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RESEARCH ARTICLE

PREDICTIVE IN-VITRO EVALUATION OF FOOD EFFECT ON THE IN-VIVO PERFORMANCE OF CHLORPROPAMIDE TABLET

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ABSTRACT

This study compared the disintegration time and dissolution profile of the hypoglyceamic drug product, chlorpropamide marketed in Nigeria as Chlorbinese in simulated gastric fluid (SGF), simulated intestinal fluid SIF, food modified gastric fluid (FMSGF) and intestinal fluid (FMSIF) as a measure of the effect of dosing condition on in-vivo drug performance. Various quality control parameters including weight uniformity, tablet hardness, disintegration, friability and assay were assessed prior the dissolution profile determination. Food containing media were prepared by blending 1.3ml full cream fat containing milk and 25mg of soluble starch was added to 500ml and 300ml of SGF and SIF to make FMSGF and FMSIF respectively. The in-vivo performance of the drug at the dosing conditions was also determined using 24 healthy volunteers with post dosing administration of drug and blood sampling. The titrimetric and spectrophotometric assays gave 99.37% and 104.12% of chlorpropamide content respectively ($P<0.05$). No significant differences were observed between the disintegration time for FMSGF, SGF, SIF and FMSIF being (5s, 4s ,4s and 6s) respectively at $P<0.05$. There was no significant difference in the percentage drug release in FMSIF compared with SIF (40% v 35%) similarly there was no difference in the release rate for media simulating dosing conditions in the stomach revealing (28% v 28%) release at $P<0.05$. There was no significant difference in the change in blood glucose level in the volunteers with respect to the dosing conditions $P<0.05$.

Dosing conditions did not affect the drug release and blood glucose reduction of chlorpropamide tablet.

Keywords: Chlorpropamide, Food effect, Simulated media, Drug release .Glucose level

INTRODUCTION

Drug interaction with food and beverages are known to occur exemplified by the well known interaction between monoamine oxidase inhibitor and tyramine containing food [1]. Grapefruit juice caused the most clinically relevant of these interactions as typified in concomitant administration of simvastatin with grape juice leading to increased risk of statin-induced adverse effects such as myopathy [2].

The dissolution and absorption of certain drugs such as tetracyclines, flouroquinolones have been reported to be markedly reduced if administered with milk and other dairy products. The absorption of aspirin and other salicylates have also been shown to be delayed by the presence of food while ketoconazole and itraconazole have been increased [3-5].

Chlorpropamide is a sulphonylurea and a long acting hypoglyceamic agent widely prescribed for patients with Type II diabetes mellitus. In non insulin dependent diabetes mellitus (NIDDM), diet is usually restricted as a supportive in the control of blood sugar. The concomitant administration of food or drink with the oral hypoglyceamic agent may affect the rate and extent of dissolution and consequently the absorption of the drug [6]. Linking drug doses to daily routines such as meal times can improve patient's compliance; however, the possible alteration of the pharmacokinetics of the drug is an issue worthy of note. Majority of reported events of therapeutic failure in the world may be due to factors that include the presence of certain food substances that can reduce the dissolution and absorption of drugs in the gastrointestinal tract [7, 8].

Chlorpropamide is indicated as an adjunct to diet and exercise to improve glyceamic control in adults. It lowers the blood glucose acutely by stimulating the release of insulin from the pancreas thereby exerting hypoglyceamic effect in normal subjects in about an hour and the maximum concentration in systemic circulation is achieved in 2-3 hours post dose. Chlorpropamide binds to plasma protein and loss of blood sugar control has been reported following concomitant administration of certain drugs such as the non steroidal anti-inflammatory drugs (NSAID) and sulphonamides. There has been no documentary evidence of the pattern of drug level of chlorpropamide when taken with certain food eaten in the tropics [9]. The presence or absence of food (state of fill of the stomach) determines the rate of emptying of the gastric content into the duodenum. Factors that tend to delay gastric emptying include fat content of meal, temperature and nature of fluid taken i.e. beverages [10-12].

Food effects are usually not predictable. Generally, the presence of food in the gastric lumen stimulates the flow of bile acids which act as surfactants involved in the solubilization of fats and lipophilic drugs [6-9].

The study had the objective of establishing whether there are differences in the dissolution pattern of chlorpropamide tablet in SGF, FMSGF, SIF and FMSIF. The study also evaluates the dosing effect on the the performance of chlorpropamide.

MATERIALS AND METHOD

Materials

Ethanol, methanol and acetone were products of Sigma Aldrich Chemicals Germany; acetic acid, sodium hydroxide, hydrochloric acid, sodium chloride, sodium dihydrogen phosphate and potassium phosphate products of Kernel Chemicals UK.

Commercial Tablet

A pack of 100 by 250mg of chlorpropamide was purchased for the study. Details of tablet description are outlined in Fig. 1.

Prepared Reagents

Study Media

Simulated Intestinal Fluid

40g of sodium hydroxide and 34g of monobasic potassium phosphate were added to 2L of distilled water and the volume made up to 5L mark in a volumetric flask [13, 14]. The resulting pH was 7.32.

Simulated gastric fluid

43ml of concentrated hydrochloric acid was added to 2L of distilled water in a volumetric flask. This was followed with 500ml of 20% sodium chloride solution and the final volume made up to 5L [13, 14] mark. The resulting pH was 1.13

Food modified SGF and SIF

Food modified SGF and SIF was prepared by adding 100ml of peak milk and 25mg of soluble starch with 500ml of SGF or 300ml of SIF to get food modified SGF and SIF respectively [15].

Calibration curve

Four tablets of chlorpropamide 250mg were crushed into fine powder and extracted in 40ml acetone. The drug in acetone was filtered and the filtrate was left in a crucible and allowed to evaporate at room temperature. 16 mg of the recovered drug was dissolved in 40 ml of methanol and 0.1 N hydrochloric acid used to make up to 50ml to obtain the stock solution. 5ml of the prepared stock was diluted to 100ml with 0.01M hydrochloric acid and this was further diluted to give concentrations of 1.6, 3.2, 4.8, 6.4, 8.0, 9.6, 11.2, 12.8 and 14.4µg/ml. The absorbance of the various concentrations was read off from the UV spectrophotometer at 232nm.The result was comapred with the titrimetric procedure involving the quantitative determination of the amount of chlorpropamide released from the tablet by the reaction of the excess base in solution with perchloric acid.

Drug administration and ethical protocols

The study protocol and the informed consent forms were approved by the Ethical Committee of the University of Uyo Health Services, Uyo, Nigeria. The whole study which meets the requirements of the declarations of Helsinki was conducted in accordance with the Current Good Clinical Practice (GCP), International Conference Harmonization (ICH) as well as Good Laboratory Practice (GLP) Guidelines [16,17].

Twenty four young adult healthy volunteers, non smokers, aged Mean ± SD (27.4 ± 5.6) years and body weight Mean ± SD 72.5 ± 6.3 Kg were recruited into the study. The volunteers were not on concomitant medications and they were free from any significant cardiac, hepatic, renal, pulmonary, gastrointestinal, neurological or hematological disease as reported from a physical examination and laboratory tests along with medical history probe conducted by a qualified physician four weeks prior the commencement of the study. The volunteers were given a written informed consent write-up which explained the nature of the study. All the volunteers were willing to participate in the study and were requested to abstain from drug and alcohol for three days prior the study. They were also requested to fast for at least 10 hours overnight before drug administration. The volunteers were randomly selected and grouped into two consisting of 6 males and 6 females per group. The first group was given 250mg chlorpropamide tablet before food. The blood sugar levels were read off before the dosing and exactly 3 hours post dose. The second group was similarly treated but dosed after ingestion of two sliced bread with 35cl of milk made with two heaped teaspoonful Peak powdered milk. The volunteers were not restrained from drinking water as desired during the study. The study had an open randomized crossover design with a 14-day washout period between the doses.

Statistical analysis

Statistical significance in the values of disintegration and dissolution outcome in the different media were evaluated through one sample hypothesis and one tail at α=0.05. Significance difference in the mean blood glucose reduction within and among the group was evaluated using one way ANOVA and chi square.

RESULT

The details of the drug used in the study are laid out in Table 1. The physicochemical parameters of the drug are expressed in Table 2. The dissolution and disintegration indices of chlorpromazine hydrochloride tablet employed in the various simulate media are presented in Table 3. The dissolution profile of the drug in the various media is given in Fig 1. The calibration curve parameters are expressed in the equation below.

$$Y=2.34x+0.0021;\ R=0.969$$

The resulting pH of the FMSGF and FMSIF are 2.7 and 7.9 respectively. The outcome of the blood sugar measurements are presented in Table 4.

Table 1: The properties of used drugs

Brand name	Chlorpropamide
Tablet Strength	250mg
Manufacturer	Neimeth Pharmaceuticals
Country of manufacture	Nigeria
Registration number	04-7517
Batch number	00117003
Manufacturing date	08-2010
Expiry date	08-2013

Table 2: Disintegration time and Dissolution indices of chlorpropamide tablet in the various media

Disintegration time and dissolution C_{45} in the media							
Disintegration time (min)				C_{45} values (%) from dissolution profile			
SGF	SIF	FMSGF	FMSIF	SGF	SIF	FMSGF	FMSIF
4.0±0.5	4.0±0.6	5.0±0.5	6.0±0.4	28.0	35.0	28.0	40.0

Table 3: The analysis of physicochemical properties of chlorpropamide tablet

Physicochemical properties of chlorpropamide				
Friability (%)	Crushing Strength (Kg/cm^2)	Weight Uniformity (mg)	Chemical content determination (%w/w)	
			Back titration	UV spectrophotometer
0.079±0.001	2.1±0.6	317.29±0.67	99.37±0.43	104.12±0.67

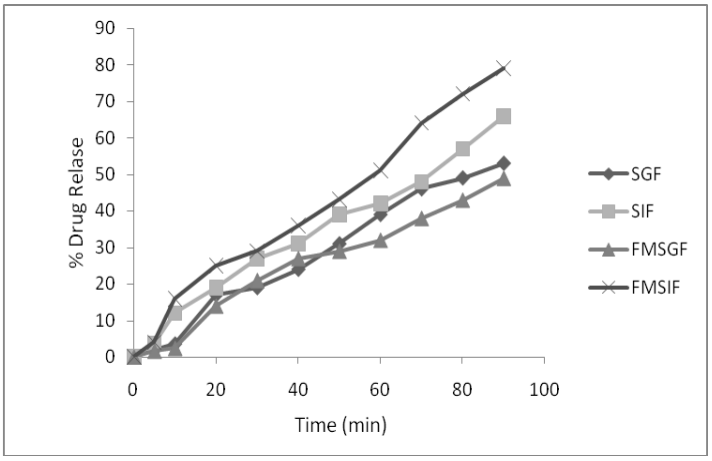

Fig 1: The dissolution profile of chlorpropamide in the four dissolution media

Table 4: The statistical analysis of the blood sugar level outcome of the groups of volunteers (n=12) on administration of chlorpropamide at different dosing conditions

The statistical indices of the groups				
n(12)				
Groups	∑ΔBS	∑ΔBS/n	SD	P
Group A (+F)	170	14.2	8.6	0.835
Group A (-F)	145	12.1	9.8	0.409
Group B (+F)	185	15.4	6.8	0.545
Group B (-F)	210	17.5	9.5	0.633

-F= with food ; +F= without food, ∑ΔBS=Change in Blood sugar level(mg/dl)
α=0.05 and significance at P<0.05

DISCUSSION

The quality control parameters of the studied drug complied with the official specifications in BP 1973, this gives the confidence of the choice of brand of drug used for the study [18]. UV spectrophotometric determination and titrimetric methods were employed for the chemical content determination in this work as these are the commonly accessible means of quantitative analysis in developing countries. The methods were validated and the difference in the assay values was found to be statistically insignificant. Routine determinations like this may be performed using the available instrumentation method such as UV spectrophotometry. The disintegration time and dissolution profile of chlorpropamide respectively in SIF (4.0s,35%) and SGF (3.5s,28%) also gives the impression of better release pattern despite the delay in

the disintegration time of the dosage form when compared to the fed state simulated condition FMSIF (6.0s, 40%) and FMSGF (5.0s, 28%). Chlorpropamide a basic compound disintegrates to more or less the same extent in SIF (pH 7.32) and SGF (pH 1.13). The wide difference in pH did not affect the kinetics of disintegration contrary to expectation. This may be due to the formulation characteristics of the drug i.e. other brands may exhibit difference in disintegration profile. Drugs which occur as salt may have common ion effect influencing the dissolution profile. For food to significantly affect the dissolution of the drug it is expected that the T_{70} for the food modified media be higher than 45 min [19].The SIF and SGF revealed unsatisfactory T_{70} values just as the FMSGF and FMSIF hence the values of the food simulated media being found to be statistically not different from the fasted simulated conditions simply indicates that food did not influence the drug disposition. The food modified media were designed to simulate the food composition possibly available after a typical African diet [20]. The presence of dissolved solutes is typified in the presence of the food materials added to the media which are expected to reduce the solvent power and invariably the release rate of the drug from the drug product [9]. The one sample statistics gave the various means with mean difference of 2.45 and a hypothesized mean difference of 0. The confidence limit at both one tail and two tail consideration produced F values indicating that no statistical difference in the change in blood sugar levels of the group with respect to the dosing conditions. The single factor ANOVA revealed no difference in the mean blood sugar reduction for the groups (*P* 0.05).

CONCLUSION

The dosing conditions did not significantly affect the disintegration and dissolution profile of chlorpropamide.

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