of new drug products was published by FDA in 1977.[1-4] The *in vitro* dissolution tests as a surrogate for in vivo bioequivalence studies was introduced with the biopharmaceutical classification system (BCS) in 1995 [5] and reviewed in 2000. [6] The FDA published regulatory guidances for *in vitro-in vivo* correlations (IVIVC), and regulatory authorities in Europe followed suit in 2000 [3-7] to reduce the need for *in vivo* bioequivalency studies. In 2000, the USFDA launched the Guidance for Industry, 'Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage form based on a biopharmaceutics classification system [8]. In addition, in 2001, the Committee for Proprietary Medicinal Products (CPMP) released the 'Note for guidance on the investigation of bioavailability and bioequivalence [9] biowaivers can only be requested for drug substances belonging to BCS Class I (highly soluble-highly permeable) housed in rapidly dissolving immediate release products, i.e., more than 85% of active ingredient is dissolved within 30 minutes. Later, the European regulatory authority, EMEA, followed with a set of guidelines of similar principles [4].

The acyclovir drug is an effective agent in the therapy of herpvirus infections in both immuno-competent and immuno-compromised patients.[10-17] Acyclovir is the first line option for

treatment and prophylaxis of herpes simplex virus (HSV) [15-18] and varicella zoster virus (VLZ) infections.[18-22]

Acyclovir is commonly used as the free acid form in solid dosage forms, where as the sodium salt is used in parenteral dosage form [24-25]. Valayclovir, the L-valyl ester of acyclovir, has been used orally to increase its bioavailability. [26-29] Several dipeptide ester prodrugs are being tested to assess their usefulness in therapeutics. Acyclovir is normally present in a hydrated form consisting of three acyclovir molecules to two molecule of water, corresponding to a theoretical water content of about 5%, but dose and solubility are normally expressed in units of anhydrous acyclovir. [23, 31] A stable anhydrous form can be obtained by drying hydrated acyclovir at temperature above 150 ^{0}C [31]. Although only slight and insignificant differences in solubility values exist between these two forms, the anhydrous form of the acyclovir possesses poorer dissolution properties than the hydrated form [32]. Acyclovir is described as "slightly soluble in water" in different pharmacopoeias [23-24, 30-32]. The partition coefficient (log P) in n-octanol at 22^{0}C is -1.57. [32]. Acyclovir is an ampholyte with both week acid and basic groups. The pK$_a$ values for acyclovir are 2.16 and 9.04 at 37 ^{0}C. [30-32]

Absorption of oral acyclovir across the small intestine appears to be passive and is incomplete, resulting in 15-30 % bioavailability and mean peak plasma concentrations 1.5 to 2.5 hours post dose.[33-35] The pharmacokinetic disposition of the drug is not affected buy dose, duration or frequency of administration. Plasma protein binding occurs in a range of 9 to 33%, irrespective of plasma concentrations. Acyclovir appears to be distributed to a wide range of tissues and fluids in human after oral and intravenous administration. The elimination half-life of acyclovir after intravenous administration is 2 to 3 hours. [37-38] The main metabolite of acyclovir, 9-carboxymethoxymethy guanine, is pharmacological inactive. The main route of elimination of acyclovir is via renal excretion, with 45 to 79% of an intravenous dose recovered unchanged in the urine, which decreases with reduced creatinine clearance. The renal impairment affects the plasma concentrations, extent of metabolism and rate of elimination of the drug. [38-39]

This report emphasized on appraisal of the biopharmaceutical characteristics of the BCS Class III drug, acyclovir, by determining the relationships between in vitro dissolution properties and in vivo absorption behavior obtained following oral administration of three different acyclovir tablet formulations with a broad spectrum of release patterns. Also, *in silico* determination using computer programs was performed to simulate drug absorption patterns *in vivo*.

Materials and Methods

Materials

The ingredients used for test tablet formulations were: acyclovir raw materials, micro-crystalline cellulose (Avicel® PH101), sodium starch glycolate, lactose, purified talc, magnesium stearate and sodium lauryl sulfate, FD&C Blue No. 2, titanium oxide, methacrylate copolymer (retarding agent) and reference product was reference product (Zovirax® 800mg IR tablet).

Methods

Acyclovir pure drug substance

The pH solubility and dissolution test of acyclovir pure raw materials were investigated in various buffer media in quadruplicate e.g., 0.1 N HCl (pH 2.2), pH 1.2 in SGF$_{sp}$ (simulated gastric fluid without enzymes), phosphate buffer pH 4.5, pH 6.8 in SIF$_{sp}$ (simulated Intestinal fluid without pancreatine) and deionized water (pH approx. 5.5) for fasted study evaluation according to the BCS criteria within different physiological conditions (pH range) of the gastrointestinal tract. Analysis of acyclovir concentration was conducted at 0.5,1.0,1.5,2.0,3.0,4.0,6.0,8.0,10.0,12.0 and 24.0 hours using UV-spectrophotometric method

against the calibration curve at the wavelength of 260 nm. Dissolution testing of acyclovir raw material was performed using USP Apparatus II (paddle method) with the revolution of 50 rpm at 37 ± 5^0C and aliquots were collected at 15, 30, 45, 60 and 90 minutes respectively.

Commercially available Acyclovir 800mg IR Products

The dissolution behaviors of ten commercially available acyclovir 800mg tablet products in different zones of the India were selected and evaluated for their release patterns and whether they were fall within the "rapidly dissolving" range of the BCS criteria [8-9]. The dissolution and disintegration test (12 tablets in each products) were conducted by using USP Apparatus II with dissolution media 0.1 N HCl (pH 2.2), pH 1.2 in SGF_{sp}, pH 4.5 phosphate buffer and pH 6.8 in SIF_{sp} representing acidic and basic environment in accordance with human GI physiology, respectively. The dissolution media volume was 900ml with a paddle agitation speed of 50 rpm at 37 ± 5^0C and aliquots were collected at 15, 30, 45, 60 and 90 minutes respectively and analyzed by UV spectromatrically method.

Acyclovir 800mg IR Tablet Formulations

The three acyclovir tablets formulations (0%, 5% and 10% retarding agent) comprising 800 mg of acyclovir with deliberately different release behavior ranging from "rapid enough to facilitate absorption" through to "slow enough to retard or even possibly reduce absorption" in various conditions in physiological GI tract environment were manufactured by means of direct compression technique. The qualitative compositions of these three formulations were same, but the release-controlling variable(s), e.g., the amount of excipients, or a property of the drug substance such as particle size, was varied. The physical properties, weight variation, thickness, diameter and hardness test of tablet formulations were conducted in accordance with the current compendial criteria [22]. The friability and content uniformity of formulated tablets was determined based on the USP 27 [23].

The disintegration and dissolution testing (12 tablets of each product) of three acyclovir tablet formulation and reference product (Zovirax® IR 800mg Tablets) were performed using USP Apparatus II (paddle method) with the revolution of 50 rpm in 0.1 N HCl (pH 2.2), pH 1.2 in SGF_{sp}, pH 4.5 phosphate buffer and pH 6.8 in SIF_{sp}, in order to evaluate the dissolution behavior of pure drug substance without the effect of inactive ingredients at 37 ± 5 ^{0}C. The disintegration test was performed by USP apparatus for 30 minutes and dissolution test by using different medium volume 900ml with a paddle agitation speed of 50 rpm at 37 ± 5^0C and aliquots were collected at 15, 30, 45, 60 and 90 minutes respectively and analyzed by UV spectromatrically method. The dissolution profile of three acyclovir tablet formulations and reference product in various dissolution media were compared in accordance with the model independent approach recommended by USFDA[40] using a difference factor ($f_1 < 15$) and a similarity factor ($f_2 > 50$) respectively. [40]

In Vivo **Bioavailability Study**

Study Design

The study was designed as a single dose, four-treatment, randomized, and four-period crossover comparative bioequivalence study of three test formulations and reference product (Zovirax® IR 800mg Tablet) under fasting conditions with washout period of 07 days between two phases. [41] Six volunteers for each group were selected based on clinical laboratory measurements, physical examinations, and medical drug history was performed during screening. Another group of six subjects were selected based on above criteria for intravenous administration (500mg/ml) of

acyclovir reference product (Zovirax®) for evaluation of bioavailability and comparative rate and extent of absorption of the acyclovir tablet formulations.

The study protocol was approved by the institutional ethics committee and study was conducted in accordance with good clinical practice and the declaration of Helsinki 2008. All subjects were attended a briefing session conducted by the investigator where the details of the study and elements of informed consent were explained. Each subject had an opportunity to ask questions and signed an informed consent statement, properly witnessed, prior to participation in the study. All subjects were fasted overnight at least 10 hours before administration of test formulations or reference product (both tablet and injection) with 240 mL water as per randomization schedule. All subjects were fasted 4 hours after drug administration. The vitals signs were measured at pre-dose and 1.0, 3.0, 4.0, 6.0 and 12.0 hours post dose were assessed for general clinical safety of the drug. Blood samples were collected at pre-dose and 0.33, 0.67, 1.0, 1.25, 1.50, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 24 hour post dose administration. The blood samples were centrifugation at 4000 rpm for 10 minutes and plasma was separated and stored at −20 ± 5°C until analysis. [42-50]

Chromatographic Conditions

The analytical method used for determination of drug concentrations in in vitro plasma samples was a validated LC-MS/MS liquid chromatography method.[32-37] The assay method involves a solid phase extraction and chromatographic separation on a Hypersil GOLD C_{18}, 4.6 x 50 mm, 5μi.d (Thermo Electron Corporation) column using a gradient detection. The 500 μL of human plasma, 20 μL internal standard (ganciclovir) working solution (1.00ng/mL in diluents water: methanol, 50:50v/v) were added and samples were vortexed for 15 seconds and stored in a refrigerator for about 10 minutes. The samples were centrifuged at 10000 rpm and 10 ^{0}C for 30 minutes and the clear upper layer was transferred into vials and an aliquot were injected into LC-MS/MS system for analysis. [36-39]

Pharmacokinetics and Statistical Analysis

Pharmacokinetic parameters, i.e., AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, MRT and $t_{1/2}$ were estimated from plasma acyclovir concentration-time data by using WinNonlin® software program. The 90% confidence intervals for the estimates of the difference between the test formulations and reference product and least squares means for the pharmacokinetic parameters (AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) were calculated by two one-sided t-test procedure using SAS software program for meet the bioequivalence acceptable ranges (80-125%) respectively.[29-30] The multiple comparison of PK parameters of different acyclovir test formulations and reference product (both tablet and injection) were conducted by using LSD method at 5% level of significance.[30, 38-41]

In Vivo-In Vitro Correlation (IVIVC)

The mean fraction of acyclovir dissolved (Fd) and mean fraction of acyclovir observed (Fa) were calculated by numerical deconvolution method using WinNonlin® software program for IVIVC analysis of acyclovir test formulation and reference products. The IVIVC analysis for immediate release formulations with dissolution rate-limited absorption and complete absorption was expected to exhibits level A plot with slop of one and zero intercept.[39-40] The acceptable average percent prediction error for level A IVIVC model was acceptable at less than 10% but percent prediction error of each formulation should not be exceeding 15% respectively. [42-45]

Furthermore correlation of immediate release formulation and IVIVC analysis, in vitro-in vivo relationships (IVIVR) was evaluated for overall absorption kinetics of acyclovir.[7, 35] This analysis determined the *in vitro* dissolution- *in vitro* absorption relationship regardless whether linear correlation was obtained by simulation techniques. *In silico* prediction of acyclovir

absorption was performed using two computational simulation PK-Slim[®] software program for prediction of acyclovir absorption patterns were compared and evaluated between test formulations and reference products. The permeability data of acyclovir through Caco-2 monolayer model were obtained from the literature. [36-37, 45-49]

Results

Acyclovir pure drug substance

Acyclovir is an ampholytic (both weak acid and basic groups) drug and solubility of acyclovir is dependent on its ionization constant and the pH of the environment. Since the pKa of acyclovir was reported as 2.27 and 9.04 at 37 [0]C. [21, 50-51] The pH-solubility in deionized water at 37 [0]C showing the solubility to vary slightly with pH, with a lowest solubility of 2.4 mg/mL at pH 5.5 at 37 [0]C.[51, 52] The acyclovir concentrations values evaluated dose to solubility (D:S) ratio of 250 ml upto 24 hours and were higher than 3.5 mg/ml, while the lowest aqueous solubility determined in the pH range 1-7.8 at 37°C was found as 2.4 mg/ml confirming that acyclovir solubility was more in acidic medium pH conditions as anticipated in the upper GI tract. [1, 22]

Commercially available Acyclovir 800mg IR Products

The dissolution and disintegration behaviors of all commercially available acyclovir 800mg tablet products dissolved quicker in both 0.1 N HCL and SGF$_{sp}$ medium, which was more than or equal to 85% of drug substance is released within 30 minutes.[8, 9] The results indicating that permeability, rather than dissolution properties of the acyclovir products in acidic medium and were rate determining step to overall drug absorption. The solubility was possibly because of the component of micro-crystalline cellulose and magnesium stearate composed in the tablet formulations as well as the physical appearance of tablets facilitating their rapidly dissolving properties.[8,9]

Acyclovir 800mg IR Tablet Formulations

The physical properties like tablet hardness, weight and drug content of different acyclovir tablet formulations shows that the easier the compression where higher retarding agent was used. More flowability and consistent in hardness values was observed in higher strength of retarding agent (10%) used among other tablet formulations. The tablet weight values obtained and acyclovir content uniformity in all three tablet formulations were consistent and within the acceptance range. [22]
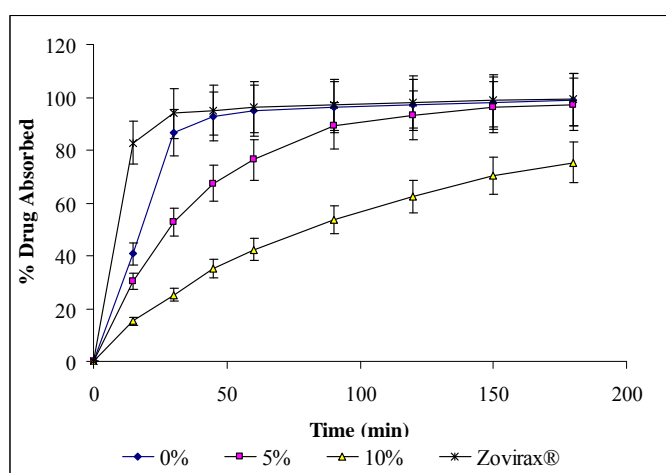

Figure 1. Release profiles of acyclovir tablets formulation in 0.1 N HCl. Each data represents mean ± SD of twelve determinations (n = 12).

The release profile of different acyclovir tablet formulations and reference products in 0.1 N HCl (pH 2.2) and pH 1.2 in SGF$_{sp}$ medium are shown in Figures 1 and 2 respectively. The dissolution and disintegration results exhibited that the release profiles of each tablet formulation and reference product acquired were similar across the different dissolution medium indicating their robustness of release characteristics in the different conditions extent in the upper GI tract environment.[1] The similarity of dissolution patterns obtained was interpreted by the physicochemical properties of acyclovir itself. The significance of the differences in dissolution profiles obtained was confirmed by the model independent approach, one of the dissolution profile comparison methods recommended by the US FDA.[23] Based on the model independent approach, acyclovir tablet formulation (without retarding agent) dissolution profile when compared with reference product (Zovirax®) shows similarity profile (f$_1$<15) in all media and dissimilarity profile (f$_2$ >50) in 0.1 N HCL and SGF$_{sp}$ medium. The results shows that this tablet formulation exhibited dissolution characteristics that have borderline similarity to those of reference product as per USFDA and CPMP criteria i.e. 85% of acyclovir was dissolved within 30 minutes. [8,9] However, the 5% and 10% retarding agent containing tablet formulations failed to meet the BCS criterion of 85% dissolution in 30 minutes. [8,9]
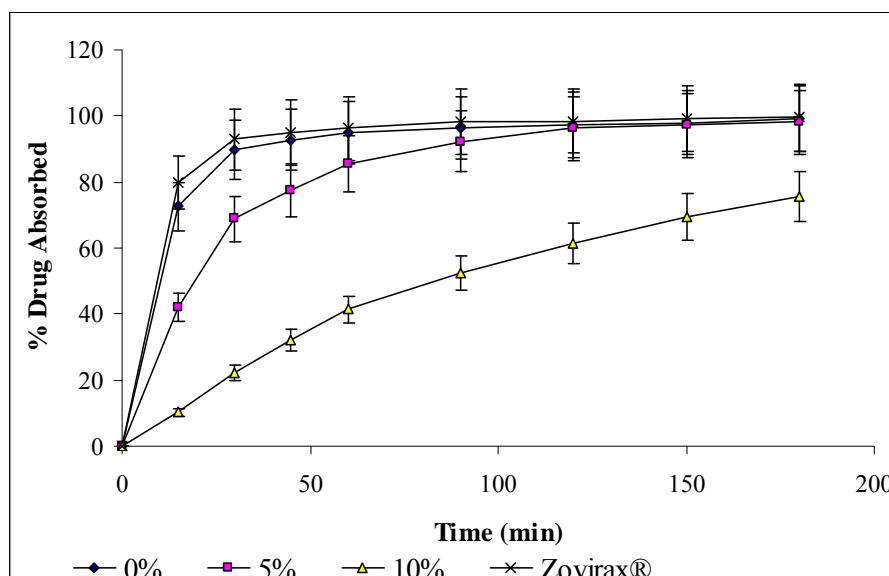

Figure 2. Release profiles of acyclovir tablets formulation in SGF$_{sp}$ medium. Each data represents mean ± SD of twelve determinations (n = 12).

Comparative bioequivalence study of acyclovir tablets
Three acyclovir test formulations and reference product were administered to healthy Indian male subjects (six subjects in each group) in a four-way cross-over design on separate occasions for evaluating bioavailability study. All subjects were completed all periods of the study and no serious adverse events and no clinical significant changes in vital signs, clinical laboratory variables or physical examination findings were observed in fasting study. [52-55]

Pharmacokinetic parameters determination
The mean plasma acyclovir concentration-time profiles after single oral dose administration of acyclovir tablet formulations and reference product are shown in Figure 3 and mean values of AUC$_{0-t}$, AUC$_{0-\infty}$, C$_{max}$, T$_{max}$, K$_{el}$ and MRT are shown in Table I respectively. The mean T$_{max}$, t$_{1/2}$

and MRT ranges of three acyclovir test and reference product were ranged from 1.88 to 1.58 h, 6.410 to 5.179 h and 5.17 to 4.48 h respectively. The mean C_{max}, AUC_{0-t} , and $AUC_{0-\infty}$, values of three acyclovir test and reference product were ranged from 1258.12 ng/mL to 1013.12 ng/mL, 5292.13 to 4929.87 ng.hr/mL, and 5692.13 to 5129.87 ng.hr/mL respectively. The bioavailability of acyclovir intravenous administration was compared with the different test and reference formulations and reference product. The results based on multiple comparison methods shows that 10% retarding containing test formulations was significantly ($p<0.05$) longer ($t_{1/2}$) and shorter (C_{max}) than the other test formulations and reference product. The statistical data of pharmacokinetic parameters of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are summarized in Table II. The results shows that the 90% confidence intervals of the C_{max} obtained from 10% retarding agent test formulations lies outside and AUC_{0-t} and $AUC_{0-\infty}$ were within the acceptable range of 80-125% that of the reference product. However, 90% confidence intervals other two formulations AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} parameters were shows similar plasma concentrations-time profile and lie within the bioequivalence determined range of 80-125%. Considering the biowaiver criteria indicated by the FDA and the CPMP for the BCS Class I drug products [8,9], by analogy to BCS Class III drug products, acyclovir test formulations (without and 5% retarding agent) and reference products were similar plasma drug concentration-time profiles and however, 10% copolymer acyclovir tablet formulation lie outside the bioequivalence determination limits. [53-55]

Table I. Mean pharmacokinetic parameters obtained following oral administration of Zovirax[®] tablets and acyclovir tablets formulated with various amounts of retarding agent

Parameters	Acyclovir tablets formulation with amounts Retarding agents			Zovirax® Tablets
	Geometric mean ± SD (CV%)			
	0.0%	5.0%	10.0%	
Cmax (ng/mL)	1258.12 ±152.34 (22.48)	1168.19 ± 142.39 (21.86)	1013.12 ± 159.68 (19.28)	1293.65 ± 164.51 (21.68)
AUC0-t (ng.hr/mL)	5292.13 ± 348.65 (25.69)	5092.54 ± 355.62 (23.99)	4929.87 ± 421.35 (24.19)	5217.32 ± 346.58 (24.16)
AUC0-inf (ng.hr/mL)	5692.13 ± 326.18 (27.53)	5392.54 ± 349.55 (24.53)	5129.87 ± 366.87 (26.44)	5517.32 ± 388.47 (28.45)
Tmax (hr)	1.88 ± 0.53 (17.58)	1.76 ± 0.51 (22.34)	1.58 ± 0.48 (22.35)	1.95 ± 0.63 (19.26)
Kel (1/hr)	0.155± 0.055 (25.25)	0.155 ± 0.067 (23.26)	0.134 ± 0.050 (27.78)	0.121 ± 0.048 (19.89)
t1/2 (hr)	5.889 ± 3.372 (22.56)	5.179 ± 1.982 (28.26)	6.410 ± 3.947 (21.57)	6.181 ± 4.233 (28.95)
MRT (hr)	4.48 ± 0.59 (18.75)	4.14 ± 0.62 (19.15)	5.17 ± 0.77 (22.15)	4.84 ± 0.67 (18.75)

Table II. Bioequivalence comparison of Zovirax® tablets and acyclovir tablets formulated with various amounts of retarding agent

Parameters	Mean % Ratio and 90 % confidence intervals (CI) between test and reference Acyclovir product					
	B/A		C/A		D/A	
	% Ratio	90% CI	% Ratio	90% CI	% Ratio	90% CI
Cmax (ng/mL)	104.12	92.74-106.41	99.95	82.35-106.85	75.16	75.71-131.38
AUC0-t (ng.hr/mL)	102.62	92.26-105.23	99.18	89.22–08.69	87.69	87.59-124.56
AUC0-inf (ng.hr/mL)	101.13	97.88-121.99	101.23	88.59-118.36	85.63	85.88-123.59

A= Zovirax[®] tablet; B= 7.5 % methacrylate copolymer tablets; C= 15 % methacrylate copolymer tablets; and D= 25 % methacrylate copolymer tablets
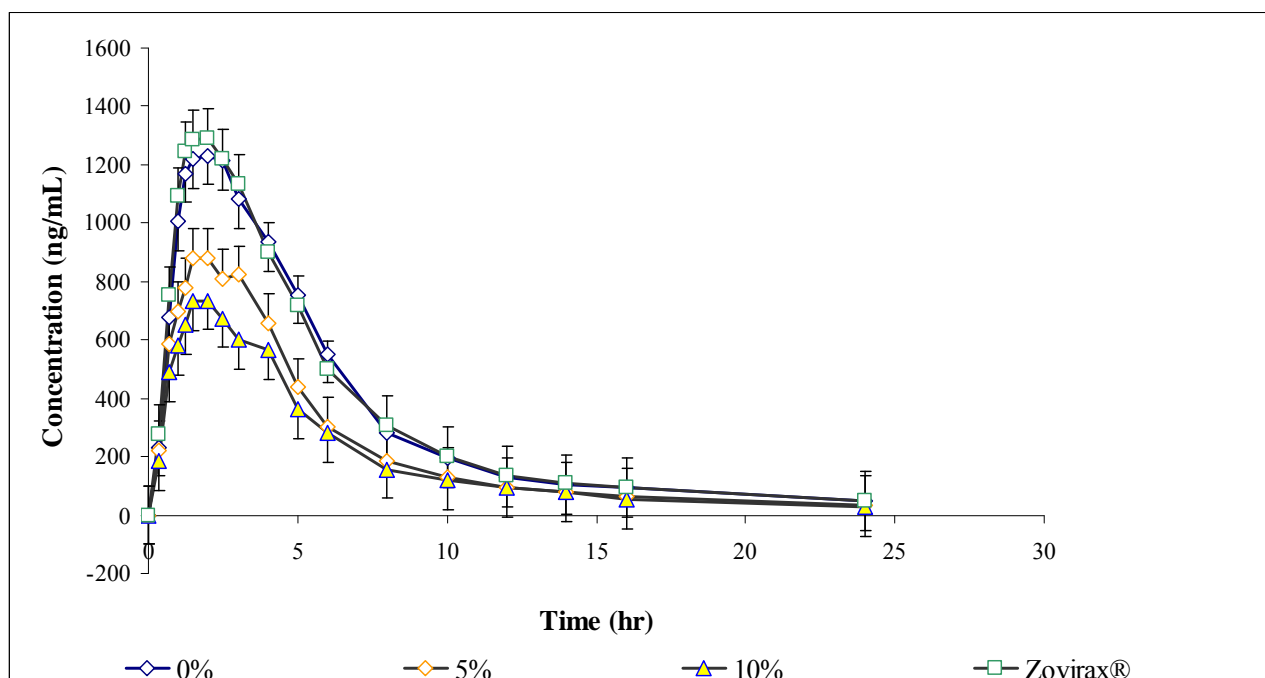
Figure 3. Comparison of plasma acyclovir concentration-time profile obtained following oral administration of Zovirax® tablets and acyclovir tablets formulation. Each data represents mean ± SEM of Six subjects.

In vitro-in vivo **correlation (IVIVC) analysis**
The dissolution to immediate release acyclovir products overall absorption kinetics and IVIVC analysis by correlating F_a and F_d values were calculated and applied to the pharmacokinetic data obtained. The average mean fraction of acyclovir observed values numerically deconvoluted from each plasma acyclovir concentration-time profiles gained after oral administrations of acyclovir products are illustrated in Figure 4. The fraction absorbed-time profiles and acyclovir release curves, the percentage values of F_a and F_d were correlated on the same time basis. [54-58] The comparison plots of mean F_a against mean F_d from each oral formulation are illustrated in Figure 5. The average percent prediction error for level A IVIVC model of three different test formulations and reference products were within the acceptable range (<10%) and each formulations (<15%), respectively.[42-45] The acyclovir tablet formulations (except 10% retarding agent) exhibited permeability rate-limited properties.
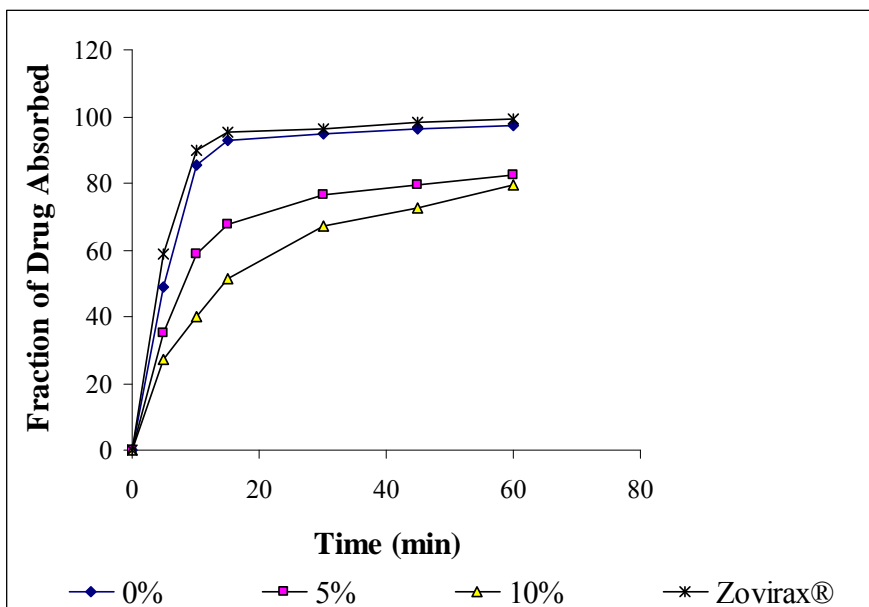
Figure 4. Fraction of acyclovir absorbed obtained by numerical deconvolution method after acyclovir administrations.   Each data represents mean ± SEM of 06 subjects.
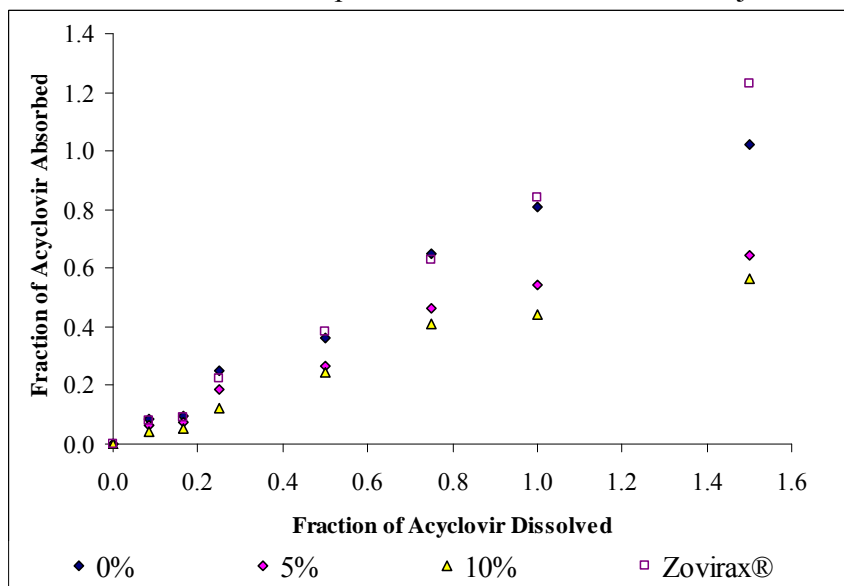

Figure 5. Plot of mean fraction acyclovir dissolved (n = 6) and mean fraction acyclovir absorbed (n = 6) obtained after administration of Zovirax® tablets and acyclovir tablets formulations.

The *In silico* prediction of acyclovir absorption was conducted and results were compared experimentally by GastroPlus® programs a physiologically based pharmacokinetic "whole-body" model to describe the GI absorption process and iDEA® program for acyclovir plasma profile simulation using PK-Sim® program. The physicochemical properties of acyclovir and human physiological parameters were collected and applied to the programs for interpreted the data and resulted in plasma profiles. The comparison of computational simulated and experimentally observed plasma acyclovir concentration-time profiles obtained from reference products containing different retarding agents are shown in Figure 6 and 7.A level A IVIVC with

specific time point estimation of reference product and three test formulations were established with a correlation coefficient (R^2) were 0.9998, 0.9862, 0.9745 and 0.9523, respectively.
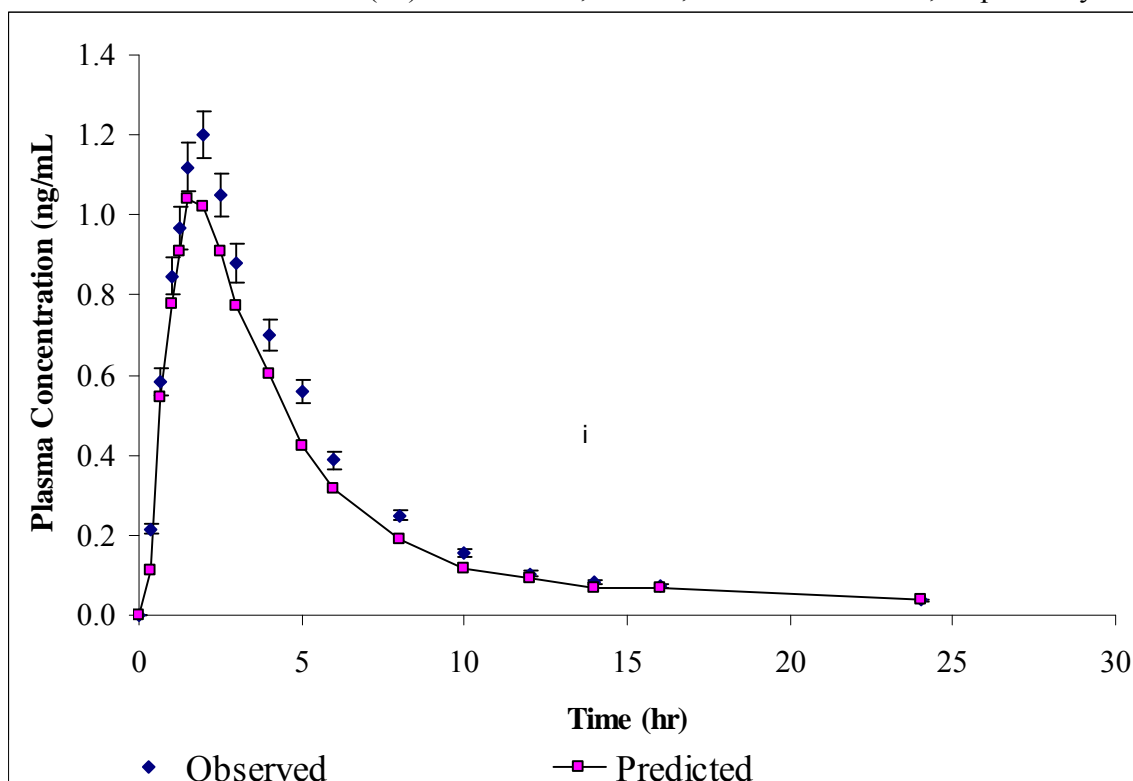

Figure 6. PK-Sim® predicted (-) and observed (•) plasma acyclovir concentration- time profile following oral administration of Zovirax® tablet.

The linear relationship (R^2 = 0.9523) of 10% retarding agent formulation indicating that this formulation dissolution was limiting to acyclovir absorption and significant differences between simulated and observed values were shown by the computational program can speculate tendency of the acyclovir product in humans effectively. The acyclovir solubility results both obtained from this study and from those reported in the literature as well permeability confirms the BCS Class III drug. The literature data of Caco-2 monolayer permeability studies [21] of acyclovir are shown the apparent permeability coefficient of about 1.19 x 10 cm/s [50] and partition coefficient data [56-61] suggested the low permeability. [7, 59, 561]
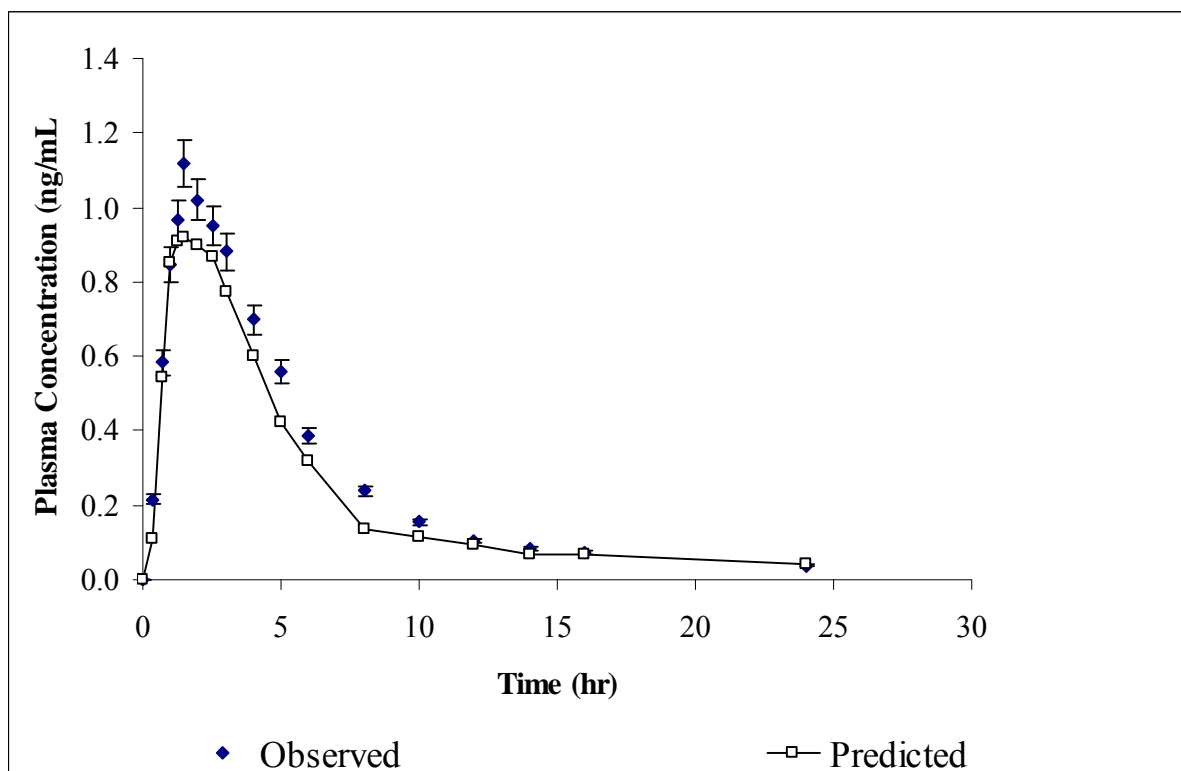
Figure 7. PK-Sim® predicted (-) and observed (•) plasma acyclovir concentration- time profile following oral administration of acyclovir tablet formulation without retarding agent.

The *in vitro* excipient interaction study using Caco-2 with sodium laurylsulphate shows a limited effect and no effluence on the absorption of acyclovir.[61] The permeability is the critical step in the absorption of the BCS Class III APIs, excipients that alter the GI motility and/or membrane permeation have the highest potential to affect the absorption. The results of this study clearly revealed that a dissolution specification for acyclovir, a BCS Class III compound,[62-63] of 85% drug release in 30 minutes under BCS-conform conditions would result in comparable pharmacokinetic parameters, indicating bioequivalency of these products and permeability-limited absorption. However, the formulations of immediate release solid oral dosage forms containing acyclovir 800mg seem to exhibit little risk in terms of bioequivalence.[58,64]

Conclusion

The results suggest that the new acyclovir 800mg formulation from IVIVC criteria and dissolution profile applied to other BCS Class III drugs with similar absorption pattern, provided that any influence of excipients and/or the manufacturing process on the permeability can be excluded. Therefore extension of biowaiver concepts to immediate release drug products containing acyclovir thus seems to be feasible and appropriate, assuming that product selection of excipients is made.

Acknowledgements

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