Correlation of *in vitro* Dissolution Profiles with *in vivo* Pharmacokinetic Parameters of Some Commercial Brands of Aspirin Tablets Marketed in Nigeria

Emmanuel Adelaja Bamigbola

Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Niger Delta University, Wilberforce Island, Amassoma, Bayelsa State, Nigeria

1. Introduction

From biopharmaceutical point of view, *in vitro*-*in vivo* correlation (IV-IVC) is a predictive mathematical treatment describing the relationship between an *in vitro* property of a dosage form (usually the rate or extent of drug release) and a relevant *in vivo* response (e.g. plasma or urine drug concentrations or amount of drug absorbed). IV-IVC is recommended by various regulatory bodies and mostly applicable to drug dosage forms for oral routes and sustained release products. It is a useful tool for drug dosage form development, because a successful correlation can assist in the selection of drug formulation with appropriate and acceptable dissolution criteria, and depending on its predictiveness, it can be used as a forecast or surrogate for further bioequivalence studies. There are different categories of IV-IVC; A, B, C and D.

In biopharmaceutics classification system (BCS), aspirin belong to class 2, and because of its poor water solubility, the dissolution rate is the rate limiting step, which controls the absorption and bioavailability parameters of oral aspirin drug products. This criterion makes aspirin a good candidate for IV-IVC evaluation. *In vitro*-*in vivo* correlation of four commercial brands of aspirin tablets (one soluble brand and three regular brands) marketed in Nigeria are presented. USPXXI rotating basket apparatus and urinary excretion profiles from eight human volunteers were employed for *in vitro* and *in vivo* assessments respectively. Various dissolution parameters such as percent dissolved in 30 min, dissolution rate constants (k) and time for 50% dissolution (DT_{50%}) and pharmacokinetic parameters such as cumulative amount excreted up to 8 h (E_{8}), maximum excretion rate (dE/dt)_{max} and time for maximum excretion rate (T_{max}) were obtained for all the brands.

The soluble aspirin had the highest percent dissolved in 30 minutes and highest dissolution rate constant with shortest time for 50% dissolution compared with other regular aspirin brands. Comparatively, the soluble aspirin had the highest E_{8} and highest (dE/dt)_{max} with the shortest T_{max}. Significant rank order correlations were observed between all the *in vitro* dissolution parameters such as percent dissolved at 30 min, dissolution rate constants (k) and time for 50% dissolution (DT_{50%}) and all the *in vivo* bioavailability parameters such as...
cumulative amount excreted up to 8 h ($E_8$), maximum excretion rate ($dE/dt_{max}$) and time for maximum excretion rate ($T_{max}$). However, no correlation could be established between the cumulative amount excreted up to 24 h ($E_{24}$) and any of the in vitro dissolution parameters. Moreover statistical analysis showed no significant inter-subject variation among the human subjects that participated in the experiments.

Soluble aspirin tablet exhibited a higher in vitro dissolution and in vivo bioavailability profiles than regular aspirin tablets. The three regular aspirin brands were not bioequivalent to the soluble brands of aspirin. Good IV-IVC was established for the four brands of aspirin tablets. Therefore, with proper standardization of methods of assessment, in vitro dissolution parameters can be used to predict in vivo bioavailability of these aspirin tablets marketed in Nigeria.

1.1 Quality assessment of drug products

1.1.1 In vitro quality assessment of drug products

The quality of drug product especially oral solid dosage forms such as tablets and capsules are often assessed by carrying out certain in vitro tests as contained in the monographs of various pharmacopoeias. Such test include: assay of active ingredients; weight uniformity; content uniformity; hardness; friability; disintegration and dissolution tests. These are to ensure batch to batch uniformity of quality during manufacturing processes.

The general assumption was that if the physical and chemical integrity of a drug product were assured, satisfactory pharmacologic or therapeutic performance would be obtained $^{1,2}$

1.1.2 In vivo quality assessment of drug products

In addition to the vitro quality assessment of drug products as prescribed in various pharmacopoeias, in vivo bioavailability requirement is now an essential parameter in quality control of a number of medicinal products, particularly, those which have low or high therapeutic index or those which are poorly water soluble. This became necessary in view of apparent inadequacy of the in vitro pharmacopoeia tests which did not take into consideration whether or not the active ingredient would be released from the dosage form, nor at what rate it gets into the biologic system. $^3$ Many formulations were produced and marketed that satisfied all the required legal standards but which were not therapeutically active. $^4$

Events and certain realizations have revealed that percentage chemical strength was not the sole criterion for clinical effectiveness. It became obvious that a dosage form must not only contain the correct amount of labeled drugs, but must also release the drugs on administration for absorption in the patient. So apart from chemical purity and percentage strength, bioavailability, clinical efficacy and safety became additional criteria for effective product development. $^5$ It is now recognized that various physicochemical properties and formulation factors can influence the biologic availability of medicaments from dosage from in the body system. $^6$

1.2 Rate limiting step in drug bioavailability

Systemic absorption of most drug products consists of a succession of rate processes. These processes include: (i) disintegration of the drug product and subsequent release of the drug;
(ii) dissolution of the drug in an aqueous environment: and (iii) absorption across cell membrane into the systemic circulation. In the process of drug disintegration, dissolution and absorption, the rate at which drug reaches the circulatory system is determined by the slowest step in the sequence.

The slowest step in a series of kinetic process is called the rate-limiting step, except for sustained release or prolonged-action products; disintegration of a solid drug product is usually more rapid than dissolution and drug absorption. For drugs that have very poor aqueous solubility for example aspirin, the rate at which the drug dissolves (dissolution) is often the slowest step, and therefore, exerts a rate-limiting effect on drug bioavailability. In contrast, for a drug that has a high aqueous solubility, the dissolution rate is rapid and the rate at which the drug crosses or permeates cell membranes (absorption) is the slowest or rate limiting step.

1.3 In vivo dissolution and drug bioavailability

In biologic systems, drug dissolution in an aqueous medium is an important condition for systemic absorption and subsequent bioavailability. The rate at which drug with poor aqueous solubility dissolve from an intact or disintegrated solid dosage form in the gastrointestinal tract often controls the rate of systemic absorption of the drug.

Dissolution is the process by which a drug substance is released from the dosage from into a dissolution medium. A drug administered in a tablet or capsule form must be released, dissolved and reach its site of action before it can exert a pharmacological response. Dissolution of drug in the body represents the end of the release process and precedes the absorption of drugs from solid dosage forms. Various theories of tablet dissolution that have been proffered include: (i) the diffusion layer model, (ii) the Noyes-Whitney theory, (iii) the Wagner’s, (iv) the Kitazawa, (v) the El-Yazigi, (vi) the Carstensen’s theories, (vii) the Danckwert’s model.

Dissolution kinetics of a drug product can be influenced by various factors such as (i) the physicochemical characteristics of the drug substance e.g. particle size, particle shape, polymorphism, crystal form, salt ester formation; (ii) formulation factors such as the nature and amount of excipients e.g. diluents, disintegrants, binders, lubricants, etc. (iii) manufacturing procedures such as the method of granulation, the size and density of the granules, moisture content, age of the granules, compressional force used in tabletting process, the quality of the personnel, the sophistication of the equipment and level of in-process quality control.

Drug in the body particularly, in the gastrointestinal tract, is considered to be dissolving in an aqueous environment. Therefore, temperature of the medium and the agitation rate also affect the rate drug dissolution. The in vivo temperature is maintained at a constant temperature of 37°C, and the agitation (primarily peristaltic movement in the gastrointestinal tract) is reasonably constant.

1.4 In vitro dissolution tests

Dissolution test is an in vitro physicochemical testing of solid oral dosage form. It determines the amount of active ingredient(s) released from a solid oral dosage from,
such as from tablets or capsules, using a known volume of dissolution medium, with a predetermined length of time. The general principle of dissolution test is that the solid dosage form is tested under uniform agitation in an attempt to achieve dissolution. Agitation is accomplished by either using stirrer inside the apparatus or rotating the container holding the dosage form. In vitro dissolution test can be used to guide formulation development, identify critical manufacturing variables, monitor formulation quality from batch to batch, predict in vitro performance, monitor manufacturing process, assure batch to batch product performance and serve as a surrogate for bioavailability and bioequivalence.

The choice of dissolution apparatus varies from one drug to another, depending on the nature of the drug. Conditions employed for the in vitro dissolution test are made in such a way to give the best and reproducible results for the particular drug under test. Such conditions include the size and shape of the dissolution vessel, the agitation rate, temperature of the dissolution medium which for most dissolution test is temperature of 37°C which is similar to the in vivo temperature. The nature and volume of the dissolution media is also important e.g. simulated gastric fluid, simulated intestinal fluid, water, 0.1N HCl, phosphate and acetate buffer depending on the nature of the drug and the location in the gastro-intestinal tract where the drug is expected to dissolve. The volume of the dissolution medium ranges from 500ml to 1000ml.

There are several official methods of carrying out dissolution test of tablets and capsules e.g. rotating basket method (Apparatus 1); paddle method (Apparatus 2); transdermal product testing (Apparatus 3) transdermal product testing (Apparatus 4); transdermal product testing (Apparatus 5). Other unofficial methods are rotating bottle method; flow-through dissolution method; intrinsic dissolution method, and peristalsis method.

1.5 Bioavailability assessment

Bioavailability of a drug refers to the measurement of the rate and extent of active drug that reaches the systemic circulation. The in vivo behaviours of a dosage form can be explained more precisely by its bioavailability. Bioavailability studies are carried out for both approved drugs and those not yet approved for marketing by drug regulatory agencies. This is to ensure that such drugs are safe and effective for their labeled indications for use and that they meet all applicable standards of identity, strength, quality and purity. In vivo bioavailability assessments are also performed for new formulations of active drug ingredients or therapeutic moieties that have full new drug application approvals. Various factors affecting the dissolution of a drug will invariably affect its bioavailability e.g. the physicochemical properties of the drug, formulation factors and manufacturing processes.

1.6 Methods of assessing bioavailability

There are several direct and indirect methods of assessing bioavailability in humans. The selection of a method depends on the purpose of the study, analytical method of drug measurement, and nature of the drug product. The methods are namely:

i. Pharmacokinetic method: this is the measurement of the active drug substance or its metabolite(s) in biological fluids such as blood, plasma, urine, saliva, bile, sweat, milk, breath, faeces and other tissues.
ii. Acute pharmacologic effect. An acute pharmacologic effect such as effect on pupil diameter, heart rate or blood pressure can be useful as an index of drug bioavailability. This may require demonstration of dose related responses.

iii. Clinical observation: such as lack of response (therapeutic failure) good response or toxicity in patient receiving similar drug products may be used to determine drug bioavailability.

iv. In-vitro dissolution test: this is done in selected case where in vitro / in vivo correction has been established for such drug product.

Because the free or therapeutically active drug can be accurately quantified in biological fluids, pharmacokinetic method is often preferred. Among all the body fluids, plasma and urine data gives the most objective information on bioavailability while the rest are less reliable.

The urine method of assessment has some advantages over the blood:

i. Samples are more easily obtained than blood,

ii. Urine collection is more pleasant to the subjects and more convenient,

iii. The concentration of the drugs in the urine is often higher than in the blood, so, simple analytical method (e.g. U.V. spectrophotometer) can be used,

iv. Lack of protein in the urine of a healthy individual obviates the need for denaturation step.

However, the following conditions are necessary for obtaining valid urinary excretion data.

i. Frequent sampling is necessary for a good curve description.

ii. Urine sample should be collected periodically until almost the entire drug has been excreted (a period of approximately seven elimination half lives)

iii. Urinary pH must be kept constant to avoid significant variation in urinary excretion rate.

iv. Subject participating in the study should submit a complete urine specimen i.e. completely emptying the bladder.10, 1, 11, 2, 5

1.7 Pharmacokinetic parameters for bioavailability assessment

There are various pharmacokinetic parameters usually employed in evaluating bioavailability when drugs are assessed in biological fluids.

Plasma:

i. AUC- area under the plasma level-time curve and it reflects the total amount of active drug reaching the systemic circulation.

ii. C_max - is the maximum plasma drug concentration obtained after administration of drug.

iii. T_max – time of maximum plasma concentration, it corresponds to the time required to reach maximum drug concentration. At T_max, rate of absorption equals rate of elimination. Absorption continues after T_max but at a slower rate.

Urine:

i. [E]∞ - Cumulative amount of drug excreted in the urine over a sufficient period of time (usually above 7 half-lives). It is directly related to the total amount of drug absorbed
ii. $[dE/dt]_{\text{max}}$ – Maximum rate of drug excretion, is the maximum rate at which drug is excreted in the urine after the administration of the drug.

iii. $T_{\text{max}}$ - Time of maximum urinary excretion rate, it is the time required to reach maximum rate of drug excretion after drug administration.

The AUC and $[E]_\infty$ are similar in the sense that they both measure the extent of drug absorption (bioavailability) while $T_{\text{max}}$ indicate the rate of drug absorption. $C_{\text{max}}$ and $[dE/dt]_{\text{max}}$ are analogous in the sense that they reflect both the rate and extent of absorption. If the rate of drug excretion in urine is proportional to the concentration in blood, the curve obtained by plotting $[dE/dt]$ against time will be the same as the plasma concentration-time curve, and $T_{\text{max}}$ will be the same. 12, 4, 2, 13, 3, 5

1.8 *In vitro – in vivo* correlation of aspirin tablets

The formulation and implementation of regulations concerning bioavailability of drugs made considerable attention to be given to correlation of *in vitro* dissolution rate with *in vivo* bioavailability14. It has been observed that with proper attention to the operating conditions, dissolution test can become a valuable indicator for potential *in-vivo* performance. *In vitro-in vivo* correlation (IV-IVC) is a predictive mathematical treatment describing the relationship between an in vitro property of a dosage form (usually the rate or extent of drug release) and a relevant *in vivo* response (e.g. plasma drug concentrations or amount of drug absorbed). Establishing an IV-IVC needs an extensive study of drug release from an oral drug delivery system. The study of drug in vitro availability and bioavailability are important part of the IV-IVC procedure for suitable drugs.15 In order to develop safe and effective drugs and validate their formulation, it is important to identify the exact drug pharmacokinetic parameters and biopharmaceutical properties of the dosage forms.

The main objective of establishing IV-IVC is to use dissolution test as a surrogate for *in vivo* bioavailability studies and reduce the need for expensive human studies.16, 17 When *in vitro-in vivo* correlations are established on a formulation, dissolution specifications can be used as a means of controlling drug bioavailability and hence a substitute for human bioequivalence studies.5 There are different categories of IV-IVC; A, B, C and D. Level A correlation represents a point-to-point relationship between *in vitro* dissolution rate and *in vivo* input rate of drug from the dosage form.

Level B correlation utilizes the principle of statistical moment analysis, where the mean *in vitro* dissolution time (MDT$_{\text{vitr}}$) of the product is compared to either mean *in vivo* resident time (MRT) or the mean *in vivo* dissolution time (MDT$_{\text{vivo}}$). Level C correlation, compares one or several dissolution time points (t$_{50}$%$, t_{90}$%, etc.) to one or several mean pharmacokinetic parameter such as AUC, $t_{\text{max}}$, or $C_{\text{max}}$.

Level D correlation is a rank order and qualitative analysis and is not considered useful for regulatory purposes. It is not a formal correlation but serves as an aid in the development of a formulation or processing procedure.14

In the last few years aspirin has become a life saver against cardiovascular complications in addition to its age long usefulness as an analgesic, antipyretic and anti-inflammatory agent.
Aspirin is rapidly absorbed by first order kinetics, following oral administration but is subjected to extensive metabolism to form salicylates which is rapidly and extensively distributed throughout body fluids. The salicylate level in the urine rapidly increases and can be easily detected and analyzed through colorimetric method.\textsuperscript{18,19,20,11} In biopharmaceutics classification system (BCS), aspirin belong to class 2 (drug with low solubility but high permeability). Therefore, because, of its poor water solubility, the dissolution rate is the rate limiting step, which controls the absorption and bioavailability parameters of oral aspirin drug products. This criterion makes aspirin a good candidate for IV-IVC study, because any physico-chemical and formulation factors influencing its in vitro dissolution profile is expected to affect its in vivo bioavailability. In vitro–in vivo correlation of four commercial brands of aspirin tablets (one soluble brand and three regular brands) marketed in Nigeria are presented\textsuperscript{21, 22}. Good correlations between various dissolution and bioavailability parameters of some drugs have been documented\textsuperscript{12, 23, 24, 25, 26, 27}. However, in some cases, no good correlation could be obtained as reported by some investigators\textsuperscript{28, 29, 30}. The following investigations were conducted:

\textbf{a. In vitro dissolution profiles}

\textit{In vitro} dissolution profiles of the four brands of aspirin were evaluated, using USPXXI rotating basket apparatus. The dissolution profiles expressed as percents aspirin dissolved as a function of time for all the brands are shown in Figure 1. Various dissolution parameters such as percent dissolved in 30 min, dissolution rate constants (k) and time for 50% dissolution (D\textsubscript{T50%}) were obtained for all the brands using standard methods \textsuperscript{2}. These are presented in Table 1.

<table>
<thead>
<tr>
<th>Brand</th>
<th>Percent dissolved at 30 min</th>
<th>Dissolution rate constant, k (hr\textsuperscript{-1})</th>
<th>Time for 50% dissolution, D\textsubscript{T50%} (min)</th>
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</thead>
<tbody>
<tr>
<td>A1</td>
<td>75.71</td>
<td>0.059</td>
<td>11.79</td>
</tr>
<tr>
<td>A2</td>
<td>65.75</td>
<td>0.040</td>
<td>17.41</td>
</tr>
<tr>
<td>A3</td>
<td>63.47</td>
<td>0.037</td>
<td>18.53</td>
</tr>
<tr>
<td>A4</td>
<td>68.90</td>
<td>0.043</td>
<td>16.23</td>
</tr>
</tbody>
</table>

Table 1. Dissolution parameters obtained from the dissolution tests of the various brands of aspirin tablets

Figure 1 shows that A1 exhibited the highest dissolution rate while the other three brands (A2 - A4) has similar dissolution rates (p <0.05). Table 1 shows that overall relative ranking of all the brands in terms of the percent dissolved in 30 min and dissolution rate constant (k) followed the order of A1>A4>A2>A3 while the ranking of time for 50% dissolution (D\textsubscript{T50%}) follows the reverse order (i.e. A1<A4<A2<A3). A1 is a soluble brand of aspirin containing calcium carbonate which can provide a reactive medium by changing the pH of the environment adjacent to the drug to alkaline, thus making the acidic drug like aspirin form a water soluble salt, thereby enhancing its rapid dissolution. This possibly accounted...
for its highest solubility rate and shortest time for dissolution compared with the other plain
brands. Brands A2, A3 and A4 are all plain aspirin tablets; various factors such as particle
size and shape of the aspirin content, type and/or amount of excipients, method of
formulation and compression force employed may influence their dissolution rates. The
analysis of variance (ANOVA) performed on the percent dissolved in 30 min shows no
significant difference (P>0.05) among all the brands, they all indicated similar statistical
behaviors in their in vitro dissolution profiles.

Fig. 1. Percent of actual amount of aspirin dissolved as a function of time for the four
different brands.

b. In vivo bioavailability

In vivo bioavailability of the same set of aspirin tablets were assessed in eight human
volunteers using urinary excretion profiles and various in vivo pharmacokinetic parameters
such as cumulative amount excreted up to 8 h (E8), maximum excretion rate (dE/dt)max and
time for maximum excretion rate (Tmax) were calculated using standard methods and are
presented in Table 2. The cumulative salicylate excreted and excretion rate profiles of the
soluble aspirin and the three plain aspirin tablets are presented in figure 2 and 3
respectively. Pharmacokinetic parameters determined were cumulative amount excreted up
to 8h (E8) and 24h (E24), maximum excretion rate (dE/dt)max and time for maximum
excretion rate (Tmax)
Correlation of in vitro Dissolution Profiles with in vivo Pharmacokinetic Parameters of Some Commercial Brands of Aspirin Tablets Marketed in Nigeria

<table>
<thead>
<tr>
<th>Brand</th>
<th>Cumulative amount excreted up to 8h ($E_8$)</th>
<th>Cumulative amount excreted up to 24 h ($E_{24}$)</th>
<th>Maximum excretion rate ($dE/dt)_{max}$</th>
<th>Time for maximum excretion rate ($T_{max}$)</th>
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</thead>
<tbody>
<tr>
<td>A1</td>
<td>173.49</td>
<td>290.59</td>
<td>32.76</td>
<td>2.50</td>
</tr>
<tr>
<td>A2</td>
<td>165.15</td>
<td>275.68</td>
<td>29.93</td>
<td>3.38</td>
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<tr>
<td>A3</td>
<td>164.36</td>
<td>247.63</td>
<td>29.64</td>
<td>3.50</td>
</tr>
<tr>
<td>A4</td>
<td>169.79</td>
<td>281.10</td>
<td>31.36</td>
<td>3.13</td>
</tr>
</tbody>
</table>

Table 2. Pharmacokinetic parameters obtained from urinary excretion analysis of various brands of aspirin.

Fig. 2. Cumulative amount of salicylate excreted up to 24 h for the different brands of Aspirin.

The analysis of variance (ANOVA) performed on the pharmacokinetic parameters shows that all the four brands are bioequivalent in terms of ($E_8$), ($E_{24}$) and ($dE/dt)_{max}$, but the $T_{max}$ of the three plain brands are inequivalent to the soluble brand A1 which has the fastest time for maximum excretion rate. Figure 3 shows that graphs for A2, A3 and A4 were almost superimposable attesting further to their equivalence. The formulation factors that
enhanced the in vitro dissolution of the soluble aspirin are possibly responsible for increase in its in vivo bioavailability, compared to other plain brands, since its dissolution process is the rate limiting step 14, 29.

![Fig. 3. Excretion rate profiles of the four different brands of Aspirin.](image)

**c. In vitro-in vivo correlation (IV-IVC)**

To establish the relevance of the in vitro dissolution performances to the in vivo pharmacokinetic parameters of the four aspirin brands, level C IV-IVC was employed. When various dissolution parameters were correlated with various bioavailability parameters, no significant IV-IVC could be established using $E_{24}$ value. However, significant IV-IVC was observed when cumulative amount excreted up to 8 hours ($E_8$) was employed (Figure 4) with correlation coefficients $r^2 > 0.8$. As shown in Figure 4, good quantitative correlation coefficients were observed between percent dissolved in 30 min and: (a) cumulative amount excreted up to 8 hours ($E_8$) ($r^2 = 0.9532$, $p < 0.05$), (b) Maximum excretion rate $(dE/dt)_{max}$, $r^2 = 0.9697$, $p < 0.05$) and (c) Time for maximum excretion rate ($T_{max}$) ($r^2 = 0.9932$, $p < 0.05$), thus the in vitro parameter correlated well with the in vivo parameters. Similarly, from Figure 5, good quantitative correlation coefficients were also observed between dissolution rate constant $(k)$ and $T_{max}$ ($r^2 = 0.9813$, $p < 0.05$).
p < 0.05). With regards to $E_8$ and $(dE/dt)_{max}$, the correlation was not as perfect as that of $T_{max}$, with correlation coefficients just above 0.8, with exact values of 0.8564 and 0.8879 respectively.

Fig. 4. Correlation of *in vitro* dissolution parameter (percent dissolved in 30 min) with various *in vivo* bioavailability parameters.
Finally, Figure 6 equally shows that good quantitative correlations were established between time for 50% dissolution ($DT_{50\%}$) and (a) $E_8$ ($r^2 = 0.9041$, $p < 0.05$), (b) $(dE/dt)_{max}$ ($r^2 = 0.9297$, $p < 0.05$) and (c) $T_{max}$ ($r^2 = 0.9954$, $p < 0.05$).
In all the IV-IVC performed, best correlation was obtained between the in vivo parameter $T_{\text{max}}$ and all the in vitro parameters used for the correlation. The correlation coefficient recorded in each case was higher than others. The significant IV-IVC observed were in
agreement with the observations of some workers 12, 25 who carried out their own studies on aspirin in centers outside Nigeria.

2. Summary

Using USPXXI rotating basket dissolution apparatus, soluble brand of aspirin tablet A1 exhibited the highest dissolution profile, when compared to other plain brands of aspirin.

ANOVA of pharmacokinetic data obtained from colorimetric assay of urinary salicylate excretion of the four brands of aspirin showed that all the four brands are bioequivalent in terms of \(E_8\), \(E_{24}\) and \((dE/dt)_{max}\), but the \(T_{max}\) of the three plain brands are not equivalent to the soluble brand A1 which has the fastest time for maximum excretion rate.

Good in vitro-in vivo correlations were established between various dissolution and bioavailability parameters of four commercial brands of aspirin tablets using Level C in vitro-in vivo correlation approach. Therefore, with proper standardization of methods of assessment, in vitro dissolution parameters can be used to predict in vivo bioavailability of these aspirin tablets marketed in Nigeria.

3. References


This book, "Readings in Advanced Pharmacokinetics - Theory, Methods and Applications", covers up to date information and practical topics related to the study of drug pharmacokinetics in humans and in animals. The book is designed to offer scientists, clinicians and researchers a choice to logically build their knowledge in pharmacokinetics from basic concepts to advanced applications. This book is organized into two sections. The first section discusses advanced theories that include a wide range of topics; from bioequivalence studies, pharmacogenomics in relation to pharmacokinetics, computer based simulation concepts to drug interactions of herbal medicines and veterinary pharmacokinetics. The second section advances theory to practice offering several examples of methods and applications in advanced pharmacokinetics.

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