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Research Article

EFFECT OF BLACK TEA ON THE DISSOLUTION PROFILE OF LISINOPRIL TABLETS

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ABSTRACT

Objective: The aim of the study is to determine the effect of Black tea on the dissolution profile of Lisinopril tablets.

Method: *In vitro* dissolution of Lisinopril tablets was studied in the absence of black tea as a control media and in the presence of black tea as a test media at pH 1.2, 4.5 & 6.8 (to simulate gastro intestinal condition) using USP apparatus II at 50rpm. 12 units were used according to USP specification and sampling was done at 5, 10, 15, 30, 45 and 60 minutes. Analysis of Lisinopril was done using High Performance Liquid Chromatography- coupled with ultra-violent detector.

Result: Results of the study showed that at pH 1.2, Black tea significantly decreased the dissolution of Lisinopril tablets (P = 0.0001). At pH 4.5 and 6.8 Black tea significantly increased the dissolution of Lisinopril tablets with (p = 0.004) and (p = 0.0007) respectively.

Conclusion: Co- administration of Lisinopril tablets and black tea among patients could lead to unpredictable and unexpected clinical effect, therefore health care personnel should encourage patients to take medication with portable water from credible sources and to space the consumption of beverages and administration of oral medications.

Keywords: Black tea, Lisinopril, Dissolution, Cardiovascular disease

INTRODUCTION

Tea produced from the leaves of *Camellia sinensis,* next to water is said to be the most widely consumed beverage in the world and about three billion kilograms of tea is produced yearly[1]. Black tea is prepared by crushing tea leaves causing catalysed oxidation and polymerization of tea cathechins in the process called fermentation. The fermentation leads to the production formation of oligomers (the aflavins and the arubigins) and polyphenols which have been shown to possess biological activities[2].

Black tea represents 78% of global tea consumption[3]and is consumed both as a herb for its beneficial purpose and as a beverage as part of a meal. Underlying mechanisms for this beneficial effects has been reported to include vasculoprotective, antioxidative, antithrombogenic, anti-inflammatory and lipid-lowering activity due to presence of polyphenols.[4]

Also black tea has been reported to improve endothelial function in patients with coronary artery disease, enhances the activity of nitric oxide synthase leading to vasodilation[5], slows down down the pathogenesis of cardiovascular diseases[6,7]and protect against cognitive impairment[8].

Other similar studies has also shown that Black tea (*Camellia sinensis*) posses in vitro inhibitory activity for the angiotensin cornverting enzyme – ACE[9], decreases incidence of coronary heart disease[10]and improves cardiovascular risk.[11] All this implies that hypertensive and patients with other cardiovascular disease risk factors may derive additional benefit from the consumption of black tea.

Cardiovascular diseases are the number one cause of death worldwide and more people die annually from CVDs than from any other cause. CVDs morbidity affects men and women almost evenly and 80% of mortality occurs in developing countries.[12]

The Angiotensin converting enzyme (ACE) is a major target in the management of cardiovascular diseases as the rennin aldosterone angiotensin system is an important regulator of cardiovascular function and therefore the ACEI inhibitors plays a major role in therapy.[13]

Lisinopril is routinely used in the management of hypertension[14] and is among the most widely prescribed ACEI[15]and the clinical knowledge summaries service recommends that ACEI selection should generally be limited to the use of lisinopril, ramipril or enalapril in subject with diabetic nephropathy[16].

Lisinopril is an orally active angiotensin-converting enzyme (ACE) inhibitor which at dosages of 20 to 80 mg once daily is effective in lowering blood pressure in all grades of essential hypertension[17] and also useful in the management of congestive heart failure.[16]

Lisinopril and other ACEI are sometimes preferred in therapy due to their additional benefit in improving insulin sensitivity[18], reducing proteinuria[19] and reduction of complications in diabetic subject.[20]

The tendency for drugs to be taken at meal time especially during breakfast is considerable high and it is recommended by many physicians as a means of ensuring adherence to therapy when managing chronic ailment like hypertension and other cardiovascular disease in order to establish a daily routine[21]. Furthermore black tea serve as part of breakfast in many homes and therefore necessary to investigate probable interactions between black tea and medications

Effect of beverage on drug dissolution is a growing concern as documented evidence as shown that certain beverages may increase or reduce drug dissolution and may limit therapeutic efficacy of drugs or result in increase incident of adverse drug reaction[22,23,24,25] and also, interaction between administered drugs with certain beverage needs to be studied extensively as and this can provide useful information to both health care personnel and patients[26].

This study was designed to evaluate the effect of black tea on the dissolution profile of Lisinopril tablets and to provide evidence to encourage or discourage co administration in subject with cardiovascular morbidity.

MATERIALS AND METHOD

Physicochemical Tests

Lisinopril tablets, 10mg (Zestril ®) tablets were purchased from a registered pharmaceutical chemist in Lagos, Nigeria and physicochemical tests (Uniformity of weight, Friability and Hardness test) were carried out according to the British pharmacopoeia (BP, 2007) specification to determine the suitability of the tablets for the study using Analytical weighing balance (Mettler Toledo®), Friabilator (Erweka TA®) and Hardness tester respectively.

Assay

The assay was also done according to the specifications of the BP, 2007 to determine if the percentage content of lisinopril in each tablet falls within the accepted range of 92.5% - 105% using High Performance Liquid Chromatography (HPLC) coupled with UV detector (Agilent® Technologies 1120 Compact LC).

Calibration plot

This was done using graded concentrations of Lisinopril dihydrate USP® 2 - 20µg/mL (reference standard) obtained from the United States Pharmacopoeia Convention Inc prepared in 0.1NHCl acid, acetate and phosphate buffer respectively.

Preparation of Buffers, Mobile phase and Black tea

0.1N HCL, phosphate buffer and Acetate buffer were prepared according to BP, 2007 specifications and were standardized to ᴘH 1.2 and 4.5 respectively using 2M HCL solution. Phosphate buffer was prepared according to the United State Pharmacopoeia (USP, 2004) and was standardized to ᴘH 6.8 using 1M NaOH solution.

The mobile phase was prepared in accordance with BP 2007 specifications for analysis of lisinopril using HPLC grade acetonitrile, 0.408% w/v solution of anhydrous potassium dihydrogen orthophosphate and adjusted to pH 2.0 with orthophosphoric acid.

Black tea (Lipton®) was obtained from accredited store prepared according to the manufacturer's specification, i.e. distilled water was heated to boiling point (97 – 99 degree centigrade) and each tea bag was brewed for 3 minutes in the equivalent of 200ml of water per tea bag.

Dissolution test

Dissolution study was carried out using an eight vessel dissolution test apparatus. Paddle method was used according to the specification of official monograph for Lisinopril (BP, 2007). The study was carried out using 900mL of the buffer in each vessel and was conducted in two phases. The first phase involves the use of buffer solutions and lisinopril tablet, 10mg (control media) while the second phase involves combination of buffers with black tea preparation in ratio of 1:2 and lisinopril tablet, 10mg (test media). Both phases were carried out in respective buffer preparation of ᴘH (1.2, 4.5 and 6.8) maintained at temperature of 37˚C ± 0.5˚C with the paddles set to rotate at 50 rpm. At specific intervals of 5, 10, 15, 30, 45, and 60 minutes respectively, 5ml aliquots was withdrawn from each of the vessel and sink volume was ensured. The withdrawn samples were filtered through a 0.45µm sterile syringe filter and analysis was done using High performance liquid Chromatography coupled with ultra-violet detector.

Chromatographic Conditions

200µL of diclofenac standard (100µg/mL) was added to 1ml of filtered sample to serve as internal standard and chromatographic analysis was performed at room temperature using Agilent® 1200 High performance liquid chromatography (HPLC) coupled with auto-sampler and ultraviolet detector. Isocratic method was used and the mobile phase was filtered using 0.45µm filter. The instrument was coupled with a degasser and the column compartment was thermostated. The column used stainless steel Eclipse SB-C18 4.6 x 150mm, 5µm column Agilent®. The analysis was carried out at a flow rate of 1.0 mL/min and injection volume of 20 µL at a wavelength of 215 nm.

Data Analysis

The amount of lisinopril released was determined using the respective calibration plots ~~(fig 1, fig 2 and fig 3)~~ Statistical analysis was carried out using student t test (paired t test) in graph pad prism 4.0 and Microsoft Excel. In all cases, a confidence level of 95% ($\alpha = 0.05$) was chosen and a value of ($^*p<0.05$) was considered significant.

RESULT

The result of uniformity of weight, friability and hardness test is shown in table 1. The assay of lisinopril gave a value of 96.2%. The calibration plot of lisinopril in respective media is presented in Figure 1,2 and 3. The regression equation of lisinopril at pH 1.2, 4.5 and 6.8 were y = 39.31x - 57.43, y = 23.15x - 12.15 and y = 32.3x - 63.13 respectively where y represents peak area ratio while x depicts the concentration. The correlation coefficient ranges from 0.960 to 0.996. The charts showing amount of lisinopril released in the presence and absence of black tea as a dissolution media ~~is~~ are presented in table 2a, 2b and 2c and graphs showing similar comparison in acid, acetate and phosphate media ~~is~~ are shown in figure 4, 5, and 6.

Statistical analysis shows that at pH 1.2, black tea significantly decrease the dissolution of lisinopril tablet ($p = 0.0001$). At pH 4.5 and 6.8, black tea significantly increase the dissolution of lisinopril tablet with ($p = 0.004$) and ($p = 0.0007$) respectively.

Table 1: Result of physical test

Parameter	Result
Uniformity of weight	0.214 ± 0.002
Hardness (kg-cm)	3.400 ± 0.310
Friability (%)	0.047 ± 0.001%

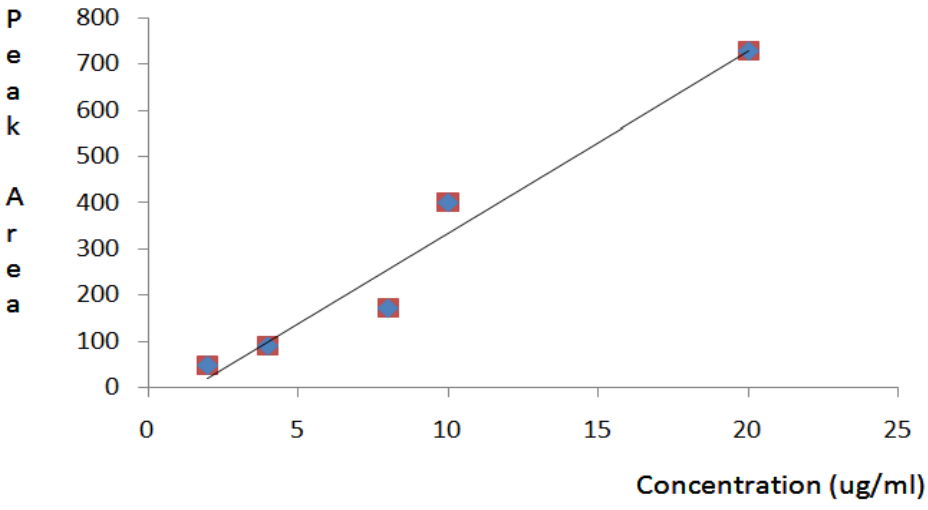

Fig. 1: Calibration plot of Lisinopril standard in 0.1N HCL (pH 1.2)

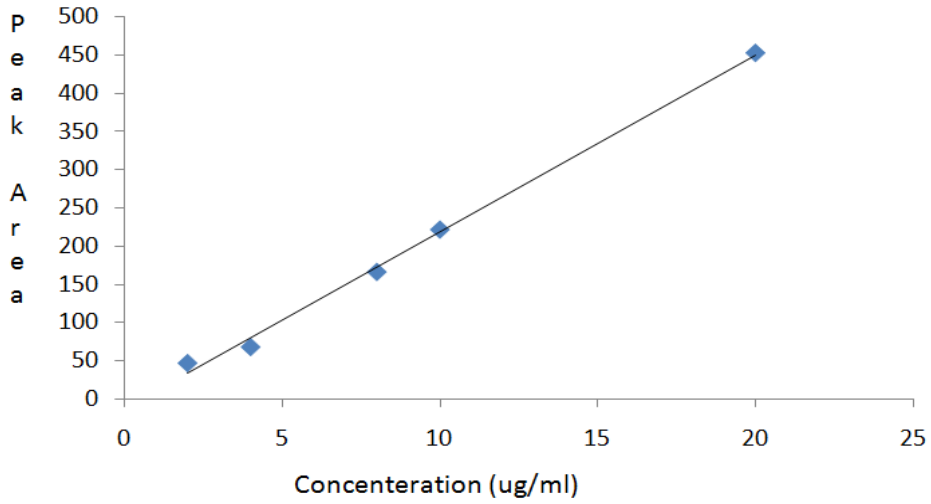

Fig. 2: Calibration plot of lisinopril standard in acetate buffer pH 4.5

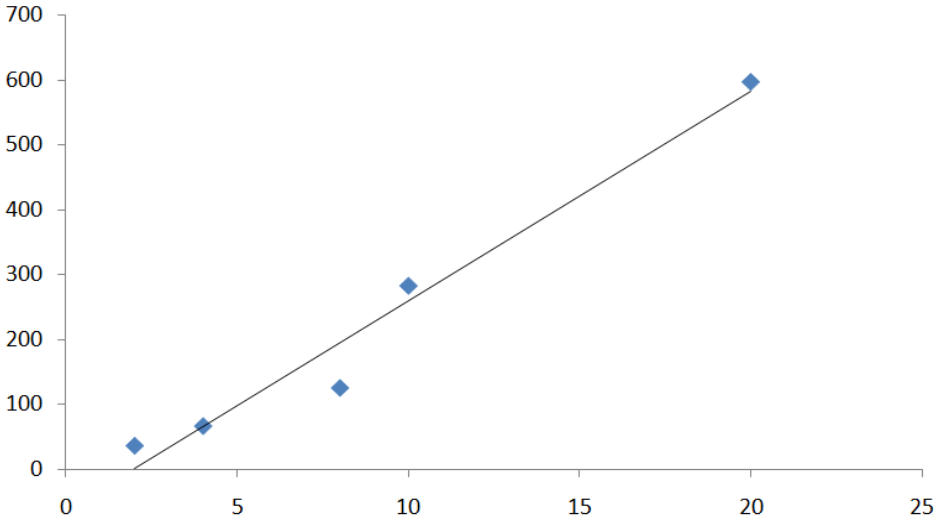

Fig. 3: Calibration plot of lisinopril standard in phosphate buffer pH 6.8

Table 2a: Dissolution data showing comparison between control and test group in 0.1N HCL (pH 1.2)

Sample	% Lisinopril released					
Sampling time (minutes)	**5**	**10**	**15**	**30**	**45**	**60**
LIS	95.8± 4.1	62.9 ± 12.15	71.8 ± 8.7	76.9 ± 16.4	81.2 ± 11.3	79.5 ± 26.2
LIS + Black Tea	35.1 ± 0.8	40.1 ± 2.0	44.2 ± 4.2	41.2 ± 3.5	43.2 ± 2.4	54.8 ± 1.9

Table 2b: Dissolution data showing comparison between control and test group in acetate buffer (pH 4.5)

Sample	%Lisinopril released					
Sampling time (minutes)	**5**	**10**	**15**	**30**	**45**	**60**
LIS	97.1 ± 4.1	105.6 ± 2.7	106.5 ± 2.6	107.9 ± 2.3	108.5 ± 2.4	108.8 ± 1.9
LIS + Black Tea	104.6 ± 20.4	111.8 ± 9.2	112.0 ± 16.3	122.6 ± 16.3	127.9 ± 15.4	125.0 ± 8.4

Table 2c: Dissolution data showing comparison between control and test group in phosphate buffer (pH 6.8)

Sample	% Lisinopril released					
Sampling time (minutes)	**5**	**10**	**15**	**30**	**45**	**60**
LIS	73.8 ± 5.0	81.9 ± 6.2	86.8 ± 7.0	87.3 ±5.0	88.4 ± 4.1	84.8 ± 8.6
LIS + Black Tea	98.0 ± 13.2	101.7 ± 8.7	99.0 ± 6.5	99.5 ± 4.5	99.2 ± 2.3	101.0 ± 7.3

Control group refers to Lisinopril tablets in respective buffer (**LIS**).

Test group refers to Lisinopril tablets in appropriate buffer and black tea preparation 1:2 (**LIS+ Black tea**)

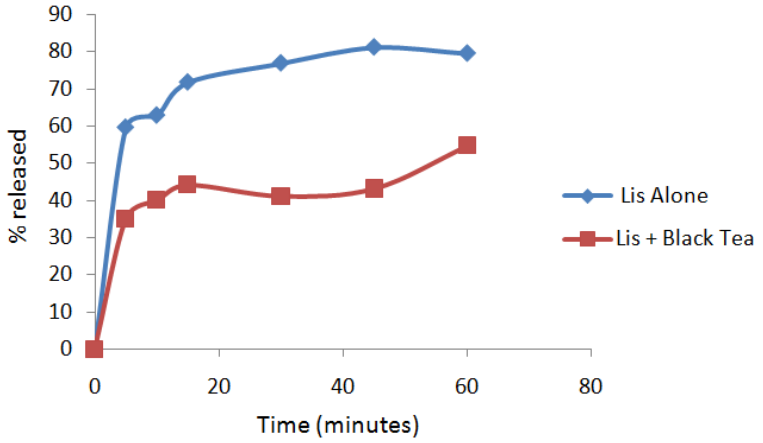

Fig. 4: Dissolution profile of lisinopril tablets alone and in the presence of Black tea in acid buffer (pH 1.2)

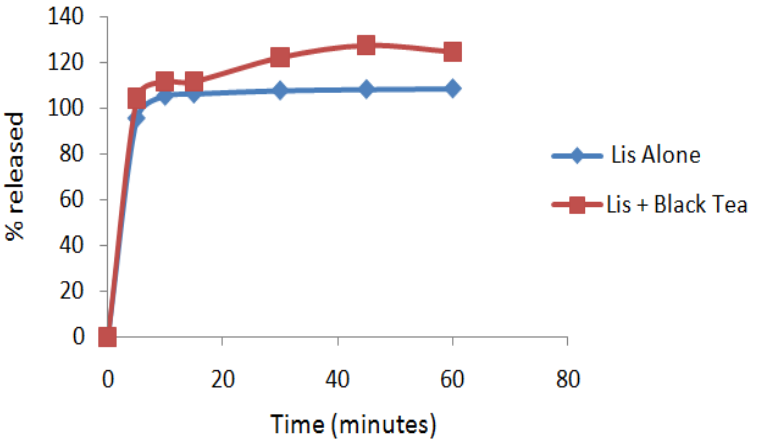

Fig. 5: Dissolution profile of lisinopril tablets alone and in the presence of Black tea in acetate buffer (pH 4.5)

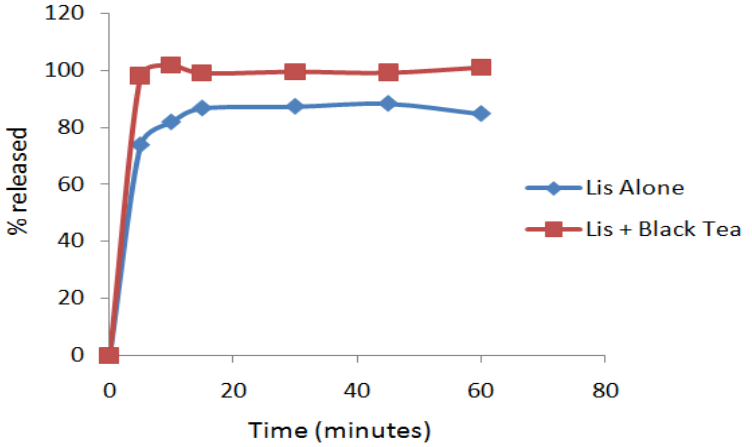

Fig. 6: Dissolution profile of lisinopril tablets alone and in the presence of Black tea in phosphate buffer (pH 6.8)

DISCUSSION

The suitability of lisinopril tablets for the dissolution test was confirmed by the uniformity of weight which conforms to the BP 2007 specifications. Likewise, the friability, hardness and assay were also found to be within the acceptable tolerance levels as specified by the official monograph of the tablets. Having satisfied the suitability, the tablets profiles in different pHs with or without black tea were investigated.

Although the release profile of Lisinopril tablets at pH 1.2 fell short of standard specified (fig 4) but it sufficed to say that the effect on black tea in decreasing the dissolution profile of lisinopril tablet was found to be statistically significant (p=0001) using the student t test. It may then be inferred that black tea may significantly lower the dissolution of lisinopril in the stomach region of the gastro intestinal tract considering that acid buffer serves to simulate gastric fluid..

At pH 4.5, the sample of tablet used passed the dissolution test with dissolution of 107.9% at 30minutes ~~(fig 5)~~. Statistical analysis using the student t test shows that black tea significantly increases the dissolution profile of lisinopril tablet in acetate media (p = 0.004). It may then be inferred that black tea could cause unpredictable increase in the dissolution profile of lisinopril tablet and may subsequently impact on bioavailability as ACEI move from the stomach region to the small intestine.

Similarly, at pH 6.8, sample of tablet used passed the dissolution test with a dissolution of 87.3% at 30minutes. ~~(fig 6).~~ Statistical analysis using the student t test shows that black tea significantly increases the dissolution profile of lisinopril tablet (p = 0.0007). It may then be inferred that black tea may have the potential to increase the dissolution and bioavailability of ACEI when co administered orally. This may subsequently lead to improve efficacy and/or toxicity considering that phosphate media serves to simulate intestinal fluid where a significant proportion of drug absorption occurs.

From the study carried out and the result obtained from statistical analysis, it can be inferred that black tea significantly affect the dissolution profile of lisinopril by either decreasing it (acid buffer) or increasing it (phosphate buffer and acetate buffer). Therefore further study is required in elucidating the exact mechanism of increase/ decrease respectively.

The analysis of black tea preparation using HPLC- UV shows the presence of several components and this may impact on the dissolution of lisinopril in respective media.

Despite the fact that available literature show that black tea may have some cardio – friendly properties[2,][11,28], co administration with ACEI should be discouraged as this can impact on tablet dissolution and may result in unpredictable effect.

Health care personnel should encourage and counsel patient to take medication with portable water from credible sources or to sufficiently space the administration of drug from the consumption of various beverages or herbal preparations until concise information is available on the spectrum of benefit or deleterious interaction that may result from co administration of drugs and selected beverages.

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