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In vitro-in vivo correlation (IVIVC) study for ibuprofen liquisolid tablet using a convolution-based modeling approach.

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Abstract

This study aimed to develop an *in vitro-in vivo* procedure for ibuprofen liquisolid tablet and evaluate its predictability via *in vivo* outcome of a bioequivalence study. By varying the excipient ratio (R), we prepared different batches of ibuprofen liquisolid (LS) tablets and subjected them to pre and post compression studies to select the optimized formulation, after which we compared and investigated the predicted plasma concentration-time profiles of ibuprofen prototype drug from *in vitro* dissolution results using mathematical convolution approach for *In vitro-in vivo* correlation (IVIVC) study. Compatibility studies using Fourier transform infra-red (FTIR) and differential scanning calorimetry (DSC) returned no major interactions between the drug and excipients. All formulations demonstrated acceptable flow properties. Tablet weight variations were insignificant, while assay and friability testing were within compendial specifications. Formulation F16 was nearest to the reference brand (Nurofen tablet®; Reckitt Benckiser, UK) at every dissolution sampling time hence it was chosen as the optimal formula. Area Under the Curve (AUC) percentage predicted errors were similar for both the test and reference product, while their peak plasma concentration (C_{max}) deviates by +6.73 and -1.77 percent from the authentic reference values derived from the literature. The percentage of predicted errors achieved revealed the convolution technique as a proficient procedure for predicting plasma drug levels of ibuprofen LS.

Key words: *In vitro-in vivo* correlation, ibuprofen, liquisolid tablet, bioequivalence, pharmacokinetics

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Introduction

The ability to predict correctly and effectively the expected bioavailability properties for a drug product from dissolution profile studies is termed IVIVC. It has been proven that the IVIVC model could reduce drug development time and lowers overall costs by minimizing the need for *in vivo* studies (Barbara et al. 2021). This model also ensures consistency between batch-to-batch, assists in quality assurance for possible scale-up and post-approval variations, and could be an important step to support biowaivers (Barbara et al. 2021). Once this model is confirmed, the inexpensive dissolution test could function as a replacement for an expensive bioequivalence test, and a properly verified IVIVC prototype would allow the setting of product requirements with dissolution bench mark that are related to applicable plasma concentrations. IVIVC in recent times has been adopted by many pharmaceutical industries in drug development strategies even when their use appears underrated in regulatory approval submission. There is therefore the need to expand this translation to provide reliable predictions. Linking *in vitro* and *in vivo* features for oral dosage forms where the absorption of active pharmaceutical ingredient is restricted by the rate of dissolution has made it possible to attain IVIVC, especially for biopharmaceutical classification system (BCS) class II compounds (Vaishav et al. 2018).

Levels A, B, C and multiple levels C are the 4 categories of IVIVC recognized by the FDA, with A being the most utilized. Level A IVIVC is a step-by-step correlation connecting *in vitro* dissolution and the *in vivo* response such as plasma drug concentration or amount of drug absorbed. Establishing IVIVC involves 2 methods; one-stage, also called the convolution method; and the two-stage or deconvolution method. The procedure of obtaining drug profiles from dissolution data is termed convolution while getting a dissolution data from a blood profile is called deconvolution (Gousous and Langguth 2018). The convolution process, though not a fashionable procedure is favored over the deconvolution technique because it will not require human study and the need to define experimental state of an apt dissolution test for various products with distinct *in vivo* release properties is absent.

Ibuprofen (the most common and most frequently used propionic acid derivative)- is a nonsteroidal anti-inflammatory drug that unselectively inhibits the cyclo-oxygenase (an enzyme implicated in the synthesis of prostaglandin via the arachidonic acid pathway) (Geih et al. 2017, Rabia and Nousheen 2010). Chemically, ibuprofen is called (RS)-2- [4-(2-methyl propyl) phenyl] propionic acid (Rabia and Nousheen 2010). Practically, it is insoluble in an aqueous medium (pKa value of 5.3), but readily soluble in most organic solvents [6]. Usually, peak serum concentration is attained within 1-2 h; and since it is rapidly bio-transformed, peak half-life ranges from 1.8 to 2 h (Shin et al. 2017). This drug is about 99 % protein bound, metabolized extensively in the liver to hydroxylated and carboxylated compounds, and eliminated after 24 h following the last dose with only a little fraction excreted unchanged (Aldalaen et al. 2021). It was first introduced to rival aspirin as a substance that could reduce mild to moderate pain, as well as treat feverish conditions and inflammation (Saumen et al. 2016).

Biopharmaceutical classification grouped ibuprofen to Class II, meaning it is highly permeable but poorly soluble (Alonso et al. 2018). This makes it a candidate for poor oral bioavailability. Improving the oral bioavailability of drugs involves enhancing the solubility of drugs with poor water solubility and boosting the permeability of poorly permeable drugs. Various techniques like ball milling, liquisolid technique, solid dispersion, particle size reduction, micronization, physical modifications, self-emulsifying drug delivery system, nano-suspension, crystal habit modifications (polymorphs, pseudo polymorphs, complexation, solubilization, salt formation) has been employed to upgrade the rate of dissolution of insoluble drugs with different degree of success (Alonso *et a*l. 2018, Mathew et al. 2022, Kapure et al. 2013, Nawal 2017, Amir et al. 2017, Han et al. 2022).

The LS technique offers superior advantages over other methods due to its simplicity, low production cost, and the prospect to scale up (Nawal 2017). The LS technique involves dissolving the poorly soluble active ingredient or suspending a drug or water-insoluble mixture of solid drug in a satisfactory non-volatile solvent and converting it to a free-flowing powder form that can be compressed. This method has been shown to increase the solubility of lipophilic drugs in water by (i) increasing the drug surface area available for release, (ii) improving the aqueous solubility of the drug substance, and (iii) enhancement of the wettability of the drug particles (Mir et al. 2017, Han et al. 2022, Bhola et al. 2022). Interestingly, the solubility of carbamazepine, famotidine, indomethacin, furosemide, hydrocortisone, piroxicam, naproxen, prednisolone, ezetimibe, chlorpheniramine, digoxin, clofibrate, nifedipine, gemfibrozil, etoposide, lacidipine, hydrochlorothiazide, methyclothiazide, spironolactone, ibuprofen have all been improved using this technique (Saumen et al. 2016, Alonso et al. 2022, Mathew et al. 2018). However, information about their *in vitro-in vivo* correlations is sketchy and open to discussion. Herein, we develop an *in vitro-in vivo* procedure for ibuprofen LS tablet and evaluate its predictability via *in vivo* outcome of a bioequivalence study. First, a solubility study for ibuprofen was carried out in selected non-volatile solvent to ascertain the ideal liquid to utilize and an investigation to demonstrate the compatibility between the API and the excipients was as well performed, thereafter we calculated the required

amount of carrier and coating materials using liquid retention potential method discussed elsewhere (Alonso *et al*, 2018). We then compressed various formulations of ibuprofen liquisolid compacts and subjected them to post compression evaluation test. A comparative study to determine the formulation closest to the reference brand was carried out before establishing the mechanism of drug release from the LS compact. Then finally, in an attempt to predict its pharmacokinetic properties, we carried out an *in vivo-in vitro* study. Our study provided promising data for predicting the pharmacokinetic properties of ibuprofen LS tablets via the convolution method.

Materials and Methods

Materials

Ibuprofen powder, potassium orthophosphate, and sodium hydroxide were products from Sigma-Aldrich Darmstadt, Germany; Span 20, Tween 20, Tween 80, and Propylene glycol (PG) were products from Loba Chemie, India; and Glycerin was manufactured by Himedia, India. Avicel PH-102, Aerosil 300, and polyvinyl pyrrolidone (PVP) were made in the UK by Fisher Scientific while magnesium stearate and talc were from FMC Corp, UK.

Non-volatile solvent suitability testing

Solubility of ibuprofen was performed in selected non-volatile solvents (Glycerin, Span 20, Tween 20, Tween 80, and Propylene glycol) to determine the ideal non-volatile solvent for dissolving ibuprofen. Accurately 1g of the drug was added to the vehicles and shaken on an incubator shaker for 12 h at room temperature to obtain a near-clear solution. The mixtures were then filtered with a 0.45 µm filter paper, diluted with absolute methanol and the absorbance read with a Cary 60 UV/vis spectrometer (Agilent Technologies) at 221 nm against a blank having similar concentration of particular non-volatile solvent used without the drug (Vemula et al. 2015).

Liquid loading factor determination

Liquid loading factor was determined using:

$$\Phi Lf = \Phi CA + \Phi CO\ (\frac{1}{R})$$

$$\Psi Lf = \Psi CA + \Psi CO\ (\frac{1}{R})$$

Where ΦCA and ΦCO are the flowabilities liquid retention potential of carrier and coating materials, whereas ΨCA and ΨCO are the compressible liquid retention potential of carrier and coating materials, and R is the excipient ratio defined as:

R=Q/q

Where Q is the amount of carrier material, and q is the amount of coating material (Bhola et al. 2022).

Tablet compression

Twenty LS compacts (F1-F20) containing 200 mg ibuprofen were prepared by dispersing ibuprofen in a non-volatile solvent (Table 1). A binary mixture of Avicel PH 102-MCC and Aerosil in a ratio already determined by the excipient ratio (R) was added to the solvent containing the drug in a pestle and mortar. After which 5 % PVP as a disintegrant was added, followed by 1 % magnesium stearate and 0.5 % talc as lubricant and glidant respectively (Han et al. 2022). The mixture was blended for about 2 min and then compressed with a single station Manesty tableting machine (Shanghai, China) after a precompression study on the blend was carried out.

Directly compressed tablets (CT) were prepared in a fashion similar to those of LS compacts but without adding non-volatile solvent (Table 1).

Composition of reference tablet (Nurofen® targeted release)

Ibuprofen (200 mg), acacia, black ink, carmellose sodium, croscarmellose sodium, macrogol, propylene glycol, silicon dioxide, sodium citrate, sodium lauryl sulfate, stearic acid, sucrose, talc, titanium dioxide.

Pre compression evaluation

Drug-Excipient compatibility study: Samples (Ibuprofen powder alone, compacts for direct compression, and compact for LS tablet) were analyzed using a Fourier-transform infrared

spectrophotometer (Magna-IR, 560 spectrometers; Perkin Elmer, USA) to check for interactions between API and excipients (Vaibhav et al. 2018); and Differential Scanning Calorimeter (DSC- 60, Shimadzu; Japan) to evaluate how physical properties of our samples changed along with temperature against time (Nawal 2017).

Powder flow properties: Angle of repose (Θ), Carr's compressibility index (CI), and Hausner ratios (HR) of formulations were determined employing established methods described in the literature (Marzia et al. 2020, Vemula et al. 2015).

Post compression evaluation

Uniformity of tablet weight, hardness test evaluation, friability testing, disintegration testing, and assay content were evaluated using methods reported elsewhere (Vaibhav et al. 2018, Shin et al. 2017).

Dissolution testing: The USP Apparatus II was used to generate the *in vitro* dissolution profiles. The dissolution tester (RC-6, China) was first mechanically calibrated and then subjected to a performance verification test using a prednisone reference tablet to ensure it conforms to the USP dissolution requirements. A 900 mL phosphate buffer (pH 7.2) was placed in each vessel of the six-station dissolution apparatus. The system was allowed to equilibrate to 37±0.5 ºC. A tablet from a formulation was placed in each of the vessels and the equipment was operated at 50 rpm for 1 h. An aliquot of 5 mL was withdrawn at 0.17, 0.33, 0.50, 0.70, 0.83 and 1 h intervals from each vessel (and replaced with the same volume) at a point halfway between the surface of the media and the top of the rotating paddle and not less than 10 mm from the wall of the vessel. The aliquot was filtered with a 0.45 µm filter paper and the absorbance read at 221 nm using a UV/vis spectrophotometer (Cary-60, Agilent technologies) to extrapolate the percentage dissolution of ibuprofen tablet (Sanjana et al. 2018).

Comparative evaluation study

The dissimilarity factor (f1) was evaluated using:

$$f1 = \frac{\{\sum_{t=1}^{n} Rt - Tt\}}{\{\sum_{t=1}^{n} Rt\}} \times 100$$

The similarity factor (f2) was determined using:

$$f2 = 50 \times \log\left\{1 + \frac{1}{n}\sum_{t-1}^{n}(Rt - Tt)^2\right\}^{-½} \times 100$$

Dissolution efficiency (DE) was extrapolated using the:

$$DE = \frac{\int_{t1}^{t2} y.dt}{y100\ x\ (t2 - t1)} x100$$

Mean dissolution time was calculated using the:

$$MDT = \frac{\sum_{j=1}^{n} tj\Delta Mj}{\sum_{j=1}^{n} \Delta Mj}$$

Where Rt= % of dissolved reference brand at a given time t, Tt= % dissolved of generic brand, j=the sample number, n= the number of sampling times of dissolution, t_j= the time at halfway connecting t_j and t_{j-1}(expressed as t_j+t_{j-1})/2) while ΔMj= the supplemental quantity of drug released betwixt t_j and t_{j-1}, y=% dissolved of product and dt= the area under the curve of dissolution between time point t1 and t2 (Sanjana et al. 2018, Remeth et al. 2017, Costa et al. 2003)

Kinetic models for drug release

Zero order model kinetic was expressed mathematically as:

$$Q_t = Q_0 + K_0 t$$

Q_t equals the amount of drug present in solution at time t, Q_0 is the initial quantity of drug available in the solution, and K_0 is the zero-order constant.

First-order model kinetic was determined as:

$$\log C = \log C_0 - K_t/2.303$$

C_0 equals the initial concentration of the active drug moiety, K is rate constant, and t is the time.

Higuchi model kinetic was postulated using the:

$$f_t = Q = K_H \times t^{½}$$

Q is the quantity of drug available at time t and K_H is the Higuchi dissolution constant.

Hixson-Crowell kinetic model was evaluated using:

$$W_0⅓ - W_t⅓ = Kt$$

W_0 is the initial quantity of the active drug moiety present in the dosage form, W_t is the quantity of drug left in the dosage form at time t, and K is a constant built in to the surface-volume relation.

Korsmeyer-Peppas kinetic model was explained using:

$$M_t \div M_\infty = Kt^n$$

$M_t \div M_\infty$ is the fragment of drug made available at time t, K is the rate constant, and n= the release exponent.

Weibull kinetic model was determined as:

$$M = M_0[1 - e^{-(t-T)\,b/a}]$$

M is the quantity of dissolved drug to time t, M_0 is the quantity of drug moiety being released, T is the lag time due to the dissolution process while a is scale variable that explains the time dependence, and b is the state of the dissolution curve sequence (Maria and Maria 2014, Suresh and Saini 2021).

In vitro-in vivo (IVIVC) kinetic study

A discrete amount of drug release was extrapolated from drug release values gotten from the dissolution test.

The rate of elimination was calculated using:

$$ke = (In\ C1 - In\ C2/(t2 - t1)$$

C1 and C2 are predicted drug quantities in blood at times t1 and t2, while Ke is the elimination rate constant for first-order (Alonso *et al*, 2018)

The anticipated blood level profile was gotten using:

$$predicted\ conc.at\ times = predicted\ total\ blood\ amount\ \times F/Vd \times body\ wt$$

F and Vd are bioavailability and volume of distribution respectively (Vaibhav et al. 2018).

Percent predicted error (% PE) was extrapolated using the:

$$\%\ PE = (Observed\ parameter - Predicted\ parameter)\ \times 100/ Observed\ parameter$$ (Suresh and Saini 2021, Roberto et al. 2019)

Results

Solubility study

Solubility of ibuprofen in the selected non-volatile solvents was in the order, propylene glycol>glycerin>tween 20>tween 80>span 20 (Fig. 1); therefore, propylene glycol was considered suitable for this study. Similar values were previously reported while formulating ezetimibe LS tablets (Vemula et al. 2015). Information about the formulation technique of the reference tablet was not made available by the manufacturer; however, the label claim does reveal propylene glycol as one of its excipients.

Pre compression evaluation

Using 300 mg as the weight of the liquid medicament for formulation F1 and liquid load factor (Lf) of 0.69, the quantity of the expected carrier material was found to be 579.7 mg while the quantity of the required coating material was 115.9 mg at an excipient ratio (R) of 5:1 (Table 1). At this ratio Avicel PH 102 was able to retain propylene glycol without any evidence of leakage, producing tablets of reasonable hardness. This method was used to calculate the required weight for the other formulations. Flow properties of LS powders are shown in Table 2. Angle of repose (AR) values were mostly excellent (<30 º), indicating that the proportion of fine particles were less than a half the total amount of the formulations. Carr's index values were considerable acceptable (< 15%) for all formulations, while Hausner values indicates less cohesiveness for all but for formulation F1 and CT. Generally, all formulations demonstrate acceptable flow properties and hence they were considered for further studies. In the DSC analysis as shown in Figure 2, exothermic peaks at about 80 ºC were observed for ibuprofen powder similar to that reported in the ibuprofen monograph (78ºC)while in the CT formulation, no significant shifting nor disappearance of ibuprofen peak was observed. For FTIR spectra, peaks obtained in the spectra of LS compact and that of direct compression compact correlate with

the characteristic peaks of ibuprofen powder spectrum reported in monograph (Fig. 3).

Post compression evaluation

We evaluated our formulations along with the reference brand for parameters such as weight variation, hardness, friability, disintegration, dissolution and assay test. Data are presented in Table 3 and figure 4. Variations in tablet weight within a single formulation were insignificant for all formulations as no more than two tablets vary from the average weight by more than 5 %. Formulation F3, F4, F9, F14, F15, F17, F18, F19, F20, CT and N failed the hardness test by not meeting the 4-10 KgF specification. For friability testing, none of the formulations deviated from the compendial specification of less than 1 %. Only F20 and CT failed to meet the compendial specification for disintegration time of conventional tablet (< 15 min). The drug content in all formulations was ideal, meeting the 95-105 % compendial specification for ibuprofen tablets. For dissolution testing, formulations released at least 90 % of their content after 1 h with the exception of F1, F2, F14, F20, and CT (Fig. 4a and 4b). In addition, all tablets showed a dissolution graph that rises over time and sustained after an intermediate time point.

Comparative evaluation study

By fitting dissolution profiles into f1 and f2 equations we evaluated the *in vitro* bioequivalence of our formulations and most were outside the 0-15 and 50-100 range for f1 and f2 respectively (Table 4). We further subjected them to a more robust model (dissolution efficiency); and their mean dissolution time (MDT) were as well evaluated. F16 passed the f1 (10.80) and f2 (56.60) test, and also had a % DE (18.00) and MDT (0.31) values that were comparable to the reference brand (% DE=16.00, MDT=0.32).

Drug release kinetic study

We studied the kinetics of drug release of our optimized formulation (F16), CT and reference brand (N), by fitting data into kinetic models using linear regression with R^2 as the correlation coefficient (Table 5). Model with the highest R^2 value indicates the release kinetic of a formulation. The Hixson-Crowell model gave the highest R^2 value (0.9618) for F16, while the highest value for CT (0.9977) was observed with the Korsmeyer-Peppas, and that of N was the Higuchi model at a value of 0.9010

In vitro-in vivo (IVIVC) kinetic study

In vitro dissolution data obtained from F16 and N were converted into mathematically predicted *in vivo* parameters using plasma concentration-time profiles and results are presented in Table 6-9 and Figure 5. The predictability of the correlations established was evaluated by internal validation which consists of evaluating the percentage predicted errors of Cmax, Tmax, and AUC as shown in Table 10. The test and reference products attained Cmax swiftly (25.84 and 23.68 µg/mL) and fell rapidly, while the Tmax for the test formulation was much lower (0.70 h) than that of the reference (1.00 h) meaning that the reference has a lower rate of absorption than the test product. This rapid oral absorption following F16 administration is responsible for its higher Cmax value when compared to the reference brand. Also, the difference between AUC values estimated using the log-linear trapezoidal rule for the test (90.19 µgh/mL) and reference product (89.42 µgh/mL) was insignificant. However, the slightly higher AUC value of F16 will imply a better bioavailability than the reference product. The predicted plasma Cmax differed by 6.73 % and -1.77 % when compared to the observed values for the test and reference product; whereas their predicted AUC errors were similar and those for Tmax were -78.57 % and -25.00 %.

Discussion

Ibuprofen was a model drug for this study due to its water-insolubility potential, and its ability to readily obey the principles and procedures of spectrophotometry; whereas, Propylene glycol (PG) is an approved solvent in this formulation probably due to its chemical nature, lipophilicity, polarity and viscosity (Shin et al. 2017, Vemula et al. 2015). A rate-determining step in enhancing the dissolution rate of a poorly soluble drug molecule by the liquisolid technique is the ability of the drug molecule to be soluble in a selected non-volatile solvent. The solubility of

rosuvastatin (a BCS class II drug) has previously been improved using PG as a non-volatile solvent (Kapure et al. 2013).

R-value could have a notable outcome on the release of drugs from liquisolid matrix by increasing the quantity of carrier material needed and reducing the quantity of coating material (Mir et al. 2017). The R-value was also responsible for the relatively good flow properties across formulations (Vaibhav et al. 2018). Due to its ability to swell, the choice of PVP as a coating material will help release the drug from the high internal surface area of Avicel PH 102 when in contact with fluid. A less cohesive compact will have lower AR value, and a low AR value has been proven to have a lot to do with how particles undergo rearrangement under the influence of external pressure (Vaibhav et al. 2018). CI and HR, usually would relate to interparticle frictions.

Studying the polymorphic nature of ibuprofen in the liquisolid compact is necessary because the amorphous nature of a drug could interfere with the dissolution rate, bioavailability and even therapeutic equivalence of the formulation (Vaibhav et al. 2018). In the DSC study, a shift in peak in the LS compact was probably due to the drug substance being molecularly dispersed in the LS matrix where the crystalline attributes of the drug become transformed into an amorphous form; whereas in the CT formulation, the slight variations in peak temperature would probably be as a result of the dilution effect of polymers and the thermal energy supply during the DSC scan (Nawal 2017). For the FTIR spectra, the lack of major shifts nor loss of functional peaks established the fact that no well-defined interactions exist between the drug and excipients.

Less variation in tablet weight within a formulation was responsible for the little disparity observed in parameters such as disintegration, dissolution and assay test (Mir et al. 2017). A failed hardness test tablet will adversely impact friability, disintegration, dissolution and eventually bioavailability (Bhola et al. 2022). For friability testing, the type and concentration of excipients used and the characteristics of the active pharmaceutical ingredients were sufficient not to give rise to particle loss during handling and transportation. This low friability values observed in our LS formulations could be due to the well-built interparticulate sturdiness imparted by PVP on the particles of the ibuprofen. The porous nature of AVICEL is responsible for the robust disintegrating property exhibited by our formulations. AVICEL constitute mostly cluster of small subunits held together by hydrogen bonds (Vaibhav et al. 2018). Also, the disintegrating media influenced the weakening of intermolecular bonds by loosening the tablet matrix and enlarging the pores to a certain degree. The penetration of fluid into tablet matrix is requisite step for the process of disintegration and dissolution, and the capacity of tablets to fragment within the stipulated time limit is an indication of good *in vivo* drug release properties and bioavailability (Suresh and Saini 2021). Generally, a discriminating drug release prototype is a notable *in vitro* process for change in product formulation. In product development, finding *in vitro* attributes that will disclose *in vivo* performance is pre-eminent; and the test most often linked to this procedure is the dissolution test. The dissolution result demonstrates that most of our LS formulations were in consonant with the dissolution requirement for ibuprofen tablet stated in the USP, and are comparable with the reference brand. We have noticed that differences in manufacturing process (CT and LS tablets) could affect dissolution rate, and that altering the surface area of the dissolving particles as a result of the disintegration and de-aggregation of the tablets could substantially increase the rate of dissolution (Roberto et al. 2019). The release of ibuprofen from the LS matrix could as well be influenced by the amount of dissolution medium introduced at the time of drug release study, which in turn affect the rate of the absorption step. We might as well attribute these to the fact that the concentration-buildup in *in vitro* release studies carried out at predetermined medium volume is comparable to the actual *in vivo* process where only a fraction of dissolved drug is withdrawn from the fluid by absorption.

With respect to *in vitro* drug release studies, dissolution curve profiles are termed similar if f1

and f2 values are within 0-15 and 50-100 respectively. Despite the curiosity that f1 and f2 has received from several regulatory authorities, they still fall short of strong statistical arguments; and evaluating the likelihood and extent of false positive or negative results via these techniques is stretching; thirdly, f1 and f2 values basically respond only to time points selected for a definite dissolution profile, just as they do not exhibit the degree of dissimilarity between *in vitro* dissolution profiles (Costa et al. 2003). These limitations have made comparison between newly developed product with an innovator brand not to yield reliable results, hence we supported these data with statistically significance models such as DE and MDT. With DE been a more robust model that could sum up drug release data into a single chart to enable contrasting between large numbers of formulations and as well as relate *in vivo* data theoretically, we could therefore infer that the overall dissolution profile of F16 is similar to the reference brand at every dissolution sampling time and hence was the ideal formula for further *in vitro in vivo* study.

Drug release kinetics data revealed that only the Hixson-Crowell model was sufficient enough to define the release kinetics of the optimized formulation thereby implying that the surface area of the drug carrier reduces slowly as a result of dissolution while the reference brand followed super cell transport mechanism by obeying the Korsmeyer-Peppas model (Maria and Maria 2014, Suresh and Saini 2021).

At the early stage of product development, an ultimate search of a characteristic *in vitro* model for dissolution that could reveal *in vivo* performance is of primary significance. The development of bioequivalence for most BCS Class II drugs are demanding as a result of their poor absorption driven half-life which will make the conventional bioequivalence process to lengthen (Martinez et al. 2022). Previous works intricating likely IVIVC models for ibuprofen usually will utilize the deconvolution approach which calls for extrapolating *in vivo* dissolution data from blood profile. The ability to employ figures from dissolution tests and hypothesize them to a pharmacokinetic outcome (convolution approach) via IVIVC can simplify the formulation development process. The convolution IVIVC inceptive process usually would start with utilizing the USP defined methodology for dissolution of ibuprofen such as Apparatus II, 900 mL of phosphate buffer pH 7.2, 37 ºC, 50 rpm for 60 min (Martinez et al. 2022). This methodology produced a sigmoid curved relationship between cumulative percent release and release time, followed by the evolution of a tie-in between plasma drug concentration and their corresponding time. By involving the mean *in vitro* dissolution and mean *in vivo* pharmacokinetics data, we validated the IVIVC model by assessing how well they could predict the rate and extent of the test and reference product as characterized by the area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, the maximum plasma concentration, and the time to achieve maximum plasma concentration. Although there is currently no ibuprofen LS product on the market, we have attempted to confirm the IVIVC of our test product and the reference, and the sameness in their dissolution release was obvious in their plasma concentration profile as shown in figure 5. This is expected if the location in which both drugs will be absorb in the gastrointestinal tract is parallel (Jirage et al. 2017). The percentage of predicted errors (% PE) values achieved for AUC, Cmax and Tmax clearly exhibited the convolution technique as a discriminative approach for predicting plasma drug levels of formulation F16 as per FDA guideline, since almost all values were below 10 % (Costa et al. 2003).

Conclusion

Extensive investigation is ongoing for discovering the usefulness of convolution-based approach for better evaluation of IVIVC and assessment of drug pharmacokinetics properties. This is one of such fact-finding; and based on the data generated, we have attempted to utilize this approach in determining optimal formulation composition for ibuprofen LS tablets to achieve the desired pharmacokinetic properties

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Figures

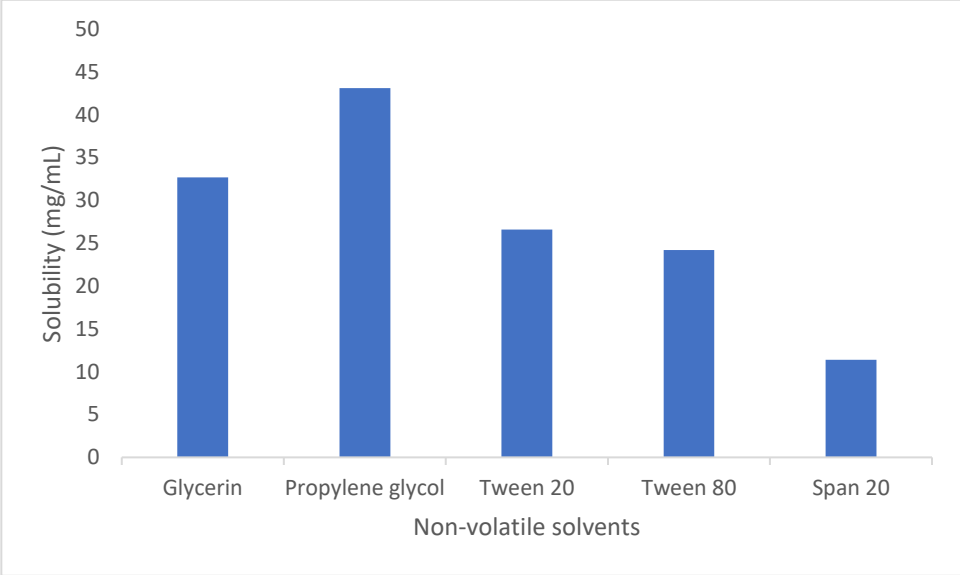
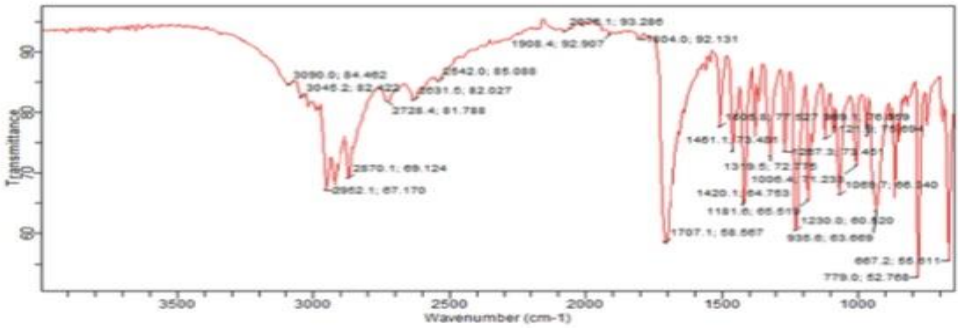
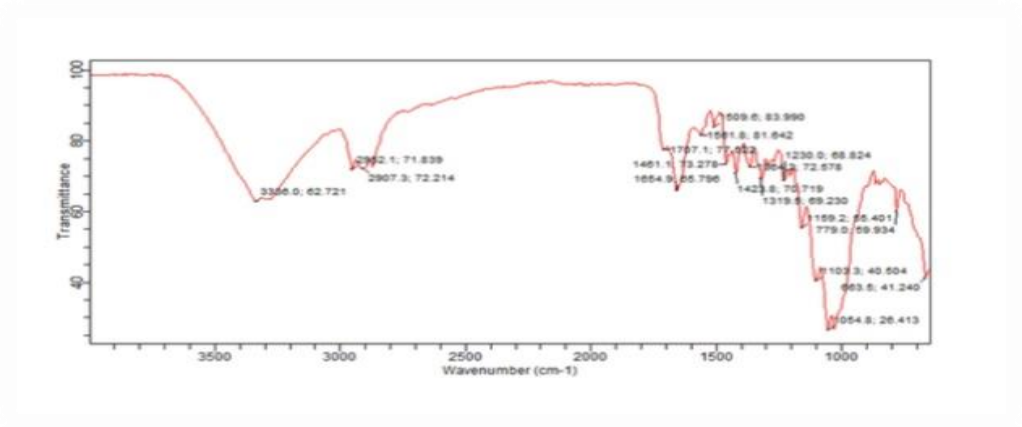


Fig. 1. Histogram diagram of solubility of ibuprofen powder in some selected non-volatile solvents.



A



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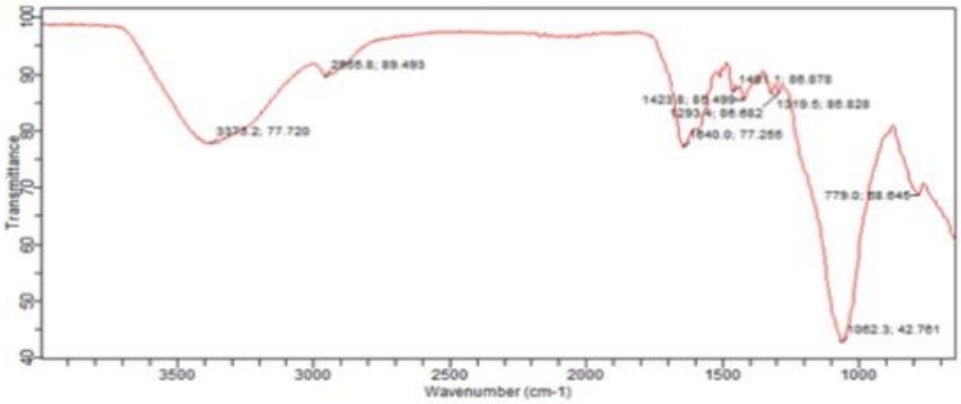
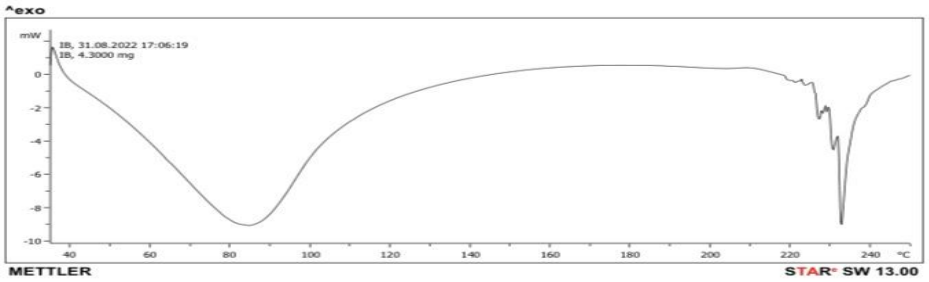


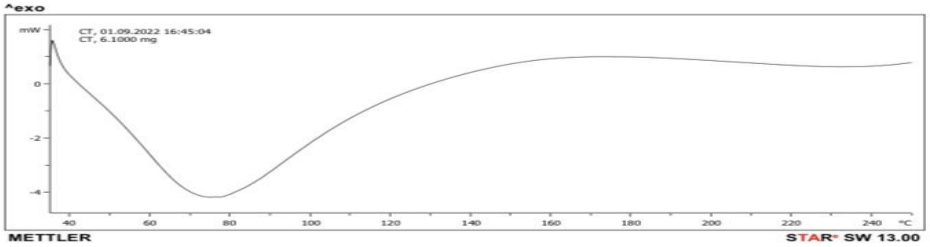
C

Fig. 2 FTIR spectra for pure ibuprofen powder (A), liquisolid tablet mixture (B), and conventional ibuprofen tablet mixture (C).

A



B



C

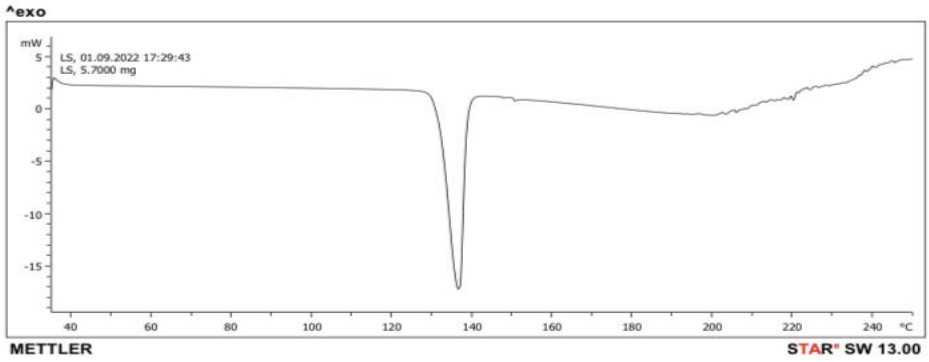


Fig. 3 DSC thermogram for pure ibuprofen powder (A), conventional ibuprofen tablet mixture (B) and liquisolid tablet (C) mixture.

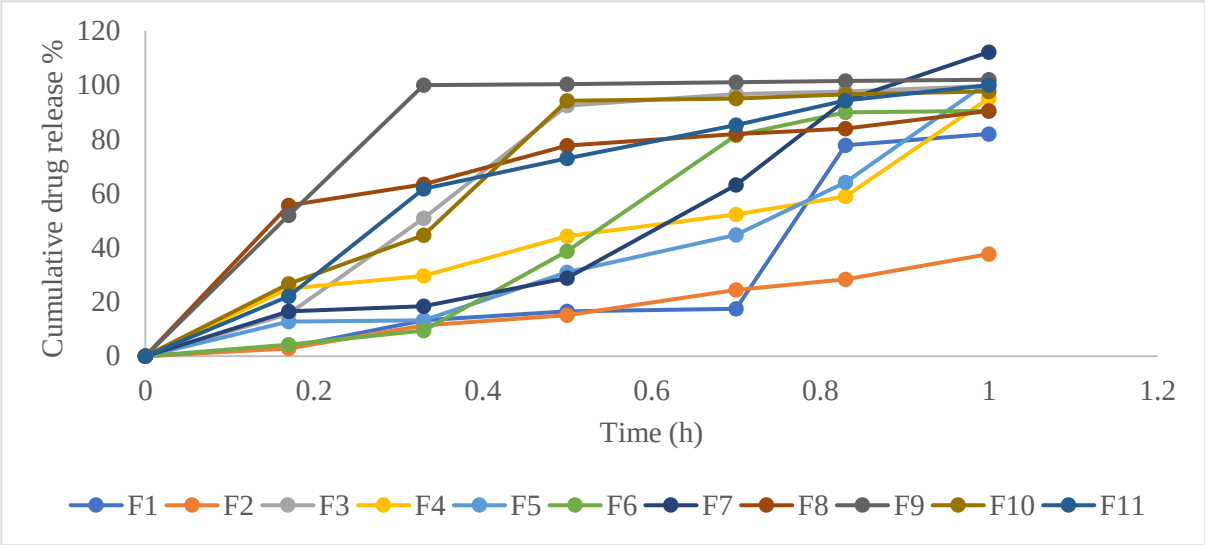


Fig. 4.a Dissolution profiles for liquisolid formulation F1 to F11. *n=6*

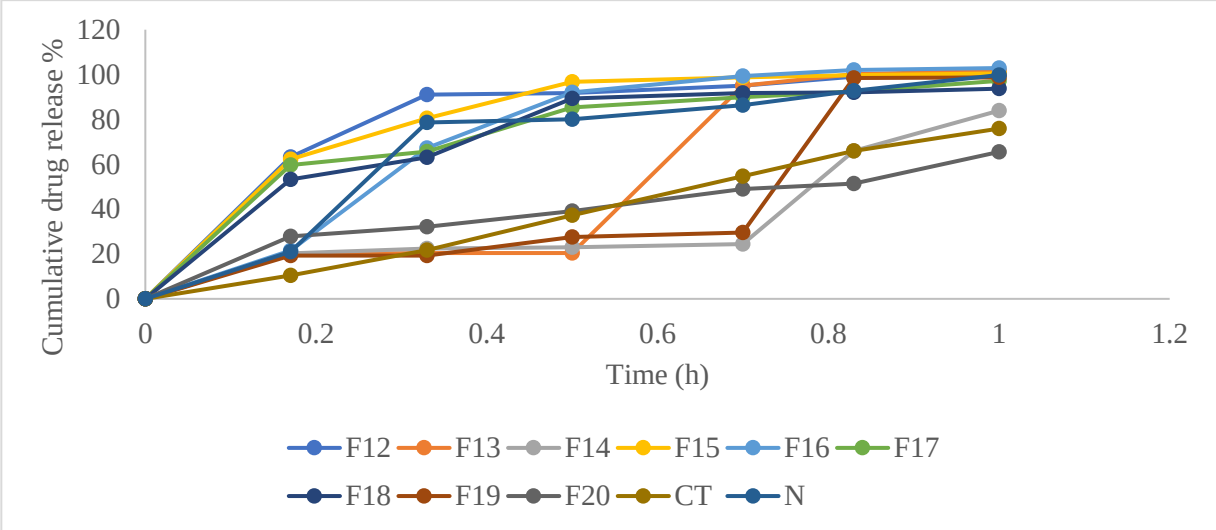


Fig. 4.b Dissolution profiles for liquisolid formulation F12 to F20, conventional tablet (CT) and reference tablet (N). *n=6*

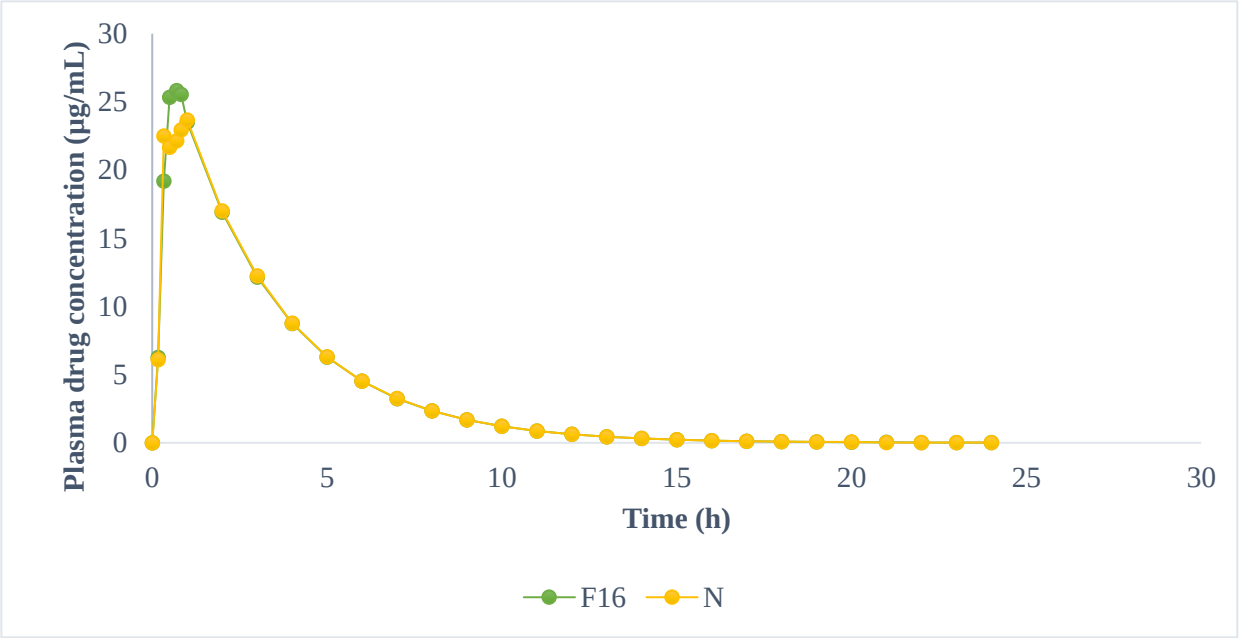


Fig. 5 Plasma drug concentration time profile derived from *in vitro* dissolution profiles for F16 and reference tablet (N) *n=6*

Tables

Table 1 Tablet composition.

	API	Solvent	Q	q	R	Lf	Total (mg)
F1	200.00	100.00	579.90	115.90	5.00	0.69	1065.10
F2	200.00	80.00	565.20	113.00	5.00	0.69	1018.10
F3	200.00	60.00	550.70	110.10	5.00	0.69	970.80
F4	200.00	40.00	536.20	107.20	5.00	0.69	919.10
F5	200.00	20.00	521.70	104.30	5.00	0.69	872.50
F6	200.00	100.00	833.30	83.30	10.00	0.48	841.60
F7	200.00	80.00	812.50	81.20	10.00	0.48	1238.70
F8	200.00	60.00	791.60	79.10	10.00	0.48	1184.70
F9	200.00	40.00	770.80	77.80	10.00	0.48	1131.80
F10	200.00	20.00	750.00	75.00	10.00	0.48	1075.80
F11	200.00	100.00	1000.00	50.00	20.00	0.40	1450.00
F12	200.00	80.00	975.00	48.70	20.00	0.40	1377.90
F13	200.00	60.00	950.00	47.50	20.00	0.40	1319.00
F14	200.00	40.00	935.00	46.40	20.00	0.40	1261.10
F15	200.00	20.00	900.00	46.00	20.00	0.40	1203.00
F16	200.00	100.00	1176.40	39.20	30.00	0.34	1617.60
F17	200.00	80.00	1147.00	38.20	30.00	0.34	1551.20
F18	200.00	60.00	1117.60	37.30	30.00	0.34	1491.80
F19	200.00	40.00	1088.20	36.30	30.00	0.34	1422.50
F20	200.00	20.00	1058.80	35.30	30.00	0.34	1364.10
CT	200.00		579.70	115.90	5.00		941.60

*API=active pharmaceutical ingredient, Q=carrier material, q=coating material, Lf=loading factor.

Table 2 Authentic pharmacokinetic parameters for Ibuprofen tablet obtained from literature

F	Vd	Cmax	Tmax	AUC	ABW
0.90	0.10 L/Kg	24.10 µg/mL	1.25 h	80.70 µgh/mL	62.00 kg

*F=bioavailability, Vd=volume of distribution, Cmax=peak plasma concentration, Tmax=time to reach maximum concentration, AUC=area under the curve, ABW=avaerage body weight. (Geith et al. 2017, Rabia 2010, Shin et al. 2017, Aldalaen et al. 2021, Hedaya et al. 2021, Matinez et al. 2022).

Table 3 Some pre-compression and post-compression study results

	AR (°)	HR	CI (%)	WV	F	H	D	A %
F1	28.5±0.9	1.8±0.6	12.2±0.4	998.7±9.0	0.2	4.5±0.5	1.1±0.2	97.2
F2	19.9±0.2	0.2±1.1	14.1±1.1	998.1±3.9	0.5	7.3±0.1	1.0±1.1	99.5
F3	14.8±2.3	0.5±1.7	12.5±2.2	998.1±0.8	0.4	1.7±0.5	3.0±3.1	101.9
F4	19.1±2.4	1.1±0.5	12.5±0.9	913.4±2.8	0.2	0.1±0.1	8.2±0.5	100.5
F5	23.1±1.5	0.1±0.1	10.1±3.1	860.4±2.7	0.2	6.3±0.1	8.1±2.2	95.7
F6	31.3±0.3	0.6±2.9	13.0±2.1	1298.5±2.4	0.1	4.1±0.1	7.5±2.7	95.4
F7	21.0±2.1	0.3±0.2	14.1±0.3	1232.6±0.9	0.1	4.2±0.3	8.6±0.5	102.6
F8	19.2±4.2	0.2±1.2	14.7±0.6	1184.8±0.3	0.1	4.3±1.3	2.1±1.7	99.1
F9	11.1±2.6	0.2±0.9	10.1±0.8	1142.5±1.1	0.2	3.2±0.0	3.1±5.1	99.0
F10	25.6±0.4	0.2±0.3	11.3±1.6	1102.9±2.0	0.3	6.4±0.0	5.0±2.4	101.4
F11	15.7±0.6	0.1±0.2	11.7±1.1	1341.1±4.6	0.2	5.3±1.3	10.0±4.0	98.1
F12	33.6±1.6	0.9±1.1	12.1±6.2	1287.4±0.1	0.2	4.9±1.0	2.0±±2.2	98.5
F13	22.1±9.3	1.2±0.7	10.8±8.0	1230.6±2.9	0.2	5.4±0.3	3.3±0.1	97.5
F14	20.7±0.8	1.0±1.6	14.4±0.3	1249.6±0.8	0.1	3.6±0.6	4.1±0.8	99.2
F15	28.5±1.1	0.1±0.8	11.1±1.4	1146.4±21.9	8.6	2.0±0.6	5.8±0.2	100.9
F16	19.0±1.3	0.2±0.6	11.5±3.1	1511.2±2.5	0.4	7.1±0.4	0.6±0.2	100.1
F17	22.8±0.9	0.1±0.2	10.4±5.5	1471.8±14.4	0.4	1.3±1.6	0.1±1.5	98.3
F18	20.2±2.2	0.5±0.2	11.8±0.5	1468.5±0.5	0.4	3.8±0.8	0.2±0.5	95.8
F19	10.5±1.1	0.6±1.1	12.9±2.9	1411.8±1.0	0.4	3.9±1.0	0.2±0.1	99.0
F20	16.1±0.8	1.1±0.2	12.6±2.5	1365.2±14.2	0.3	24.2±2.7	37.0±0.3	103.0
CT	27.5±1.2	1.7±0.1	13.3±1.8	949.3±0.5	0.9	14.4±0.6	58.5±0.1	97.9
N				441.3±2.8	0.2	12.6±3.1	14.0±0.3	101.6

*AR=Angle of repose, HR=Hausner ratio, CI=Carr's compressibility index, WV=weight variation, F=friability, H=hardness, D=disintegration, A=assay test. *n=3*

Table 4 Comparison study results.

	f1	f2	% DE	MDT (min)
F1	54.10	21.40	15.00	0.66
F2	78.90	17.00	6.00	0.55
F3	13.30	49.10	16.00	0.32
F4	37.30	30.50	7.00	0.55
F5	42.40	25.80	15.00	0.64
F6	31.40	29.00	1.00	0.51
F7	33.40	28.90	11.00	0.59
F8	16.30	44.70	18.00	0.26
F9	21.50	41.70	27.00	0.18
F10	14.90	45.70	18.00	0.30
F11	6.30	61.50	12.00	0.36
F12	17.80	41.50	24.00	0.20
F13	29.80	28.80	3.00	0.51
F14	47.70	23.70	13.00	0.61
F15	17.40	41.50	24.00	0.20
F16	10.80	56.60	18.00	0.31
F17	14.60	44.10	19.00	0.25
F18	15.10	46.00	21.00	0.23
F19	38.80	25.50	11.00	0.59
F20	45.20	27.20	4.00	0.41
CT	42.00	28.20	1.00	0.50
N	-	-	16.00	0.32

*f1= dissimilarity factor, f2=similarity factor, MDT=minimum dissolution time, DE=dissolution efficiency.

Table 5 Kinetic model study results.

	ZO	FO	HC	WB	KP	HG
F 16	0.8455	0.9155	0.9618	0.8684	0.8435	0.9229
N	0.8050	0.7820	0.1437	0.7744	0.9010	0.7744

*ZO=zero order, FO=first order, HC=Hixson-Crowell, WB=Weibull, KP=Korsmeyer-peppas, HG=Higuchi.

Table 6 Percent dissolution at different times with correlated quantities gotten within sampling interval for F16

T (h)	CPR	QR (mg)	DQR (mg)
0.17	21.60	43.20	43.20
0.33	67.20	134.40	91.20
0.50	92.00	184.00	50.00
0.70	99.30	198.60	14.60
0.83	102.00	204.00	5.40
1	102.90	205.80	1.80

*QR= quantity of drug release, CPR= cumulative percent drug release, DAR= discrete quantity of drug release within sampling interval, T= time

Table 7 Calculated drug level at different times from F16

TA (h)							PQA (mg)	PC (µg/ml)
0	0.00						0.00	0.00
0.17	43.20						43.20	6.27
0.33	40.98	91.20					132.18	19.19
0.5	38.74	86.22	49.60				174.56	25.34
0.7	36.27	80.71	46.43	14.60			178.01	25.84
0.83	34.75	77.32	44.48	13.99	5.40		175.94	25.54
1	24.98	74.07	42.61	13.40	5.17	1.80	162.03	23.52
2	17.96	53.25	30.63	9.63	3.72	1.28	116.48	16.91
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
23	0.02	0.05	0.03	0.01	0.00	0.00	0.11	0.02
24	0.01	0.04	0.02	0.01	0.00	0.00	0.08	0.01

*PBA= predicted blood quantity after oral absorption, PC= predicted concentration at times, PTQ= predicted total blood quantity following oral absorption, TA= time following absorption.

Table 8 Percent dissolution at different times with correlated quantities obtained within sampling interval for reference tablet.

T (h)	CPR	QR (mg)	DQR (mg)
0.17	21.00	42.00	42.00
0.33	78.60	157.20	115.20
0.50	80.00	160.00	2.80
0.70	86.40	172.80	12.80
0.83	92.70	185.40	12.60
1	99.80	199.60	14.20

*QR= quantity of drug release, CPR= cumulative percent drug release, DQR= discrete quantity of drug release within sampling interval, T= time

Table 9 Calculated drug level at different times from reference tablets.

TA (h)	PBQ (mg)						PTQ (mg)	PC (µg/ml)
0	0.00						0.00	0.00
0.17	42.00						42.00	6.10
0.33	39.84	115.20					155.04	22.51
0.5	37.64	108.93	2.80				149.40	21.69
0.7	35.26	101.97	2.60	12.80			152.63	22.16
0.83	33.78	97.69	2.51	11.50	12.60		158.08	22.95
1	31.94	92.37	2.37	10.87	11.35	14.20	163.10	23.68
2	22.96	66.40	1.71	7.81	8.16	10.21	117.25	17.02
.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.
23	0.22	0.06	0.00	0.01	0.01	0.01	0.11	0.02
24	0.22	0.05	0.00	0.01	0.01	0.01	0.10	0.01

*PBQ= predicted blood quantity following oral drug absorption, PC= predicted concentration of drug at times, PTQ= predicted total blood quantity following oral drug absorption, TA= time after absorption.

Table 10 Predicted and observed pharmacokinetic parameters for F16 and reference tablets, along with their correlated percentage prediction error

PARAMETERS	PV	F16 OV (% PE)	N OV (% PE)
C_{max}	24.10	25.84 (6.73)	23.68 (-1.77)
T_{max}	1.25	0.70 (-78.57)	1.00 (-25.00)
AUC	80.70	90.19 (10.50)	89.42 (9.75)

*AUC= area under the curve, C_{max} =peak plasma concentration, T_{max}, =time to reach maximum concentration, OV= observed values, % PE= percentage predicted error, PV= predicted values

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