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Research Article

Biopharmaceutics and pharmacokinetics of plain and soluble brands of aspirin tablets embedded in food bolus orally administered to human volunteers

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Abstract

Many people ingest solid drugs embedded in food bolus to alleviate the problems of gastric irritation, unpleasant taste and odour which may affect the biopharmaceutics and pharmacokinetics of the drugs. This study investigated the biopharmaceutics and pharmacokinetics of plain and soluble brands of aspirin tablets embedded in food bolus orally administered to human volunteers. The pharmacokinetic profiles of two brands of commercial, uncoated aspirin tablets (300 mg) were assessed in eight healthy human volunteers when taken unembedded and when embedded in food bolus. The tablet samples were coded as S (soluble or dispersible aspirin tablet), P (plain or immediate-release aspirin tablet), SB (soluble aspirin tablet embedded in food bolus) and PB (plain aspirin tablet embedded in food bolus). Pharmacokinetic parameters generated from the salivary excretion data were evaluated. The biopharmaceutics factors of the drugs were also considered. The cumulative drug excreted up to 24 hours [E_{24h}] and maximum excretion rate $[dE/dt]_{max}$ of S were significantly higher ($P < 0.05$) than P, SB and PB. Time for maximum excretion rate [T_{max}] of S was significantly lower ($P < 0.05$) than P, SB and PB. There was no significant difference ($P > 0.05$) between P and SB, but PB had significantly lower E_{24h}, and $[dE/dt]_{max}$ ($P < 0.05$) and significantly higher T_{max} ($P < 0.05$) than P and SB. Food coating and excipients were observed as the biopharmaceutics factors that influenced the pharmacokinetics of the aspirin tablets. Biopharmaceutics and pharmacokinetics of aspirin tablets may be significantly altered when embedded in food bolus.

Keywords: Biopharmaceutics; Pharmacokinetics; Bioavailability; Food Bolus; Aspirin.

INTRODUCTION

Oral route is mostly preferred over other routes for drug administration because it is non-invasive, convenient to administered and acceptable by most patients [1]. However, oral administration of some drugs is associated with some problems such as unpleasant taste, nauseating odour and irritation of the gastric mucosa [2]. In order to alleviate these problems, some people take oral solid drugs concomitantly with food, while other people embed the solid drugs in the food bolus to be ingested.

Concomitant administration of food with drugs can affect the pharmacokinetics of the drugs in many ways [3]. Food can alter the physiological environment of the gastrointestinal tract which can in turn significantly influence drug's solubility, dissolution and bioavailability in the body system [2, 4]. The bioavailability of many drugs is greatly reduced by concomitant food ingestion, while the bioavailability of some poorly water-soluble drugs is enhanced when taken with fatty food [5, 6]. Therefore, it is believed that embedding oral solid drugs in food bolus before ingestion may significantly alter the biopharmaceutics and pharmacokinetics of the drugs.

Oral ingestion of solid drugs embedded in food bolus is commonly practiced by many in Africa, especially Nigeria with the aim of alleviating the problems associated with these drugs. Food bolus mostly used to embed drugs are carbohydrate (polysaccharides) such as 'eba' and 'fufu' (made from cassava flour), 'amala' (made from yam flour), 'semovita' (made from wheat flour), etc. Embedding aspirin tablets in food bolus can modify it from immediate release dosage form to delayed release dosage form by forming a coating barrier on the surface of the tablets. This modification can prolong the disintegration and dissolution

processes, affect drug absorption, pharmacokinetics and *in vivo* bioavailability of the drug when ingested [7].

Aspirin is a non-steroidal anti-inflammatory drug (NSAID) used for pain, inflammation, arthritis, fever and thrombosis and is usually embedded in food bolus by many people to alleviate the problem of gastric mucosa irritation. Aspirin absorption follows first-order kinetics and it is partly hydrolyzed to salicylic acid during absorption. The serum half-life of the absorbed aspirin is approximately 20 minutes as it is rapidly hydrolyzed systemically to salicylic acid. The salicylic acid is metabolized and distributed as salicylate in many biological fluids such as blood, plasma, urine, saliva, bile, sweat, milk, breath, feaces and other tissues before it is excreted [8, 9, 10]. Salicylate concentration can be easily assayed in biological fluids using colorimetric method and can therefore be used to quantify the concentration of aspirin in the body. Salicylates concentration in saliva has a linear correlation with free salicylate concentration in serum, therefore, assay of salivary salicylate concentration may serve as a useful non-invasive technique in the evaluation of bioavailability of different formulations of aspirin [9, 11, 12].

Biopharmaceutics is the study of the effects of physicochemical properties of a drug, formulation factors, type of dosage form, manufacturing process and route of administration on the bioavailability of the drug [12, 13]. Bioavailability is the study of the rate and extent of drug absorption in biological systems while pharmacokinetics is the study of the kinetics of drug absorption into the body and its disposition (distribution, metabolism and excretion) inside the body. Pharmacokinetics parameters are obtained from the measurement of the concentrations of drug substances or its metabolites in biological fluids and is one of the ways of evaluating drug bioavailability apart from clinical observation and assessment of acute pharmacological effects [9, 13]. Biopharmaceutics and pharmacokinetics are two inter-related specialties in pharmaceutical sciences that are important for drug product development, drug therapy optimization, design of pharmacokinetic-pharmacodynamics mathematical models and correlations of *in vitro* and *in vivo* parameters [14, 15].

Whereas, so many works have been done on concomitant administration of food and drug, information on drug embedded in food bolus is very scarce. Bamigbola et al, (2018) in the earlier study, reported that the *in vitro* disintegration and dissolution parameters of both soluble and plain aspirin tablets were significantly altered when embedded in "eba" food bolus. However, work on the biopharmaceutics and pharmacokinetics of aspirin tablets embedded in food bolus orally administered to human has not been documented, which is the focus of this study [7].

MATERIALS AND METHOD

Two brands of commercially available uncoated, immediate release (IR) aspirin tablets were obtained from a retail pharmacy at Yenagoa, Bayelsa State, Nigeria. The tablets were well within their expiry dates and the labelled amount of drug substance for each brand is the same (300 mg). The primary and secondary packages were well examined to ensure physical integrity of the products. The tablets were coded P (Plain aspirin tablet), S (Soluble aspirin tablet). Some of these tablets were embedded in 3 g of freshly prepared "eba" food bolus - a polysaccharide staple food made from cassava flour and labelled PB (Plain aspirin tablet embedded in food bolus) and SB (Soluble aspirin embedded in food bolus).

Iron (III) chloride solution, a complexing agent (containing 0.02M iron (III) chloride, 0.025M hydrochloric acid and 0.025M potassium chloride) was prepared by dissolving 3.24g of iron (III) chloride (BASF, Germany), 1.86g of potassium chloride (ABSCO, UK) and 2.0 ml of concentrated hydrochloric acid (May and Baker, England) in distilled water and made up to 1 L. Sodium salicylate (BDH, England) dissolved in iron (III) chloride solution was used to prepare a standard calibration graph using UV spectrophotometer (Spectronic 21, Milton Roy, USA) at 265 nm. All other materials used were of high analytical grade.

Preparation of aspirin tablets embedded in food bolus

The method of Bamigbola, et al (2018) was adopted to produce "eba" food bolus from cassava flour obtained from cassava tubers (*Manihot esculenta*) [7].

Production of cassava flour (Garri)

The tubers were washed and peeled. The peeled tubers were thoroughly washed and grated into a mash to initiate the process of fermentation and detoxification. The mash was packed in a porous polypropylene bag and compressed by hydraulic press machine for five days to remove poisonous hydrocyanic acid and excess water while fermentation take place. After five days, the bag containing the mash was further pressed for one hour to extract the remaining fermented liquor. The detoxified mash was disaggregated by screening through a sieve and dried in a large frying pot. The mash was consistently stirred with a paddle while drying to prevent sticking and charring. The resultant dried "garri" granules were further screened into fine flour and packed in appropriate bags and stored.

Preparation of food bolus

One litre of water was heated to the boiling point of 100 ^{o}C and 500 g of cassava flour (garri) was added to the boiled water followed by continuous stirring to form a smooth, firm, gelatinized solid mass (eba). This was allowed to cool down. 3 g of "eba" was weighed on an electronic balance (Mettler Toledo, Switzerland) and one sample P aspirin tablet was embedded in it and molded into a spherical bolus with hands and labelled PB. Twenty samples of P were embedded individually using the same method. The same procedure was used to prepare twenty samples of sample S aspirin tablets labelled as SB. The average thickness of the food bolus on PB and SB were 3.72 $\pm$ 0.15 mm and 3.65 $\pm$ 0.21mm respectively.

Clinical study design

The Clinical Study Protocol and Written Informed Consent Form were reviewed by the Institution's Research Ethic Committee before giving ethical clearance to conduct the study. The clinical study was conducted in accordance with the Committee guidelines on Conduct of Human Experiments and rules of Good Clinical Practice (GCP).

An open randomized two-way cross-over single dose design study with 7 days washout period was conducted in eight healthy adult volunteers (4 males and 4 females; age, 21 - 28 yr; weight, 55 - 82 kg; height, 1.55 - 1.75 m) that have no history of liver, kidney or gastro intestinal disease. The volunteers did not take any medication, alcohol, and other beverages or food that might interfere with the drugs, one week prior and throughout the entire study period.

Following an overnight fast, each subject was asked to produce saliva for zero hour, after which two tablets of aspirin (600 mg) were ingested with 100 ml of water. No food or liquid other than water was permitted for over 4 hr., following ingestion of the dose. The subjects were instructed to masticate their mouth by chewing gum to facilitate saliva production and flow. Cumulative saliva samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hr. Aliquot of the saliva samples stored at 4 ^{o}C immediately and protected from light. A uniform meal was served after the 4-hr sampling.

Determination of salicylate excreted in saliva

The total amount of salicylate excreted in the saliva sample was measured through colorimetric analysis. Iron (III) chloride solution was used as a complexing agent to react with the salivary salicylate to form a violet tetraaquosalicylatrioiron (III) complex that was assayed using spectrophotometer. A 1ml sample of the saliva was pipetted into a 25 ml volumetric flask and the sample was diluted by adding iron (III) chloride solution to the marking of the volumetric flask. The absorbance of the violet solution produced was measured at 540 nm using a UV spectrophotometer (Spectronic 21, Milton Roy Company, USA). The iron (III) chloride solution was used for 100% transmittance adjustment. The concentrations of salicylate excreted in the saliva samples was determined from a calibration curve prepared with sodium salicylate.

Pharmacokinetic profiles and data analysis

The Pharmacokinetic parameters determined from the data obtained include cumulative amount of salicylate excreted up to 24h [E_{24h}], maximum excretion rate $[dE/dt]_{max}$ and time for maximum excretion rate $T_{(max)}$. Comparative analysis of pharmacokinetic parameters generated for the embedded and unembedded aspirin tablets was carried out using analysis of variance (ANOVA). At 95% confidence interval, 2 tailed p values less than 0.05 were considered to be significant.

RESULTS AND DISCUSSION

Pharmacokinetic data from the clinical study

The various pharmacokinetic parameters employed in the assessments of embedded and unembedded aspirin tablets in this study include:

- Cumulative amount of salicylate excreted in the saliva over 24hr [E_{24h}]. It indicates the total amount of aspirin absolved after administration.
- Maximum excretion rate $[dE/dt]_{max}$. This is the maximum rate at which the salicylate is excreted in the saliva after administration of aspirin.
- Time of maximum salivary excretion rate (T_{max}) is the time required for salicylate to reach the maximum rate of excretion after the administration of aspirin.

The cumulative amount of salicylate excreted in the saliva up to 24hr [E_{24h}] for all the sample tablets are shown in figure 1 and table 1 below, while the salicylate excretion rate profiles i.e., maximum excretion rate $[dE/dt]_{max}$ and time for maximum excretion rate $T_{(max)}$ for are shown in figure 2 and table 1 below. The [E_{24h}] and $[dE/dt]_{max}$ for the tablet samples are in the order of S > P > SB > PB while $T_{(max)}$ followed the reverse order of S < P < SB < PB. The [E_{24h}] and $[dE/dt]_{max}$ of S were significantly higher ($P < 0.05$) than that of P, SB and PB while the $T_{(max)}$ of S was significantly lower ($P < 0.05$) than that P, SB and PB. There was no significant difference ($P > 0.05$) between P and SB in terms of $E_{24h,}$ dE/dt_{max} and T_{max}. However, PB had significantly lower $E_{24h,}$ and $[dE/dt]_{max}$ ($P < 0.05$) and significantly higher T_{max} ($P < 0.05$) than P and SB.

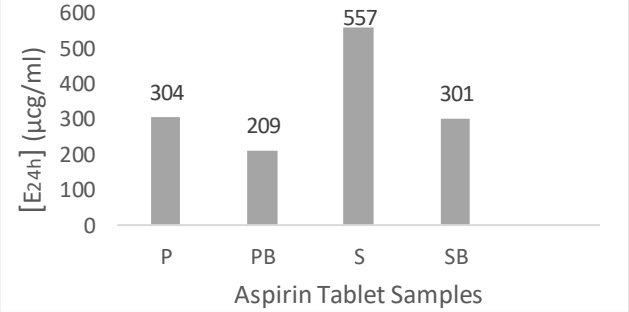

Figure 1: Cumulative salicylate excreted up to 24 hours for embedded and unembedded plain and soluble aspirin tablets in 8 healthy human volunteers

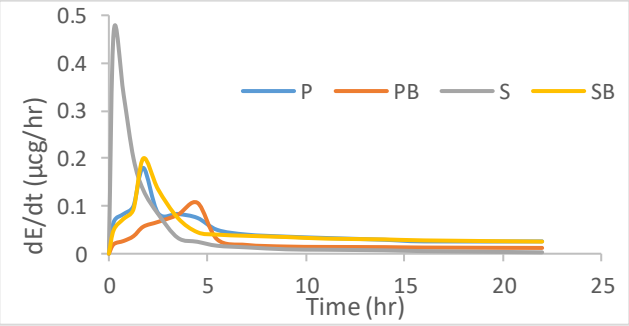

Figure 2: Excretion rate profiles of embedded and unembedded plain and soluble aspirin tablets in 8 healthy human volunteers

Table 1: Pharmacokinetic parameters of embedded and unembedded plain and soluble aspirin tablets in 8 healthy human volunteers

Tablet samples	E_{24h} (µcg/ml)	$[dE/dt]_{max}$ (µcg/hr)	T_{max} (min)
S	557 ± 0.0594	0.4667 ± 0.0013	15 ± 0.0133
P	304 ± 0.0403	0.1800 ± 0.0025	105 ± 0.0203
SB	301 ± 0.0393	0.2000 ± 0.0043	105 ± 0.0155
PB	209 ± 0.0304	0.1067 ± 0.0033	270 ± 0.0270

Biopharmaceutic factors of embedded and unembedded plain and soluble aspirin tablets

The four major biopharmaceutic factors of embedded and unembedded plain and soluble aspirin tablets that may affect their pharmacokinetic profiles considered in this study are show in table 2 below. These include physicochemical property (solubility) of the active pharmaceutical ingredient (aspirin), special excipient used in the formulation of the tablets (solubilizing agent), route of administration and the coating of the food bolus on the embedded tablets samples.

Table 2: Biopharmaceutic factors of embedded and unembedded plain and soluble aspirin tablets in food bolus

Tablet Samples	Physicochemical properties	Excipient	Formulation Type	Route of administration
S	Poorly soluble	Solubilizing agent	unembedded/uncoated	Oral
P	Poorly soluble	No solubilizing agent	unembedded/uncoated	Oral
SB	Poorly soluble	Solubilizing agent	embedded/coated	Oral
PB	Poorly soluble	No Solubilizing agent	embedded/coated	Oral

DISCUSSION

Clinical implications of the pharmacokinetic parameters

There is a direct relationship between the pharmacokinetic parameters of a drug and its pharmacological effects or clinical manifestations. Pharmacokinetic data such as E_{24h}, $[dE/dt]_{max}$ and T_{max} obtained from the salivary excretion of aspirin samples are all indicative of *in vivo* bioavailability parameters. E_{24h} and $[dE/dt]_{max}$ are measures of the extent of drug absorption (bioavailability) and are reflection of the systemic drug concentration required for therapeutic effect. T_{max} is a measure of the rate at which drug is absorbed and indicates the onset of therapeutic effect. The higher the E_{24h} and $[dE/dt]_{max}$, the higher the extent of absorption and bioavailability of the drug in the body system, conversely, the lower the T_{max}, the faster the onset of therapeutic effect of the drug absorbed [9,12,13].

The values of E_{24h} and $[dE/dt]_{max}$ for sample S were significantly higher ($P < 0.05$) than all other samples. Also, the T_{max} for S was significantly lower ($P < 0.05$) than other samples. These showed that Sample S is not bioequivalent to all other samples in terms of bioavailability and onset of therapeutic effect. There was no significant difference ($P > 0.05$) between P and SB in all of the three pharmacokinetic parameters considered, both sample can be said to be bioequivalent in terms of bioavailability and onset of action. However, PB had significantly lower $E_{24h,}$ and $[dE/dt]_{max}$ ($P < 0.05$) and significantly higher T_{max} ($P < 0.05$) than P and SB indicating that it is not bioequivalent to any of the samples in terms of bioavailability and onset of therapeutic effect.

Effects Biopharmaceutic Factors on the Pharmacokinetic parameters

Various biopharmaceutic factors that can affect the pharmacokinetics and bioavailability of a drug includes physicochemical properties, excipients, formulation type, route of administration and manufacturing process [12]. The four major biopharmaceutic factors of the various samples of aspirin tablets considered in this study are physicochemical property (solubility) of the active pharmaceutical ingredient (aspirin), special excipient used in the formulation of the tablets (solubilizing agent), route of administration and the coating of the food bolus on the embedded tablets samples are shown in table 2 above.

The two biopharmaceutic factors common to all the tablet samples are the physicochemical property of the active pharmaceutical ingredient and the route of administration. Aspirin, the active pharmaceutical ingredient (API) in all the tablet samples is a poor water-soluble drug. All the tablet samples were administered through the oral route to the same set of human subjects and there was no significant inter-subject variation in the salivary excretion of salicylate among the human volunteers used. The variable biopharmaceutic factors among the tablet samples that can influence the dissolution and absorption are the formulation excipient and the food coating. Sample S contained calcium carbonate, a solubilizing agent while P has no solubilizing agent. Sample SB and PB were embedded in food bolus.

Both samples P and S were not embedded in food bolus. Sample P is a plain immediate-release aspirin tablet without solubility - enhancing excipient, while sample S is a soluble aspirin tablet that contained calcium carbonate, a solubility - enhancing excipient. The dissolution of aspirin in sample P is neither enhanced by any solubility - enhancing excipient nor retarded by food coating. Since, aspirin belongs to class II of Biopharmaceutic Classification System (BCS) with low solubility and high absorption properties, the dissolution rate of aspirin is the rate limiting step that controls its absorption and bioavailability in the human subjects. The dissolution of aspirin and subsequent absorption from sample P will follow its normal diffusion mechanism into the dissolution medium [16]. Calcium carbonate in sample S provides a weakly alkaline reactive microenvironment around aspirin, a weakly acidic drug to form a salt derivative that is more soluble in water thereby enhancing the solubility and diffusion of the saturated aspirin salt from the surface of the tablet to the dissolution medium. This may significantly enhance the dissolution of Sample S when compared to Sample P [17]. Bamigbola et al (2018) confirmed this in an earlier study carried out, by showing that Sample S had higher *in vitro* dissolution parameters compared to sample P [7]. The significantly higher bioavailability parameters of sample S over sample P observed in this study may be connected to its enhanced solubility and dissolution because of the excipient as documented earlier. Furthermore, Bamigbola et al (2009) and Kanani et al (2015) in other separate reports have also demonstrated that fast releasing (dispersible/soluble) tablets had significantly ($P<0.05$) higher bioavailability than plain aspirin tablets [10, 18].

Samples PB and SB were embedded in food bolus and their bioavailability was significantly reduced because of the food coating around the tablet. Tablet coating can change immediate release formulations to modified released dosage forms such as sustained release, prolonged release and controlled released formulations [19]. The "eba" food bolus coating on the SB and PB would prolong the disintegration time and retard the penetration of gastric fluid into the core where the drug is embedded. These two effects can delay the dissolution, modify drug release pattern and affect the bioavailability of the embedded tablets [20, 21].

Previous studies conducted by Bamigbola et al (2018) showed that the disintegration time for the embedded SB (16 minutes) and PB (18 minutes) were significantly higher than that of unembedded S (12 seconds) and P (30 seconds). Subsequently, the prolonged disintegration time was found to affect the dissolution profiles. While S and P released 44.83% and 33.9% of their content respectively within 5 minutes *in vitro*, SB and PB released 23.73% and 2.7% respectively within the same time. The effects of the food bolus on the *in vitro* disintegration and dissolution of PB and SB might be replicated in the *in vivo* disintegration and dissolution processes and eventually the *in vivo* bioavailability [7].

In this study, PB and SB were embedded in "eba", which is a polysaccharide food that served as a coating material on the tablets. Polysaccharides are examples of hydrogels used as coating materials. Hydrogels swell when they come in contact with gastric fluid. The food coating and solubilizing agent modified the mechanisms of drug release from PB and SB. The viscous gel produced from eba can hinder the release of aspirin from the embedded tablets by delaying the penetration of the gastric fluid into the embedded tablets. It also reduced the diffusion of aspirin out of the tablets core into the gastric fluid because of the increased diffusion path length caused by the swollen gel [22, 23]. In this case SB would have an advantage over PB because of its enhanced solubility that will facilitate the diffusion of aspirin through the gel into the gastric fluid. On the other hand, PB containing poorly soluble aspirin would depend solely on the disintegration or erosion of the food bolus to become dissolved in the gastric fluid. This made the effect of food bolus to be more pronounced on PB than on SB [24, 25].

Food bolus counteracted the effects of the solubility - enhancing excipient in SB and the bioavailability was reduced and became bioequivalent to P. Though, the solubility of SB was reduced, it may still be therapeutically effective, although with longer onset of action. The bioavailability of PB was more affected in terms of rate and extent of absorption, it had significantly lower bioavailability ($P < 0.05$) than all other tablet samples. This may cause delayed onset of action or sub-therapeutic drug concentration which can lead to therapeutic failure of the drug.

CONCLUSION:

Bioavailability of plain and soluble aspirin tablets may be significantly reduced when embedded in food bolus. The embedded soluble aspirin tablet may still be therapeutically bioequivalent to the unembedded plain aspirin tablet, whereas the embedded plain aspirin tablet may have delayed onset of action or become therapeutically ineffective.

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Amaka Victoria Ekezie: Literature search, writing of manuscript

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