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Research Article

COMPARATIVE *IN VITRO* DISSOLUTION STUDY OF LOSARTAN POTASSIUM MARKETED TABLETS IN FOUR DIFFERENT DISSOLUTION MEDIA BY VALIDATED ANALYTICAL METHOD

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ABSTRACT

There are only 22 pharmaceutical companies out of 151 in Bangladesh producing quality product maintaining the cGMP, where more than 40 companies manufacturing Losartan Potassium 50 mg tablets. So, the clinicians and pharmacists are facing difficulty to choose a suitable brand or alternative use. The aim of the present study was to predict the bioequivalence of four top ranked brands of Losartan Potassium tablets marketed in Bangladesh using *In Vitro* tests. The *In Vitro* dissolution study was carried out with the five brands of 50 mg Losartan Potassium tablets according to FDA dissolution method. The process was done for 12 tablets of each brand; using 900 ml of pH 1.2 0.1 N HCl, pH 4.5 Acetate Buffer, pH 6.8 Phosphate Buffer and water separately as dissolution media; 50 rpm as rotation speed; 37°C ± 0.5°C as media temperature; 10, 15, 20, 30, 45 and 60minutes as sample collection time points. The results were carried out by interpreting data on the equations of Dissolution Efficiency (DE), Difference Factor (f_1), Similarity Factor (f_2). There were significant differences in the dissolution profiles of the five brands specially when considered according to different media. In pH 1.2 0.1 N HCl all brands showed poor drug release but most were close to innovator brand, but in pH 4.5 Acetate Buffer was unlike due to decrease of ionic strength by media, which affect preferably to innovator brand. pH 6.8 Phosphate Buffer and water gave best results for drug release of most of the brands and proved reliable to claim RRR, SSS and NNN as bioequivalent and interchangeable with each other as well as with the innovator brand. The BBB showed poor dissolution profile, which will likely result in poor bioavailability. The results show the need for constant monitoring of new brands of Losartan Potassium introduced into the drug market to ascertain bioequivalence and conformity with pharmacopoeia standards.

Key words: Losartan Potassium, dissolution study.

INTRODUCTION

There are only 22 pharmaceutical companies out of 151 in Bangladesh producing quality product maintaining the cGMP[1], where more than 40 companies manufacturing Losartan Potassium 50 mg tablets. But there are growing concerns that various Losartan Potassium formulations may have different bioavailability and that development of resistance will accelerate if suboptimal doses are used[2,6]. The availability of numerous brands of Losartan Potassium tablets in our drug market today places clinicians and pharmacists in a difficult situation of choice of a suitable brand or the possibility of alternative use. Despite the considerable use in Bangladesh, there are no reports on the bioavailability and bioequivalence of the various marketed brands of Losartan Potassium tablets. Hence the present investigation has been carried out. Prediction of *In Vivo* bioavailability in most oral drugs has been shown to depend on the *In Vitro* dissolution studies[3,4,5]. The bioavalability of Losartan Potassium from different formulations of the drug is thus an important parameter to assess when comparing the clinical performance of various brands. Again, both branded (innovator's) versions and generic (marketed) products are available in the market but people like to use generic product as they are far cheaper than its branded (innovator's) versions. The problem with multi-source (i.e., generic/marketed) products is, however, not unique to medicine and brand loyalty has been bought dearly and will be fought for by the originators of the brand. Clinicians all over the world are usually skeptical for the following reasons:

- Distrust in the regulatory authority
- Unknown brand - brand loyalty
- Distrust in the generic industry
- Perverse incentives not to change
- Leap of faith to prescribe a generic
- Unfound anecdotal evidence of generic inferiority

With this as background it is easy to appreciate clinicians/patient's skepticism in multi-source products and why it is easy to convince them to stick to a brand even if it is going to cost them more. So, the present work was undertaken to check whether our local products are equivalent to innovator brand products or not. The aim of the present study was to predict the bioequivalence of four top ranked brands (out of 10) of Losartan Potassium tablets marketed in Bangladesh using *In Vitro* tests, which will provide a rationale for the interchangeability or otherwise of the selected brands with the innovator brand.

MATERIAL AND METHODS

Drug Products

The Losartan Potassium 50 mg tablets were taken from 4 manufacturing companies of Bangladesh as market products. The companies are Renata Ltd., Square Pharmaceuticals, Incepta Pharmaceuticals, Beximco Pharmaceuticals coded as RRR, SSS, NNN and BBB. The innovator/ reference drug was from Merk Sharp & Dohm BV, Haarlen, Netherland coded as IB.

The parameters studied in this project are-

- Dissolution
- Dissolution Efficiency (DE)
- Difference Factor (f_1)
- Similarity Factor (f_2)

Dissolution

According to the US FDA guidelines for its dissolution methods the process was on done on tablet dissolution machine -Auto Sampling Dissolution Tester with 14 Vessels (AT_7 Smart Duel, Sotax, Switzerland) which consisted of a l000ml flask with 900ml dissolution media. The flask used here was a cylinder which had a hemispherical bottom. The software was set to take the sample tablet automatically from the fixed place on each flask when the software get the set temperature is obtained and then dissolution sampling time counting was). The temperature was maintained 37°C ± 0.5°C by the water bath and the motor of the paddle was adjusted to rotate at 50 rpm (as commanded in software). The 5 ml of filtered sample solution was withdrawn with the help of auto-sampler in the test tubes combined tray; at an interval of 10, 15, 20, 30, 45 and 60minutes to determine the amount of drug in solution. Each time the process was done at the interval; there was a simultaneous addition of 5ml buffer to the solutions in the flask automatically. This was done with 12 tablets of each brand. The multi-source product exhibits similar dissolution profiles, as determined with the f_2 value or equivalent statistical evaluation, to those of the comparator product in buffers at all three pH values (PH 1.2, 4.5 and 6.8). Hence dissolution was done on all the three pH values as well as in water.

The absorbance was taken with UV visible spectrophotometer (Shimadzu® UV-1700, Kyoto, Japan), connected to a computer loaded with Shimadzu UV PC version 3.9 software.

Spectra of Losartan Potassium standard were built in the range from 400 to 200 nm using 1 cm quartz cuvettes in the fast scan speed, 2.0 nm data interval and 2 nm band width. The percentage of drug release (DR %) was assayed at the wavelength of 240 nm.

The different dissolution requirements according to the different pH dissolution media

Comparative dissolution in pH 1.2 0.1 N HCl solution as dissolution media

Preparation of pH 1.2 0.1 N HCl solution as dissolution media: 8.3 ml 37% HCl solution is added into distilled water to prepare per liter of pH 1.2 0.1 N HCl solution as dissolution media after the pH adjustment by dilute HCl solution.

Preparation of standard solution: Losartan Potassium working standard is weighted accurately equivalent to 25 mg of Losartan Potassium in a 50 ml volumetric flask and volume up to 50 ml with methanol to dissolve and dilute the Losartan Potassium with the help of sonication. 1 ml solution is transferred to another 50 ml volumetric flask and volume up to the mark with the dissolution medium and mixed well.

Preparation of sample solution: 1 tablet in each basket is allowed to dissolve in 900 ml of media maintaining other dissolution parameters. 5 ml of filtered sample is collected for each time point along with same volume of media replacement. These 5 ml samples are diluted up to 50 ml with the same media and mixed well.

Comparative dissolution in pH 4.5 acetate buffer as dissolution media

Preparation of pH 4.5 acetate buffer as dissolution media: 1.803 gm Sodium Acetate Trihydrate and 1.6 ml of ml of Glacial Acetic Acid is added into distilled water to prepare per liter of pH 4.5 acetate buffer as dissolution media after the pH adjustment by dilute Acetic acid or Sodium Hydroxide solution.

Preparation of standard solution: Losartan Potassium working standard is weighted accurately equivalent to 25 mg of Losartan Potassium in a 50 ml volumetric flask and volume up to 50 ml with methanol to dissolve and dilute the Losartan Potassium with the help of sonication. 1 ml solution is transferred to another 50 ml volumetric flask and volume up to the mark with the dissolution medium and mixed well.

Preparation of sample solution: 1 tablet in each basket is allowed to dissolve in 900 ml of media maintaining other dissolution parameters. 5 ml of filtered sample is collected for each time point along with same volume of media replacement. These 5 ml samples are diluted up to 50 ml with the same media and mixed well.

Comparative dissolution in pH 6.8 0.2 M phosphate buffer solution as dissolution media

Preparation of pH 6.8 0.2 M phosphate buffer solution as dissolution media: 896 mg Sodium Hydroxide and 6.8045gm Potassium Dihydrogen Phosphate is added into distilled water to prepare per liter of pH 6.8 0.2 M phosphate buffer solution as dissolution media after the pH adjustment by dilute Phosphoric acid or Sodium Hydroxide solution.

Preparation of standard solution: Losartan Potassium working standard is weighted accurately equivalent to 25 mg of Losartan Potassium in a 50 ml volumetric flask and volume up to 50 ml with methanol to dissolve and dilute the Losartan Potassium with the help of sonication. 1 ml solution is transferred to another 50 ml volumetric flask and volume up to the mark with the dissolution medium and mixed well.

Preparation of sample solution: 1 tablet in each basket can dissolve in 900 ml of media maintaining other dissolution parameters. 5 ml of filtered sample is collected for each time point along with same volume of media replacement. These 5 ml samples are diluted up to 50 ml with the same media and mixed well.

Comparative dissolution in water solution as dissolution media

Preparation of dissolution media: Distilled water was used as dissolution media.

Preparation of standard solution: Losartan Potassium working standard is weighted accurately equivalent to 25 mg of Losartan Potassium in a 50 ml volumetric flask and volume up

to 50 ml with methanol to dissolve and dilute the Losartan Potassium with the help of sonication. 1 ml solution is transferred to another 50 ml volumetric flask and volume up to the mark with the dissolution medium and mixed well.

Preparation of sample solution: 1 tablet in each basket can dissolve in 900 ml of media maintaining other dissolution parameters. 5 ml of filtered sample is collected for each time point along with same volume of media replacement. These 5 ml samples are diluted up to 50 ml with the same media and mixed well.

RESULTS AND DISCUSSION

Losartan Potassium dissolution profile in pH 1.2 0.1 N HCl solutions as dissolution media

Table 1: Representation of dissolution of different brands (RRR, SSS, BBB, NNN) of Losartan potassium 50 mg tablet with Pure drug (API) including Reference/ Innovator Brand (IB) in pH 1.2 0.1N HCl solution as dissolution media

Time (in minutes)	IB	RRR	SSS	BBB	NNN	API
0	0	0	0	0	0	0
10	4.33	3.06	0.69	3	3.48	75.66
15	5.95	4.14	3.66	7.19	5.29	81.88
20	6.85	5.44	6.69	16.6	8.44	82.36
30	10.32	9.21	13.98	24.41	13.79	84.75
45	10.34	15.77	21.73	32.79	22.5	85.23
60	13.98	25.22	27.63	37.98	29.88	90.5

Losartan Potassium dissolution profile in 4.5 Acetate Buffer as dissolution media

Table 2: Representation of dissolution of different brands (RRR, SSS, BBB, NNN) of Losartan Potassium 50 mg tablet with Pure drug (API) including Reference/ Innovator Brand (IB) in 4.5 Acetate Buffer as dissolution media

Time (in minutes)	IB	RRR	SSS	BBB	NNN	API
0	0	0	0	0	0	0
10	1.61	13.67	43.2	50.14	37.37	96.97
15	3.32	35.23	44.35	56.05	51.84	97.92
20	6.02	45.25	85.14	74.38	66.3	98.39
30	9.09	67.01	89.79	87.35	85.89	98.86
45	12.92	76.25	91.17	92.59	88.53	99.33
60	16.28	80.7	91.29	92.71	89.05	99.81

Losartan Potassium dissolution profile in pH 6.8 Phosphate Buffer as dissolution media

Table 3: Representation of dissolution of different brands (RRR, SSS, BBB, NNN) of Losartan Potassium 50 mg tablet with Pure drug (API) including Reference/ Innovator Brand (IB) in pH 6.8 Phosphate Buffer as dissolution media

Time (in minutes)	IB	RRR	SSS	BBB	NNN	API
0	0	0	0	0	0	0
10	32.24	26.89	52.19	59.42	38.58	88.25
15	48.18	34.1	73.96	86.97	58.83	91.66
20	60.51	57.62	90.2	93.79	73.82	94.1
30	74.06	83.83	95.62	94.14	85.93	95.07
45	85.74	91.57	98.57	95.86	92.57	96.53
60	86.5	92.89	99.09	96.39	94.3	96.53

Losartan Potassium dissolution profile in water as dissolution media

Table 4: Representation of dissolution of different brands (RRR, SSS, BBB, NNN) of Losartan Potassium 50 mg tablet with Pure drug (API) including Reference/ Innovator Brand (IB) in water as dissolution media

Time (in minutes)	IB	RRR	SSS	BBB	NNN	API
0	0	0	0	0	0	0
10	47	32.05	48.66	78.05	55.89	84.31
15	65.76	53.12	68.89	95.39	75.64	95.87
20	76.84	66.3	75.64	96.36	86.24	98.28
30	82.59	84.6	97.8	98.28	92.98	98.76
45	88.31	90.64	98.76	99.25	99.25	99.25
60	90.56	89.19	99.73	99.73	99.73	99.25

Dissolution Efficiency (DE) of Different Brands in Different Dissolution Media

Table 5: Representation of dissolution efficiency (DE) of different brands (RRR, SSS, BBB, NNN) of Losartan Potassium 50 mg tablet with Pure drug (API) including Reference/ Innovator Brand (IB) in different dissolution media

Media	IB	RRR	SSS	BBB	NNN	API
pH 1.2	9.62	12.20	15.56	25.00	16.65	84.66
pH 4.5	9.91	62.73	82.86	82.79	78.39	90.88
pH 6.8	72.72	75.76	91.88	92.88	82.28	94.90
Water	81.51	78.58	89.71	97.20	91.27	97.90

Dissolution Efficiency: From the tabular data and graphical representation it is observed that using FDA recommended dissolution method for *In Vitro* bioequivalence testing of Losartan Potassium, water gives best drug release (>80%) after which pH 6.8 phosphate buffer get the second position (>70%) and thus the dissolution efficiency decreased with lowering of pH (i.e. in pH 4.5 acetate buffer and in pH 1.2 0.1 N HCl solution respectively) may be due to the excipient effect on dissolution medium as well as close pka value (4.9) of Losartan Potassium.

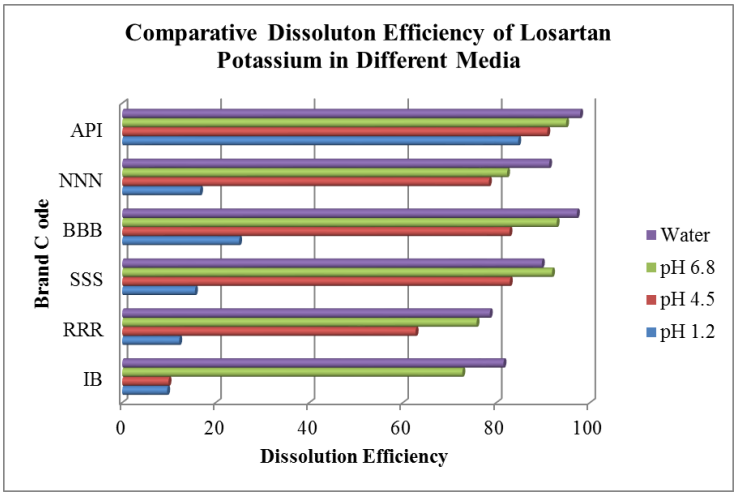

Figure 1: Graphical representation of dissolution efficiency (DE) of different brands (RRR, SSS, BBB, NNN) of Losartan Potassium 50 mg tablet with Pure drug (API) including Reference/ Innovator Brand (IB) in different dissolution media

Difference Factor (f_1) and Similarity Factor (f_2) of Different Brands in Different Dissolution Media

Table 6: Representation of Different Factor (f_1) and Similarity Factor (f_2) of different brands (RRR, SSS, BBB, NNN) of Losartan potassium 50 mg tablet with Pure drug (API) against Reference/ Innovator Brand (IB) in different dissolution media

Media ->	pH 1.2 Buffer		pH 4.5 Buffer		pH 6.8 Buffer		Water	
Code	**F_1**	**F_2**	**F_1**	**F_2**	**F_1**	**F_2**	**F_1**	**F_2**
RRR	43.02	63.7	546.02	15.63	11.44	54.09	9.11	51.87
SSS	67.2	55.73	803.61	8.3	31.61	33.52	9.05	53.14
BBB	25.72	33.75	820.43	8.22	35.98	29.51	25.72	33.75
NNN	66.89	53.82	750.89	9.87	14.67	50.27	13.01	50.28
API	866.54	6.31	1100.8	2.09	45.17	23.6	27.64	31.75

Media Based Dissolution Data Comparison

Comparison of dissolution data using pH 1.2 0.1 N HCl solutions as dissolution media

Table 7: Representation of dissolution profiles along with Difference Factor (f1), Similarity Factor (f2) and Dissolution Efficiency (%DE) of different brand (RRR, SSS, BBB, NNN) of Losartan Potassium 50 mg tablet with Pure drug (API) against Innovator Brand (IB) in pH 1.2 0.1N HCl solution as dissolution media

Time (in minutes)	IB	RRR	SSS	BBB	NNN	API
0	0	0	0	0	0	0
10	4.33	3.06	0.69	3	3.48	75.66
15	5.95	4.14	3.66	7.19	5.29	81.88
20	6.85	5.44	6.69	16.6	8.44	82.36
30	10.32	9.21	13.98	24.41	13.79	84.75
45	10.34	15.77	21.73	32.79	22.5	85.23
60	13.98	25.22	27.63	37.98	29.88	90.5
F1		**43.02**	**67.2**	**25.72**	**66.89**	**866.54**
F2		**63.7**	**55.73**	**33.75**	**53.82**	**6.31**
%DE	**9.62**	**12.2**	**15.56**	**25**	**16.65**	**84.66**
%DF	**0**	**2.54**	**5.94**	**15.38**	**7.03**	**75.04**

Comparison of dissolution data using pH 4.5 Acetate Buffer as dissolution media

Table 8: Representation of dissolution profiles along with Difference Factor (f1), Similarity Factor (f2) and Dissolution Efficiency (%DE) of different brand (RRR, SSS, BBB, NNN) of Losartan Potassium 50 mg tablet with Pure drug (API) against Innovator Brand (IB) in pH pH 4.5 Acetate Buffer as dissolution media

Time (in minutes)	IB	RRR	SSS	BBB	NNN	API
0	0	0	0	0	0	0
10	1.61	13.67	43.20	50.14	37.37	96.97
15	3.32	35.23	44.35	56.05	51.84	97.92
20	6.02	45.25	85.14	74.38	66.3	98.39
30	9.09	67.01	89.79	87.35	85.89	98.86
45	12.92	76.25	91.17	92.59	88.53	99.33
60	16.28	80.7	91.29	92.71	89.05	99.81
F1		546.02	803.61	820.43	750.89	1100.8
F2		15.63	8.30	8.22	9.87	2.09
%DE	9.91	62.73	82.86	82.79	78.39	90.88
%DF	0	5.82	72.95	72.88	68.48	80.97

Comparison of dissolution data using pH 6.8 Phosphate Buffer as Dissolution Media

Table 9: Representation of dissolution profiles along with Difference Factor (f1), Similarity Factor (f2) and Dissolution Efficiency (%DE) of different brand (RRR, SSS, BBB, NNN) of Losartan Potassium 50 mg tablet with Pure drug (API) against Innovator Brand (IB) in pH 6.8 Phosphate Buffer as dissolution media

Time (in minutes)	IB	RRR	SSS	BBB	NNN	API
0	0	0	0	0	0	0
10	32.24	26.89	52.19	59.42	38.58	88.25
15	48.18	34.1	73.96	86.97	58.83	91.66
20	60.51	57.62	90.2	93.79	73.82	94.1
30	74.06	83.83	95.62	94.14	85.93	95.07
45	85.74	91.57	98.57	95.86	92.57	96.53
60	86.5	92.89	99.09	96.39	94.3	96.53
F1		11.44	31.61	35.98	14.67	45.17
F2		54.09	33.52	29.51	50.27	23.6
%DE	72.72	75.76	91.88	92.88	82.28	94.9
%DF	0	3.04	19.16	20.16	9.56	22.18

Comparison of dissolution data using water as dissolution media

Table 10: Representation of dissolution profiles along with Difference Factor (f1), Similarity Factor (f2) and Dissolution Efficiency (%DE) of different brand (RRR, SSS, BBB, NNN) of Losartan Potassium 50 mg tablet with Pure drug (API) against Innovator Brand (IB) in water as dissolution media

Time (in minutes)	IB	RRR	SSS	BBB	NNN	API
0	0	0	0	0	0	0
10	47	32.05	48.66	78.05	55.89	84.31
15	65.76	53.12	68.89	95.39	75.64	95.87
20	76.84	66.3	75.64	96.36	86.24	98.28
30	82.59	84.6	97.8	98.28	92.98	98.76
45	88.31	90.64	98.76	99.25	99.25	99.25
60	90.56	89.19	99.73	99.73	99.73	99.25
F1		9.11	9.05	25.72	13.01	27.64
F2		51.87	53.14	33.75	50.28	31.75
%DE	81.51	78.58	89.71	97.2	91.27	97.9
%DF	0	2.93	8.2	15.69	9.76	16.39

Comparison of the therapeutic performance of two or more medicinal products containing the same active substance is a critical means of assessing the possibility of alternative use between the innovator and any essentially similar medicinal product. The results so far show that the four brands of Losartan Potassium tablets, RRR, SSS, and NNN can be interchanged in clinical settings as well as with the innovator brand, IB.

CONCLUSION

In conclusion, the results indicate that all the brands of Losartan Potassium tablet included in this study apart from BBB seem to have high dissolution rate and hence very good bioavailability. So, can be considered bioequivalent and interchangeable with each other as well as with the innovator brand, IB. So, all the brands apart from BBB could be substituted for one another in the therapy of Hypertension. The results also show the need for constant monitoring of new brands of Losartan Potassium introduced into the drug market to ascertain bioequivalence and

conformity with pharmacopoeia standards. If the other drugs of other companies undergo the same tests, it will be fruitful to decrease the difference gap from the innovator brands.

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