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Research Article

# Predictive *In-Vitro* Evaluation of Food Effect on the *In-Vivo* Performance of Chlorpromazine Hydrochloride Tablet

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**ABSTRACT**

The study compared the disintegration and dissolution time of the antipsychotic drug, chlorpromazine hydrochloride (CPZH) tablet in the presence of simulated intestinal fluid (SIF), Simulated Gastric Fluid (SGF) and food modified SIF and SGF. Various quality control parameters including weight uniformity, tablet hardness, disintegration, friability and assay were assessed. SGF and SIF were employed as disintegration and dissolution media and compared with a food (1.3 ml full cream unsweetened evaporated milk, 2.67mg soluble starch) modified SIF and SGF (FMSIF and FMSGF) at 37 ± 0.5°C. The product assessed complied with the official specification for uniformity of weight friability and assay. The disintegration test showed significantly higher disintegration time for SIF and SGF (3.7 and 6.5 min) compared to the FMSIF and FMSGF (2.9 and 4.9s) ($p < 0.05$) but a significantly lower percentage drug release at 45 min in the SIF and SGF (52% and 43%) than the FMSIF and FMSGF (52% and 60%) ($P < 0.05$). The dosing condition of CPZH tablet should preferably be after meals to optimize drug release and subsequent absorption.



## INTRODUCTION

Drug absorption from a solid dosage after oral administration depends on the release of the drug substance from the drug product, the dissolution of the drug under physiologic condition and the permeability across the G. I. T. [1,2]. Drug release and dissolution testing are therefore essential requirements for the development and establishment of in-vitro dissolution and in-vivo performance, registration and quality control of solid dosage forms [3-5]. Patients often take medications with beverages or after food because of the gastrointestinal irritations that accompany many drugs [6, 7]. In most cases, due to the unpleasant taste of oral solid dosage forms i.e. tablets and hard gelatin capsules, patients result to taking such drugs with sweetened drinks or embedding in certain meals prior to ingestion [8-10]. These may lead to unpredictable release pattern of these drugs.

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The prevalence of psychiatric disorders was reported on the increase until the introduction of psychotherapeutic agents over the past one decade or two [11]. Chlorpromazine (as chlorpromazine hydrochloride, abbreviated CPZH, marketed in the United States as Thorazine and elsewhere as Largactil) is a typical antipsychotic which acts on the central nervous system [12-14]. Chlorpromazine was the first drug developed and it serves as the prototype for the phenothiazine class of drugs used in the treatment of behavioural disturbances including schizophrenia, mania and hypomania. It is also indicated in the short term treatment of anxiety, agitation and violent impulsive behavior [15]. CPZ is highly lipophilic and is readily absorbed after oral administration. The presence of food has been reported to reduce the absorption of CPZH tablet [16]. Today, the quality control (QC) of drugs is based on the kinetics of drug release in-vitro [17-18]. Due to significance physiological differences between the stomach and the intestine, media representative of the gastric and intestinal environments are employed in dissolution testing as part of a drive to develop predictive in vitro models to forecast the in vivo

performance of drugs and drug products. The major differences are pH and presence of bile [11]. Another important consideration is the presence or absence of food in the dissolution milieu. In the gastrum when there is presence of food, the pH is usually less than 3 with the main variable being the type and volume of liquid administered with the dosage form while in the fed state condition of the stomach is highly dependents on the type and quality of meal ingested [2,19].

The objective of the work was to investigate whether there was any significant difference in disintegration time and dissolution profile of the drug in the simulated fluids modeling presence or absence of food in the gastrointestinal tract.

## MATERIALS AND METHOD

### Materials

#### *Reagents*

Hydrochloric acid, sodium hydroxide, sodium chloride and monobasic potassium phosphate were purchased from Sigma Chemicals (St. Louis, Mo).

### Commercial Tablet

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

### 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 [20]. 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 mark. The resulting pH was 1.13 [20].

#### *Food modified SGF and SIF*

Food modified SGF and SIF (FMSGF and FMSIF respectively) 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 [21].

### Methods

### Quality control parameters of the employed brand

#### *Weight uniformity*

Twenty tablets were weighted individually using a digital analytical balance and the percentage deviations of the individual tablets from the mean determined.

#### *Tablet hardness test*

The crushing strength of the tablets was determined by subjecting 10 randomly selected tablets to the force generated by a coiled spring applied diametrically using Monsanto tablet hardness tester (Mosanto, UK).

#### *Friability test*

Twenty tablets were weighed and subjected to abrasion using a Veego tablet friability tester at 25 rev/min.

#### *Tablet Disintegration Test*

Twelve tablets were in 659ml of distilled water in tablet disintegration was determined at 37$^{o}$C using Veego VTDH3 disintegration testing apparatus maintained at 37$^{o}$C and the time for complete disappearance of the disintegrated fragments from the wire mesh recorded. The procedure was employed for distilled water, SIF, SGF, FMSGF and FMSIF.

#### *Chemical content determination (titrimetry and spectrophotometry)*

Ten tablet of (100ml) CPZH were crushed in a mortar and (500mg) of the sample of chlorpromazine HCI powder weighed into a 250ml conical flash, dissolved in 50ml of glacial acetic acid and shaken vigorously before titrating with 0.01M acetous perchloric acid. The end point was determined with crystal violet giving a blue-green colour. This was performed in triplicate.

An ampoule of CPZ injection containing 25mg/ml was used to form a calibration curve after serial dilutions. 100g of the powdered drug was similarly diluted out and the absorbance at 254 nm of the final strength read and corresponding concentration obtained for the percentage weight calculation.

#### *Dissolution Test*

The dissolution rates in the simulated body fluid i.e. SGF and SIF and the food modified SGF and SIF were determined using a Veego dissolution rate testing apparatus using 500ml, 300ml of

medium for the SGF and SIF made respectively at 37°C ± 0.5°C. The speed of rotation was 100 rpm. 5ml of the dissolution medium was sampled at 0, 5, 10, 20, 30, 60, 90, and 120 min with replacement of 5ml of fresh dissolution medium for every withdrawal.

***Bioavailability studies***

***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 [22, 23].

Ten volunteers were examined and passed through a detailed history taking, physical examination, biochemical investigations (liver and renal function) haematological examination (%Hb, PCV and ESR). There was none of the subjects with contraindication to pefloxacin. None of the subjects was a smoker and had no medication in the space of two weeks prior the study.

6 healthy male volunteers mean age ± SD (24.2± 4.7 years) and mean weight ± SD (69.5 ±7.5 Kg) were recruited into the study after physical examination and complete heamatological and biochemical examinations were conducted on them. The volunteers were randomly divided into two groups of 3 and 100mg of CPZ were administered to group 1 without food and group 2 after meal and 10ml blood samples were taken at time 1, 2, 4, 8 and 12 hours post dose. The samples collected were immediately centrifuged and the plasma frozen and stored at -20°C until they were analyzed. Meal taken was 2 slices of lightly spread buttered bread with 35cl of 2 heaped teaspoonful Peak powdered milk drink. The samples were centrifuged without an anticoagulant for 5min and the 5ml of the resulting plasma carefully pipette out to labeled specimen bottles. To the 5ml samples were added 2ml of phosphate butter (pH 2.4) and 40ml of chloroform. These were shaken vigorously. 2g of anhydrous sodium sulphate was further added and shaken again to produce a solid cake. The cake was further shaken up and extracted with (10ml) of 0.5M sodium hydroxide, shaken up for 2 minutes and centrifuged. The sodium hydroxide fraction was obtained and scanned from wavelength of 220 to 400 nm against 0.05M sodium hydroxide as blank and the absorbance reading taken at 254 nm.

**Statistical Analysis**

Statistical significant differences in the values obtained for the disintegration time and dissolution profile of the tablet in the various media were assessed using the student's t-test and $\alpha$=0.05. Correlation of the bioavailability outcome for the drug in SIF and SGF; and drug with FMSIF and FMSGF were assessed using paired t-test.

**RESULTS**

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. Fig. 1 gives the dissolution profile of the drug in the various media.

**Table 1:** Properties of used drugs

| Brand Name | Romazine |
|---|---|
| Strength | 100mg |
| Manufacturer's name | Alpha Laboratories |
| Country of production | India |
| Batch number | Te 548 |
| Manufacturing date | 01-2009 |
| Expiry date | 12-2011 |
| Reg. Number | A4-1478 |

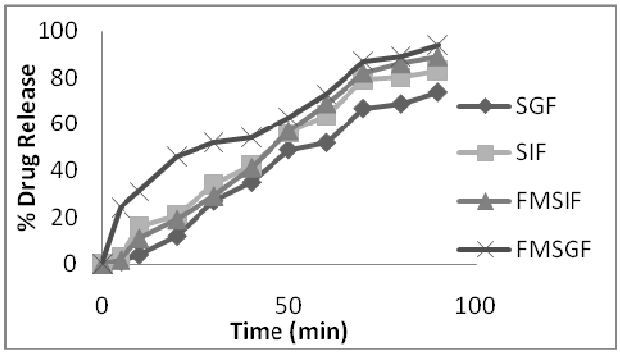


**Figure 1:** The dissolution profile of chlorpromazine hydrochloride tablet in the dissolution media

**Table 2:** The physicochemical parameter of chlorpromazine hydrochloride tablet

| Friability (%) | Crushing Strength (Kg/cm²) | Weight Uniformity (mg) | Chemical content determination (%w/w) | |
|---|---|---|---|---|
| | | | Titrimetry | UV Spectrophotometry |
| 0.023±0.001 | 1.3±0.2 | 185.32±0.92 | 89.27±1.7 | 93.43±0.9 |

**Table 3:** Disintegration time and Dissolution indices of chlorpromazine hydrochloride tablet in the various media

| Disintegration time (min) | | | | $C_{45}$ values (%) from dissolution profile | | | |
|---|---|---|---|---|---|---|---|
| SGF | SIF | FMSGF | FMSIF | SGF | SIF | FMSGF | FMSIF |
| 6.5±0.2 | 3.7±0.4 | 4.9±0.3 | 2.9±0.4 | 43.0 | 52.0 | 60.0 | 52.0 |

## DISCUSSION

Chlorpromazine was investigated for food effect because the drug was found to be widely used in psychosomatic cases in Africa even though newer drugs have emerged but these are not readily available in the study area. The side effects of chlorpromazine are dose dependent therefore the rate and extent of absorption will determine the safety and efficacy of the drug. Patients for whom the drugs are administered are majorly uncooperative so much that the likelihood of post meal administration of the drug is not certain. The extent of absorption of the drug before and after meal is therefore required to ascertain the variability in absorption in the two dosing conditions.

The tablets used in the study were within the shelf life and they complied with the compendia specification for weight uniformity test of not more than 0.5 percent deviation from the mean, for tablets weighing between 80 and 250mg (high variability in tablets weight is not desirable in drugs that have unpredictable bioavailability). The disintegration time was significantly higher in SGF than SIF ($p<0.01$) and in both cases lower than B.P specification of 15-30 minutes for uncoated tablet. Tablets with high disintegration time obviously have retarded absorption and that may be the rate limiting step of the absorption process. Drug release from drug product is a critical consideration in oral dosage form manufacture as this may lead to the therapeutic failure of the dosage form [12, 13].

A fed state composition was made with the addition of milk (low protein, moderate fat) and soluble starch to give an indication of the status of the gastrum after a typical African diet was taken. Typical African diets provide 25% of total nutritional energy from fat [7]. Drugs that are lipid soluble therefore have a better dissolution profile after meals. The dissolution profile of the FMSGF compared to SGF on account o the $C_{45}$ values revealed a significantly higher drug release in fed than the fasted dosing conditions ($P<0.01$). The presence of dissolved solute in a milieu may increase the solubility of a co-solute if hydrophobic-hydrophilic interactions co-exist with a surfactant-like action in favour of the solute being evaluated. Conversely, the presence of the other solutes may saturate the milieu and retard the dissolution of the solute considerable. What we have in the gastrointestinal tract is a picture of the emulsifying action of bile constituents that facilitate the dissolution of ingested drugs to more or less an amount depending on the physicochemical nature of the drug. A complex interplay of the hydrophilic and hydrophobic indices of the drugs and the milieu determines the final outcome of dissolution experienced. The in vitro predictive study presented does not consider the role of the biliary constituents on the solubilizing characteristics of the media. The in-vitro study however gives the idea of the solubility disposition of the drug in the presence of a typical African diet. The picture given therefore helps to adjust drug dosage regimen and explains possible drug level associated effects in the user as a result of food-drug interaction.

## CONCLUSION

The enhanced disintegration and dissolution outcome of the tablet in the food modified media shows the after food benefit of chlorpromazine hydrochloride tablet. It is recommended that the drug be taken after meals to enhance the drug absorption and drug efficacy.

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