ORIGINAL ARTICLE

In vitro-in vivo Correlation for Poly (3-Hydroxybutyrate) Base Ibuprofen Extended Release Tablets

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Abstract

Aim: The aim of this study was to develop an *in-vitro-in-vivo* correlation (IVIVC) for two ibuprofen (IF) and extended release (ER) formulations and to compare their plasma concentrations. **Materials and Methods:** *In vitro* release rate data were obtained for each formulation using the USP apparatus 2, paddle stirrer at 100 rpm in pH 6.8 phosphate buffer. *In vitro* samples were analyzed using high performance liquid chromatography (HPLC) with ultraviolet detection, and *in vivo* samples were analyzed using a HPLC assay an additional model dependent approaches for different types of release rate of IF was prepared for evaluating the external predictability. **Results and Discussion**: A Higuchi model optimally fits the *in vitro* data. The similarity factor (f_2) was used to analyze the dissolution data. *In vivo* plasma concentrations and pharmacokinetic parameters in New Zealand rabbits were obtained after administering oral, Poly-β-hydroxybutyrate, and hydroxypropyl methylcellulose base ER formulations. A linear correlation model was developed using percent absorbed data and percent dissolved data from the two formulations. **Conclusion:** Linear regression analyses of the mean percentage of dose absorbed versus the mean *in vitro* release resulted in a significant correlation (r^2>0.95) for the two formulations.

Key words: *In vitro-in vivo* correlation, extended release, poly (3-hydroxybutyrate), ibuprofen

INTRODUCTION

There is generous interest in the development of biodegradable polymer like Poly-β-hydroxybutyrate (PHB) by environmentally efficient bacterial origin. This may help to solve trouble produced by synthetic or semi-synthetic polymer. Synthetic polymer may produce hazardous problem during formulation that produces the bioaccumulation in the body.[1] This accumulated trace of polymer creates health related problems. PHB are found functionally more and can be better for use in pharmaceutical formulations. This will help to improve pharmaceutical drug delivery of different therapeutic agent.[1] This biopolymer is effective tool to control or extend the drug release rate of pharmaceutical formulation. PHB is the biopolymer include in the formulation because of their thermoplasticity and biodegradability features.[2] It is considered as more environmentally friendly and sustainable method for obtaining the polymer. These improvements contribute to make the medical treatment more efficient and to minimize side effects and other type inconvenience for patients.[1-3]

This study was based on screening of biopolymer which would satisfy the rising demand of sustainable economic biopolymer production from bacterial genera. Screened PHB has found to be an optimistic role in biomedical applications and pharmaceutical drug delivery scenario. The variety of (semi) synthetic polymer available in market and these many synthetic polymers are being used nowadays in drug delivery systems synthetic polymers have certain disadvantages such as their high production cost, non-biodegradability, toxicity, and

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so it proven their impact on probability of bioaccumulation.[4] Such accumulation for long time hampers the human health. Hence, these demerits avoided by application of screened biopolymer candidate PHB as drug release retardant tool.[4]

The buildup of inflammatory processes may be regulated by systemic administration of anti-inflammatory preparations.[2] In certain cases, however, this approach is not efficient because the local concentrations of the drugs within the region of the implantation are either not sufficient for attaining the pharmacological effect or lack stability, whereas any further increase in the dose administered systemically entails side effects.[2] Systems of controlled release of drugs, based on polymer materials, make it possible to regulate the processes of inflammation, thrombus formation, and development of new tissue within the immediate vicinity of implantation of medical devices. In designing such systems, it is important to make the right choice of the drug.[2]

Ibuprofen (IF), a non-steroidal anti-inflammatory drug, inhibits cyclooxygenase, thereby preventing the synthesis of prostaglandins (which are major mediators of inflammation), and cell proliferation.[2] It is noteworthy that IF, as well as PHB, are soluble in organic solvents (chloroform and methylene chloride), which simplifies the technology of creating polymer systems of controlled release.[5,6] Thus, a technology for the biosynthesis of PHB with a defined MW is prerequisite to creating controlled release systems for the requisite characteristics of the kinetics of the drug release from the polymer matrix. The use of such systems for controlled release of anti-inflammatory drugs is expected to regulate inflammatory processes and the rate of the implant biodegradation and capsulation. In this work, we sought to obtain and study PHB based tablet incorporating IF.

A series of IF extended release (ER) formulations was developed using a release controlling polymer, poly (3-hydroxybutyrate). The pharmacokinetics and bioavailability of IF from these ER formulations were evaluated after a single dose in animal. Further optimization development of an ER formulation involving alterations in the manufacturing process, equipment, and batch sizes would require additional human studies to prove the bioequivalence of the final formulation. These refinements would delay product development and marketing of an ER formulation. It would be desirable to develop a relationship, referred to as an *in vitro-in vivo* correlation (IVIVC), to predict *in vivo* bioavailability of any refined formulation from *in vitro* dissolution data. Establishment of an *in vitro* dissolution test as a surrogate for human bioequivalence studies was explored in this study to support IF ER formulation development and regulatory submission.

Establishing a correlation between the *in-vivo* plasma concentration profile and the *in-vitro* dissolution profile of an ER formulation has been of great interest for a number of years. ER of drugs in the gastrointestinal tract following oral administration is the intended rate-limiting factor in the absorption process. It is, therefore, desirable to use *in-vitro* data to predict *in vivo* bioavailability parameters for the rational development and evaluation process for ER dosage forms.[7,8] The ultimate goal of an IVIVC should be to establish a meaningful relationship between *in-vivo* behavior of a dosage form and *in-vitro* performance of the same dosage form, which would allow *in-vitro* data to be used as a surrogate for *in-vivo* behavior. A meaningful IVIVC for ER dosage forms would be of benefit as a surrogate for bioequivalence studies which might typically be required with scale up or minor post-approval changes in formulation equipment, manufacturing process or in the manufacturing site. A meaningful IVIVC could lead to improved product quality and decreased regulatory burden.[9-11]

It is well known that *in-vitro* dissolution testing is a powerful and useful method for determining product quality. The utility of *in-vitro* dissolution as a surrogate for *in-vivo* bioavailability is very attractive and has been demonstrated for several products. Furthermore, to utilize this dissolution test as a surrogate for bioequivalence, the IVIVC must be predictive of *in-vivo* performance of the product. Levels A, B, C, and multiple level C correlation have been described in the US Food and Drug Administration (FDA) IVIVC guidance. The most useful of these is a level A correlation, which is described as a point-to-point correlation in which the *in vivo* percent absorbed curve is compared to *in vitro* percent dissolved curve. In general, these correlations are linear and are considered most informative and very useful from a regulatory viewpoint. The FDA guidance describes the methods of evaluation of prediction error internally and/or externally. Internal validation refers to how well IVIVC model describes the data used to develop the correlation. External validation determines how well the IVIVC model describes data that was not used in the development of the model.[10] Numerous IVIVC studies of sustained or ER formulations have been previously reported;[11-17] however, there is no any ER poly (3-hydroxybutyrate) base formulations in the markets.

MATERIALS AND METHODS

Materials

IF was received as a gift sample from Asoj Soft Capsules. poly (3-hydroxy butyrate) were synthesized, hydroxypropyl methylcellulose (HPMC) microcrystalline cellulose (Avicel) and Lactose was from Unique Biologicals, Kolhapur, India. All chemicals and solvents used were of analytical reagent grade. 03 New-Zealand white rabbits (2.5-3.2 Kg) used in this study were supplied from the animal house of Tatyasaheb Kore College of Pharmacy, Warananagar, India. Each adult New-Zealand white rabbits were divided into two groups; one was tested and another was control each consisting of three subjects.

Formulations

ER formulations of IF were developed using poly (3-hydroxybutyrate) as one of the release rate controlling excipients and included microcrystalline cellulose as filler, and magnesium stearate as lubricant.[18-21] Two ER tablets were designed to release IF using different polymers and referred to as test (PHB) and reference (HPMC) for the development of the IVIVC model. The compositions of these ER tablets are shown in Table 1. The formulations were designed to release IF and underwent for dissolution test and *in vivo* absorption studies.

Dissolution testing

Due to the limited solubility of IF in conventional pH 6.8 sodium phosphate media, 6% sodium lauryl sulfate was added in early method development studies employing 10-mesh USP baskets at 100 rpm to achieve sink conditions for the 200 mg IF drug product; the sodium lauryl sulfate concentration was subsequently reduced to 2% in later experiments in accordance with FDA guidance[15,22,23] to achieve greater biorelevance but without sink conditions. Dissolution tests were performed on six tablets and the amount of drug released was analyzed spectrophotometrically at a wavelength of 220 nm. The IF tablets were placed in 900 mL of sodium phosphate media and maintained at 37°C. Samples (5 mL) were collected each at an appropriate interval. Dissolution samples were collected at the following times: 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10, 12 and 24 h.[24] The mean and standard deviation of dissolved percentages were calculated.

In vitro dissolution data analysis

The dissolution profiles for each formulation were determined by plotting the cumulative percent of IF dissolved at various time points.[25,26] The *in-vitro* drug release profiles of the two ER dosage forms were compared using the similarity factor, f_2, presented in the following equation:[15]

$$f_2 = 50 \times \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_f \left|R_t - T_t\right|^2\right]^{-0.5} \times 100\right\}$$

Where R_t and T_t are the percent dissolved at each time point for the reference product and the test product, respectively.

Bioavailability study

All procedures with animal experimental and protocol were reviewed and approved by Institutional Animal Ethical Committee of Tatyasaheb Kore College of Pharmacy, Warananagar, India. The committee confirmed that the animal experiment had followed the guidelines as set forth by the Guide.

The rabbits were allowed to eat commercial food pellets and drink water except during the first 5 h of each test.

Table 1: Summary of model performance and selection for mean *in vitro* dissolution profiles of IF test (PHB) and Reference (HPMC) extended release tablet

Release pattern	Parameter	Test (PHB)	Reference (HPMC)
Zero-order (cumulative % drug release versus time)	R^2	0.895	0.851
	Slope/Ko	2.679	3.648
	Intercept	12.55	19.99
First-order (log cumulative % drug release versus time)	R^2	0.454	0.495
	Slope/Ko	0.054	0.052
	Intercept	0.974	0.859
Higuchi (cumulative % drug release versus square root of time)	R^2	0.997	0.963
	Slope/Ko	14.90	19.96
	Intercept	−1.14	2.944
Korsmeyer-Peppas (log cumulative % drug released versus log % time)	R^2	0.992	0.960
	Slope/Ko	48.67	83.90
	Intercept	19.76	16.90
Weibull (log dissolved amount of drug versus log time)	R^2	0.137	0.489
	Slope/Ko	0.095	0.315
	Intercept	0.215	0.489
Hixson-Crowell (cube root of drug % remaining in matrix versus time)	R^2	0.972	0.983
	Slope/Ko	−0.054	−0.112
	Intercept	4.364	4.282

HPLC: High performance liquid chromatography, IF: Ibuprofen, PHB: Poly-β-hydroxybutyrate

According to rabbits body weight and surface area dose of IF was calculated (56 mg/kg). The calculated amount of drug substance and formulation component were taken, and tablets were prepared. Aforesaid tablet was administered as such way; the tablet was placed in the smoothly cut (opened) end of a 5 mL syringe (plastic) and pushed it ahead with a plunger toward the base of the rabbit's tongue for ease of ingestion, followed by a few draughts (nearly 10 mL) of water was given.[27,28] Their ear was pre-shaved, and an ear marginal vein was used as blood collection site. Blood samples (1 mL) were collected in a heparin tube at the following time intervals: 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h, after administering the reference ER tablets (100 mg) and test (ER) tablets orally. The blood samples were centrifuged at 3000 rpm for 10 min, and the plasma was taken and kept frozen for further analysis. The plasma drug concentration was determined according to a previous method.[12] The serum supernatant samples 20 µL sample from each time specified interval were injected in high performance liquid chromatography (HPLC) system (Agilent Technology, USA.) with mobile phase constituted Methanol: Water (80:20) with employed flow rate 1.5 mL/min. Serum concentrations of IF were analyzed against blank plasma without IF in HPLC-ultraviolet detector at 220 nm. Peak area of these solutions was measured (Table 2, Figure 2).

Pharmacokinetic analysis

The peak serum concentration (C_{max}) of IF in plasma concentration and time of its occurrence (T_{max}) time required to reach maximum plasma concentration were read directly from IF concentration-time data. For other pharmacokinetic parameters, the concentration-time data were analyzed using a Microsoft Excel based Pharmacokinetic sheet. The values of the pharmacokinetics parameters were determined for each individual animal by non-compartmental approach. The IF serum concentration-time data, area under the plasma level-time curve (AUC), and area under the mean plasma level-time curve (AUMC) were calculated by trapezoidal method. The ratio of AUC and AUMC was used to estimate the mean residence time (MRT) of the drug. Apparent volume of distribution (V_d), plasma clearance (Cl_t), and terminal elimination rate constant (K_E) were also evaluated.[29,30]

In vivo study, serum concentrations were used to determine various pharmacokinetic parameters, i.e., the AUC, the elimination rate constant k_{el}, and the area under the plasma concentration-time profile from time zero to infinity. The fraction absorbed (f_{abs}) for each formulation was then calculated using the Microsoft Excel based Pharmacokinetic sheet.[12,13] In this *in vivo* drug absorbed (pa) obtained by amount of drug absorbed versus time.

The measured plasma concentrations were used to calculate the area under the plasma concentration-time profile from time zero to the last concentration time point $AUC_{(0-t)}$. The $AUC_{(0-t)}$ was determined by the trapezoidal method.[15] $AUC_{(0-\infty)}$ was determined by the following equation:

$$AUC_{(0-\infty)} = AUC_{(0-t)} + \frac{C(t)}{ke}$$

ke was estimated by fitting the logarithm of the concentrations versus time to a straight line over the observed exponential decline. The Wagner-Nelson was used to calculate the percentage of the IF dose absorbed:

$$F(t) = C(t) + KeAUC_{(0-t)}$$

Where F(t) is the amount absorbed. The percent absorbed is determined by dividing the amount absorbed at any time by the plateau value, $keAUC_{(0-\infty)}$ and multiplying this ratio by 100

$$\% \text{ Dose absorbed} = 100 \times \frac{C(t) + Ke\ AUC_{(0-t)}}{ke\ AUC_{(0-\infty)}}$$

IVIVC

The data generated in the bioavailability study were used to develop the IVIVC. IVIVC of the optimized formulation (F8 with 95.33% *in vitro* drug release and hardness 4.49 kg/cm^2) was investigated by plotting the percent drug absorbed (Pa) against the percent drug dissolved/released (Pr). The percent of drug dissolved was determined using the aforementioned dissolution testing method, and the fraction of drug absorbed was determined using the method of Eddington *et al*.[16] Linear regression analysis was used to examine the relationship between percent of drug dissolved and percent of drug absorbed. The percent of drug un-absorbed was calculated from the percent absorbed. The slope of the best-fit line for the semi-log treatment of this data was taken as the first order rate constant for absorption. The dissolution rate constants were determined from % released versus the square root of time. Linear regression analysis was applied to the IVIVC plots and coefficients of determination (r^2), slope and intercept values were calculated.[12-15]

The validation of the IVIVC model can be accomplished using the internal and/or external predictabilities. The internal predictability involves the use of the initial data used to define the IVIVC model. Hence, the predicted plasma concentration profiles of formulation ER-R and ER-T were calculated using their *in vitro* dissolution data. The "predicted % *in vivo* cumulative input (t)" data were calculated using the intercept, slope, and "% *in vitro* cumulative dissolved (t)" data. In other words, the "% *in vivo* cumulative input (t) data" versus time profile was estimated from the "% *in vitro* cumulative dissolved (t) data" based on an established IVIVC model. Subsequently, the predicted *in vivo* input rates for the ER formulation were obtained from the "% *in vivo* cumulative input (t) data".

RESULT AND DISCUSSION

In vitro studies

The mean dissolution profiles of IF test (PHB) and Reference (HPMC) ER tablets are shown in Figure 1. The calculated similarity factor (f_2) value was 38.1 between these two ER tablets. The value of f_2 was <50, indicating dissimilarity between the curves. The wide variation indicated that the combinations component of formulation resulted in different drug release rates. From the *in vitro* dissolution profile shown in Figure 1, the release rate of test (PHB) was much slower than those of reference (HPMC) formulations. It is observed that the high-molecular-weight (high viscosity) polymer has a slower dissolution rate than the dosage form with the lower-molecular-weight (lower viscosity) polymer.

Under the *in vitro* conditions used, the dissolution method demonstrated discrimination between test (PHB) and reference (HPMC) formulations as test (PHB) polymer content resulted in lower dissolution rates. The difference factor (f1) between test (PHB) and reference (HPMC) formulations was 21.5%. The minimum difference factor was 10% indicating that the dissolution profiles are adequately separated. Percent *in vitro* dissolution data were fitted using Zero-order, First-order, Higuchi, Korsmeyer-Peppas, Weibull, Hixson-Crowell models with uniform weighting [Figure 1]. Based on the goodness of fit parameters for model selection [Table 1], the Higuchi model appeared to best describe the data. The Higuchi model was then further evaluated with different weighting options. As shown in Table 1, the Higuchi weighting appeared to best characterize the *in vitro* dissolution data.

In vivo studies

PHB based ER tablet comprised 56 mg of IF. The plasma concentrations were acquired within 48 h. The screened PHB was proved to be release retardant polymer in the *in vitro* dissolution study, so decide to check its efficiency *in vivo*. Therefore, synthesized biopolymer (PHB) was used for extend the drug release. This polymer when come in contact with gastric fluid content *in vivo* conditions; the insoluble particles of PHB were probably acting as barrier to drug release in the gel layer of it gets hydrated and forms a gel. The drug release from this gel will be usually diffusion controlled, and hence the release will be extended over a prolonged period time.

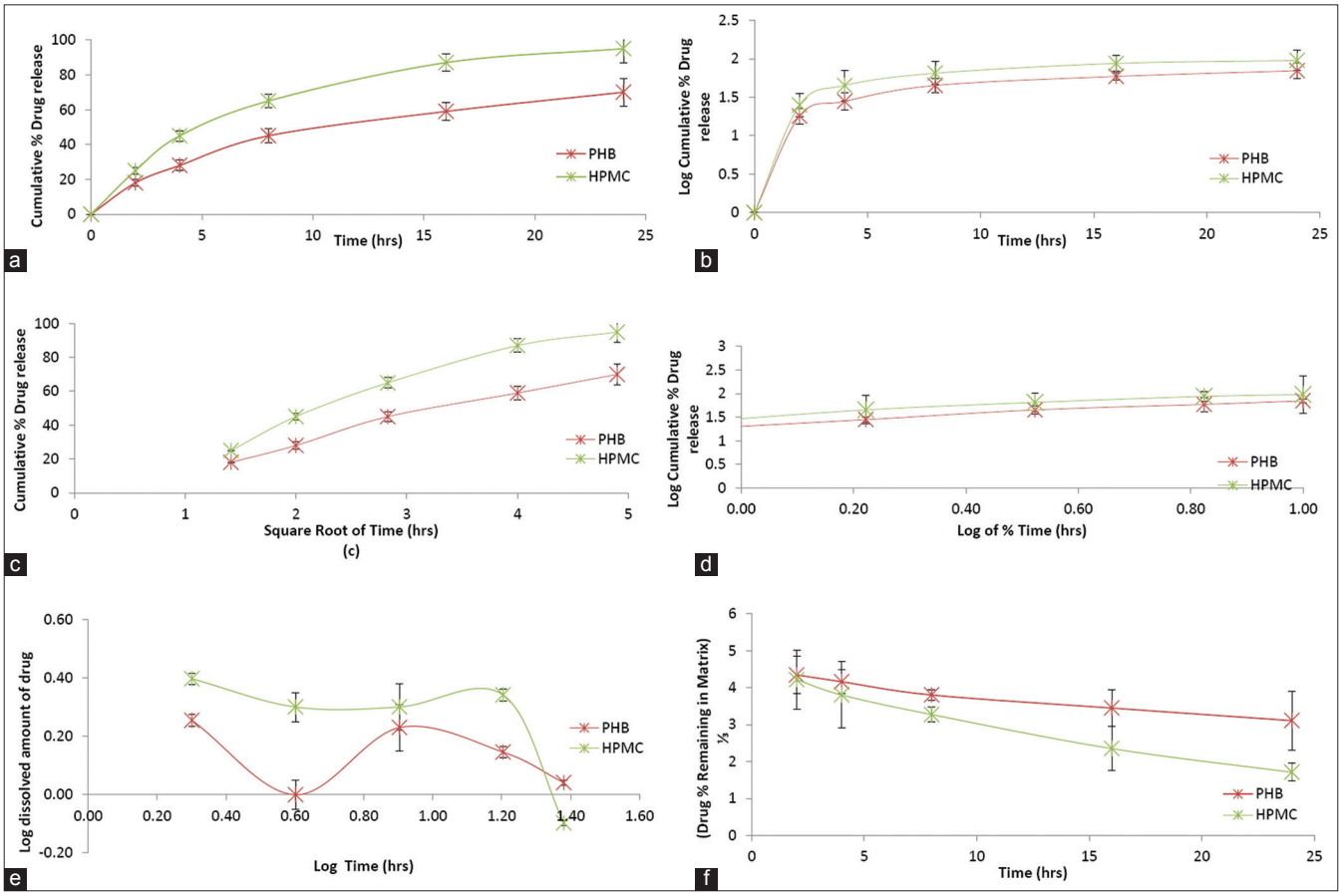

Figure 1: Mean *in vitro* dissolution profiles and model dependent approaches. (a) Zero-order, (b) first-order, (c) Higuchi, (d) Korsmeyer-peppas, (e) Weibull, (f) Hixson-Crowell of ibuprofen test (poly-β-hydroxybutyrate), and Reference (hydroxypropyl methylcellulose) extended release tablets

The plasma concentration profiles of test (PHB) and reference (HPMC) ER dosage formulations are shown in Figure 3. The mean pharmacokinetic parameters, C_{max}, T_{max}, and AUC are summarized in Table 3 and Figure 4. There was small extent of differences in the plasma level concentrations between the test (PHB) and reference (HPMC) ER dosage formulations. These profiles clearly demonstrate that the absorption of IF was prolonged when administered with PHB base ER formulation. The pharmacokinetic parameters estimated following the oral administration of IF PHB base ER tablet [Figure 3 and Table 3]. The elimination rate constant (K_{el}) of IF was found to be 0.023 h^{-1} and corresponding half-life ($t_{1/2}$) value of IF obtained in the present study is 30.09 h. The absorption rate constant (K_a) was found to be 347.99 h^{-1} following the oral administration of IF. Peak serum concentration (C_{max}) 13.36 µg was observed at 48 hr following administration. All the pharmacokinetic parameters of absorption namely K_a, C_{max}, T_{max} percent absorbed to various times and AUC indicated delayed absorption and prolonged bioavailability of IF when single dose (56 mg/kg dose) administered. This is the ratio of the dose to the AUC of the blood drug level after Oral administration [Figure 4]. The MRT was found to be 38.67 h. The volume of distribution 0.11 l/kg. The AUC 0-48 and 0-∞ h was found to be 289.55 and 406.55 µg/ml/h and AUMC of 0-48 and 0-∞ hrs was found to be 5026.02 and 15722.33 µg/ml/h for PHB base IF ER tablet [Table 3]. Thus, the result of the pharmacokinetic study indicated delayed absorption of IF which proved to be prepared ER tablet provide consistent and for prolonged period of time drug release.

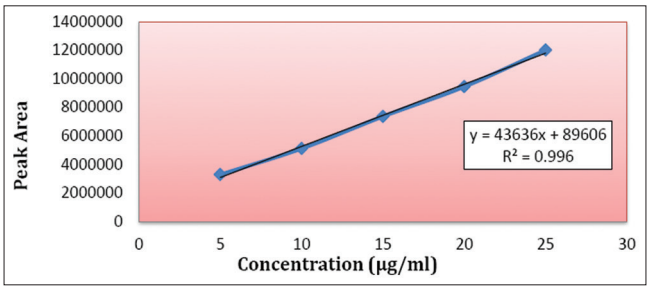

Figure 2: Calibration curve of ibuprofen in methanol (high performance liquid chromatography grade)

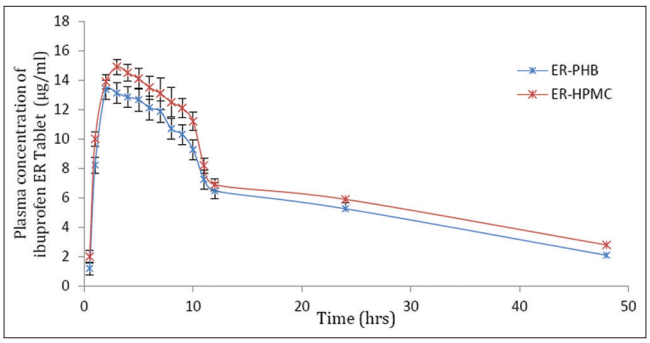

Figure 3: Plasma drug concentration of ibuprofen after single dose administration poly-β-hydroxybutyrate and hydroxypropyl methylcellulose base extended release tablet (56 mg/kg dose)

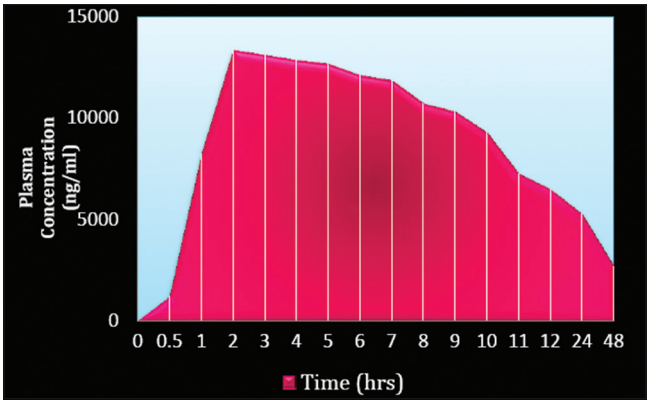

Figure 4: Area under curve of ibuprofen after single dose administration poly-β-hydroxybutyrate base extended release tablet (56 mg/kg dose)

IVIVC

IVIVC such an approach assumes similarity of variability of *in vitro* and *in vivo* systems, which may not be an appropriate

Table 2: HPLC calibration curve of IF in methanol (HPLC grade)

Concentration (µg/ml)	Peak area	Resolution factor	R factor
5	3279961	655992.2	522017.0413
10	5105211	510521.1	
15	7357141	490476.0	
20	9447548	472377.4	
25	12017961	480718.4	

HPLC: High performance liquid chromatography, IF: Ibuprofen

Table 3: Mean pharmacokinetics parameters of IF after single dose administration PHB base ER tablet (56 mg/kg dose)

Parameters	PHB base ER tablet
$AUC_{(0-48)}$	289.55 µg/ml/h
$AUC_{(0-\infty)}$	406.55 µg/ml/h
$AUMC_{(0-48)}$	5026.02 µg/ml/h
$AUMC_{(0-\infty)}$	15722.33 µg/ml/h
MRT=AUMC/AUC	38.67 h
Elimination rate constant (K_E)	0.023
Absorption rate constant (K_a)	347.99
Elimination half-life ($t_{1/2}$)	30.09 h
C_{max} (observed)	13.36 µg/ml
t_{max} (observed)	2 h
Volume of distribution (area)	0.11 L/kg

PHB: Poly-β-hydroxybutyrate, AUMC: Area under mean curve, AUC: Area under curve, ER: Extended release, IF: Ibuprofen

assumption. *In vivo* systems are potentially highly variable compared to the *in vitro* systems, e.g. variabilities in vessel sizes, medium volumes and mixing rate may be far less variable than the corresponding physiological characteristics. Not only for the comparison between *in vitro* versus *in vivo* results, even within *in vivo* comparison for bioavailability/ bioequivalence assessments, blood drug levels are not compared because of the extreme variability within and between subjects. To address this high *in vivo* variability aspect, parameters such as C_{max} and AUC are used [Figure 6]. These are in fact normalized parameters derived from drug concentration-time profiles. Therefore, rather than comparing blood levels for IVIVC, one should also evaluate C_{max} and AUC parameters.

It was investigated by plotting the percent drug absorbed (Pa) against the percent drug released (Pr). Percent drug dissolved values were taken from the *in vitro* release data, and the percent drug absorbed values were taken from *in vivo* evaluation calculated by Wagner-Nelson method. The major objective in the development of ER dosage form has been put forward to establish the *in vitro* and *in vivo* performance. IVIVC serves as a replacement for *in vivo* bioavailability. Pharmaceutical industries and academicians have accepted the value of IVIVCs. Therefore, the activity in this area for oral extended-release dosage forms has been in practice.

The *in vitro* drug release of optimized formulation is consistently proved drug release profile *in vitro* condition. To prove its efficiency, the IVIVC analysis carried out. *In vitro* drug release data are the primary integral part useful to determine IVIVC. Primary data for *in vitro* release were made by plotting the time versus cumulative % drug release [Figure 5].

A level A IVIVC was investigated using the percent dissolved versus the percent absorbed data for both the administration PHB and HPMC base ER tablet formulations, using pH 6.8 phosphate buffer dissolution media at 100 rpm. A good linear regression relationship was observed between the dissolution testing using pH 6.8 phosphate buffer at 100 rpm and the percents absorbed for the combined data of the two dosage forms (Figure 7; correlation coefficient = 0.992).

It is a second important integral parameter of the formulation to prove IVIVC. For IVIVC determination, the percent drug absorbed (Pa) percent drug dissolved (Pr) values were taken same time point graph was plotted percent drug absorbed (Pa) against the percent drug released/dissolved (Pr). It is also observed that the *in-vivo* absorption rate constant (k_a) correlates well with the pH 6.8 phosphate buffer *in-vitro* dissolution rate constant (k_{diss}), exhibiting a correlation coefficient of 0.9353. The r^2 value represents the IVIVC was successfully established for PHB-based ER tablet.

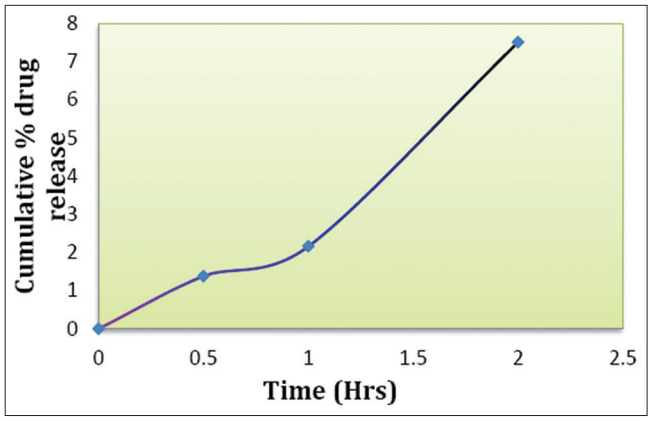

Figure 5: *In vitro* release of poly-β-hydroxybutyrate base Ibuprofen extended release formulation

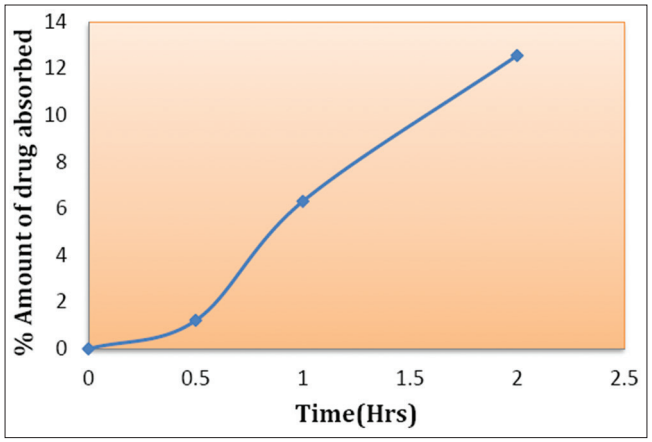

Figure 6: *In vivo* release of poly-β-hydroxybutyrate base ibuprofen extended release formulation

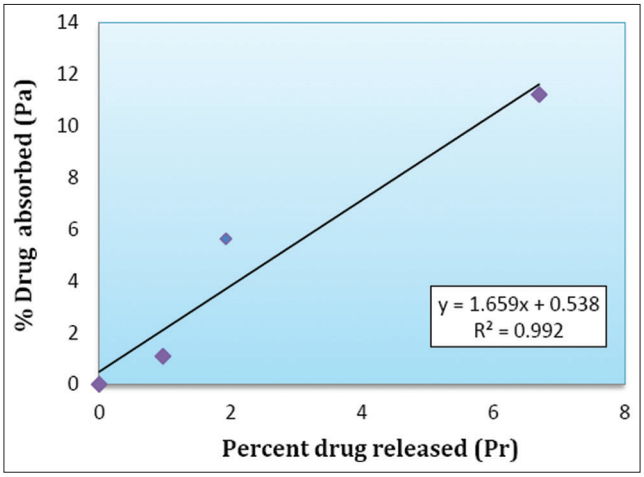

Figure 7: *In vitro-in vivo* correlation of poly-β-hydroxybutyrate base ibuprofen extended release formulation

CONCLUSION

In this preliminary study, a level A IVIVC model for PHB base IF ER dosage formulations was developed and estimated for both internal and external predictability. Although the model

was not acceptable for validating internal predictability, validation of external predictability was achieved. The significant correlations between the *in-vitro* and the *in-vivo* parameters reported here indicate that the IVIVC was excellent for predicting C_{max}. Thus, this IVIVC model might be used to predict the variation in site change, process changes, scale-up, and to predict the absorption performance of IF products with different ER polymers.

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