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Research Article

COMPARATIVE STUDY OF FOUR DIFFERENT BRANDS OF CAPTOPRIL AVAILABLE IN KARACHI, PAKISTAN

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ABSTRACT
Captopril is the first orally active and specific inhibitor of angiotensin-converting enzyme. It blocks conversion of angiotensin I to angiotensin II by inhibiting the angiotensin converting enzyme and used for hyper tension as a potent vasodilator. Captopril is used to lower hyper tension and available in several brands in the market. The aim of this study is to establish pharmaceutical equivalence among the brands available in Karachi, Pakistan. Four different brands of captopril tablets (25 mg) were included in study. Six quality control parameters: weight variation test, hardness test, thickness, friability, disintegration test and dissolution test were carried out specified by British and United state Pharmacopoeia BP/USP. Hardness value requirement was complied by all brands. Disintegration time for all brands was within 15 minutes complying the BP/USP standards. All brands of captopril showed more than 80 % drug release within forty five 45 minutes. The study suggests that almost all the brands of captopril are available in Karachi meet the specification for quality control analysis.
Keywords: Captopril, comparative study, formulations.

INTRODUCTION

Captopril was the first competitive inhibitor of angiotensin converting enzyme with sulfhydryl moiety that hinder the conversion of inactive angiotension I to organically active angiotension II and prevents the degradation of bradykinin. It reduces the arterial blood pressure by decreasing the total peripheral resistance[1-3]. Captopril act by inhibiting the renin-angiotension-aldosterone system. The kidney produces an enzyme renin which in turn produces inactive angiotension I by acting on the plasma globulin substrate. Captopril is chemically called as 1-[(2S)-3-mercapto-2-methylpropionyl]-Lproline, has the molecular weight of 217.29[4]. ACE (angiotension converting enzyme) than convert the angiotension I to biologically active angiotension II, a powerful vasoconstrictor which acts on the adrenal cortex. As a result aldosterone is produced in the kidney where it increases the accumulation of sodium and water and thereby elevates the blood pressure. Captopril blocks the conversion of angiotension I to angiotension II by hindering the production of ACE[5-7]. It is used in the treatment of patient with congestive heart failure, hypertension, Left Ventricular Dysfunction after Myocardial Infarction and diabetic Nephropathy.

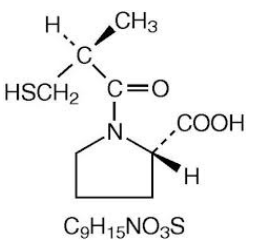

Figure 1: Captopril

It is white to off-white crystalline powder, very instable, undergoes Oxidation, sparingly soluble in chloroform and ethyl acetate but completely soluble in ethanol, methanol and water (160 mg/ml). It is available in the form scored tablets with the strengths of 12.5 mg, 25 mg, 50 mg, and 100 mg[7-9]. Captopril produces the onset of action after 15 to 30 minutes and the peak plasma level is achieved in 1 to 1.5 h. It is well absorbed orally with the bioavailability of 60 to 75 % but the presence of food reduces its absorption up to 25 to 40 %. It is highly bound to plasma protein approximately 25-30 %, mainly albumin. It is primarily metabolize by the liver up to 50 % with the main metabolites of captopril-cysteine disulfide and the disulfide dimer of captopril. Up to 95 % of the drug is excreted by urine[10,11]. Captopril is suggested as maximum dose of 150 mg /day according to the blood pressure response and patient's profile. Dose of the renal comprise patient is according to creatinine clearance, administer 50 % of the normal dose if CrCl < 10 mL/minute and 75 % of the normal dose if CrCl is 10 to 50 ml/min.[10,11]

MATERIALS AND METHODS

A comparative study was conducted by purchasing different brands of 25 mg uncoated tablets of captopril (CAPOTEN, CAPRIL, ACETOPRIL AND CAPACE) available in market. They are all been tested for following physiochemical parameters in order to compare multinational brand and other same active local brands.

Weight Variation test of 20 tablets of each brand was conducted on Electronic Balance FX-400 and observed that weight of 20 individual tablets with respect to their dose must be within BP/USP limits that NMT two tablets out of 20 tablets should cross ± 10 % deviation. Weight Variation is an in process test parameter which ensures content uniformity of dosage form units during compression.

Thickness test of 10 tablets of each brand was analyzed with the Vernier Caliper which evaluates the degree of compaction during the punching of the tablets.

Hardness test of 10 tablets of each brand was carried out on MH-1 of Galvano Scientific hardness tester. It is use as a tool for applying mechanical stress to evaluate the strength of

tablet that it must be hard enough to bear the stress of NLT 4.00 Kg to break a tablet.

Friability test of 10 tablets of each brand was analyzed on fribilator at 25 rpm or 100 rotations in 4 minutes. It is a phenomenon in which we apply mechanical shock or attrition to check the crushing strength, Capping and/or Lamination of tablet. USP limit is 0.5 to 1 %. It should be within limits i.e. NMT 1 %.

Disintegration Test of 6 tablets of each brand was performed on Curro model no DS-0702 which demonstrates whether tablets or capsules when dipped in an aqueous medium are disintegrating within the official time i.e. according to BP/USP, uncoated tablets should disintegrate in NMT 15 minutes.

Dissolution test of single tablet of each brand was conducted on GDT-7L of Galvano Scientific which concludes that when tablet or capsule dissolute in medium with recognized volume the amount of active ingredient released from a oral solid dosage form should be within specified limits i.e. according to USP, captopril Q value should NLT 80 % at 215 nm wavelength, after 20 minutes, at 50 rpm and 37 C temperature. It is a best tool to evaluate the bioavailability of drug *in vivo*.

RESULTS AND DISCUSSION

Weight Variation

Content uniformity and weight variation are the two methods to evaluate the uniformity of dosage form. According to USP, uncoated or film coated tablets having the weight of less than 130 mg should have the standard deviation of 7.5 %. Weight variation is valid for the test of uniformity of dosage form, when film coated or uncoated tablet having 25 mg or more drug substance that comprise 25 % of each tablet weight. In the current study weight variation method was performed because the amount of active ingredient is 25 mg. 20 tablets of each brand weighted and the mean weight, SD, and upper and lower control limits (mean ± 3S) were calculated, and illustrated in Table. Thus the SD of all the brands is within the official limits summarized in Table.

Thickness

The calculated values of thickness for the tablets of different brands are summarized as mean, standard deviation, upper n lower control limits in the Table. The thickness may vary with no change in weight due to difference in the granulation and pressure applied to the tablets, the speed of tablet compression as well as wear and tear on length of punches. Tablet thickness is generally controlled to assure that they can be correctly counted by the filling machine, to minimize appearance problems and to assure that tablets will fit into the container. The deviation in thickness is within ± 5 % which is tolerable for the normal manufacturing practices. Thus the thicknesses of all the brands are within upper n lower control limits, Table.

Hardness

The tablet needs a certain amount of force, or hardness, to endure mechanical shocks of handling when it is manufacture, package and transport. Additionally tablets should bear reasonable abuse when it is in the consumer hands. Consumer compliance increase when adequate tablet hardness, friability and resistance to powdering are ensured. More recently, importance of hardness increases as it has a relationship and may greatly influence tablet disintegration and, more significantly, drug dissolution release rate. It may be particularly important for drug products that possess real or possible bioavailability crisis or are sensitive to altered dissolution-release profiles by altering the applied strength should be cautiously examine for tablet hardness. The calculated values of all brands i.e. mean, SD and upper n lower control limits have been summarized and they all within control limits, Table.

Friability

Friability test is carry out to estimate how well the tablet standup to coating, packing, shipping and other processing. It is the tendency for a tablet to crumble, chip or break following compression. This is generally confined to core tablet's surfaces during handling or storage. From each brand, 20 tablets were deducted and weigh than the tablets were placed in friability tester for 4 minutes at 25 rpm (100 rotations). At last 20 tablets of each brand were de dusted and reweighed and their percentage losses of weight were calculated. Tablets need to be hard enough such that they do not break up in the bottle but friable enough that they disintegrate in the gastrointestinal tract. It can be caused by a number of factors including low moisture content, poor tablet design (too sharp edges), insufficient binder, etc. According to USP, the total weight loss should not be more than one percent and no tablet should show any type of break or crack. The percentage friability of four brands of captopril tablets are calculated and all were within official limits (Table)

Disintegration

The first step toward dissolution is usually the break-up of the tablet i.e. disintegration. It is the time required for a dosage form to break up in to granules of specified size (excluding the fragments of insoluble coating or capsule shell) which stays on the screen of the test apparatus or hold to the lower surface of the discs, it is somewhat a soft mass having no obvious firm core. An orally administered drug must disintegrate to attain good absorption of its active substance. Generally, the test is useful as a quality assurance tool for conventional dosage forms. For most uncoated tablets, the USP requires that the tablets disintegrate in 15 minutes (although it varies for some uncoated tablets) [21]. If 1 or 2 tablets fails to disintegrate completely, repeat the test on 12 other tablets. Now 16 from the total of 18 tablets should disintegrated completely than it meet the official requirement [20]. The disintegration time of all brands is compiled and within specified official limits (Table).

Dissolution

The process of disintegration and dissolution are the steps after which an Oral dosage forms only become accessible for absorption. Dissolution test is carried out to discriminate the effect of manufacturing variables for example granulation procedure, excipients type, binder effect and mixing effect [22] it can be utilized as a tool to predict the *in vivo* bioavailability of the product. Presently, dissolution test is used as an in vitro bioequivalence (BE) test for evaluating the profile comparison and dissolution profile, setting up the similarity of pharmaceutical dosage forms [23-25]. According to USP, each tablet should be completely dissolve after 20 minutes at 50 rpm and 37 C temperature. The dissolution of the tablet solution was determined on spectrophotometer at 215 nm wavelength and it should NLT 80 % after 20 minutes to

evaluate the result, Capoten (multinational brand) is taken as reference standard and all of the other brands are compared. All the brands are within official limits that are summarized in Table.

Table 1: Specification of drugs with batch no

No.	Name of product	Serial No.	Code No	Batch No
1	CAPOTEN	CT 01	006156	3F934
2	CAPRIL	CPR 02	013921	12G260
3	ACETOPRIL	AP 03	010862	93
4	CAPACE	CPA04	022465	12004

Table 2: Statistical Weight Variation Table

No.	Serial .No	Batch No.	Average Weight (mg)	S.D %	Upper Limit (UCL)(X+3S)	Lower Limit (LCL)(X-3S)
1.	CT 01	3F934	101	3.226	111	91
2.	CPR 02	12G260	124	1.191	136	112
3.	AP 03	93	124	2.455	136	112
4.	CPA04	12004	99	1.38	109	89

Table 3: Weight variation test

No	Serial No	Batch No	Results (g)	BP/USP Limit	Deviation from BP/ USP
1	CT01	3F934	0.101	7.5 %	All Passed
2	CPR02	12G260	0.124	7.5 %	All Passed
3	AP03	93	0.124	7.5 %	All Passed
4	CPA04	12004	0.099	7.5 %	All Passed

Table 4: Statistical Thickness

No.	Serial .No	Batch No.	Average thickness (mm)	S.D	Upper Limit (UCL)(X+3S)	Lower Limit (UCL)(X-3S)
1	CT01	3F934	2.31	0.057	2.481	2.139
2	CPR 02	12G260	2.25	0.053	2.409	2.091
3	AP03	93	2.17	0.048	2.314	2.026
4	CPA04	12004	2.17	0.048	2.314	2.206

Table 5: Statistical Hardness

No.	Serial .No	Batch No.	Average Hardness (Kg)	S.D	Upper Limit (UCL)(X+3S)	Lower Limit (UCL)(X-3S)
1	CT01	3F934	7.23	1.417	11.481	2.979
2	CPR 02	12G260	5.8	0.422	7.07	4.54
3	AP03	93	4.7	0.675	6.73	2.68
4	CPA04	12004	7.2	0.789	9.57	4.83

Table 6: Friability Test

Serial No.	Batch No.	Friability (%)	Limits	Comments
CT01	3F934	0.50 %	Less Than 1 %	Within Limits
CPR02	12G260	0.08 %	Less Than 1 %	Within Limits
AP03	93	0.08 %	Less Than 1 %	Within Limits
CPA04	12004	0.10 %	Less Than 1 %	Within Limits

Table 7: Disintegration Test

Serial No.	Batch No.	Disintegration time (min)	Limits	Comments
CT01	3F934	59 Sec	NMT 15 Min	Within Limits
CPR02	12G260	11Sec	NMT 15 Min	Within Limits
AP03	93	12 Sec	NMT 15 Min	Within Limits
CPA04	12004	1 Min38 Sec	NMT 15 Min	Within Limits

Table 8: Dissolution Test

No	Serial No	Batch No	Dissolution at 20 min	USP Spec	Deviation from BP USP
1	CT01	3F934	100 %	NLT 80 %	Within specified limit
2	CPR02	12G260	92.7 %	NLT 80 %	Within specified limit
3	AP03	93	99.2 %	NLT 80 %	Within specified limit
4	CPA04	12004	100.92 %	NLT 80 %	Within specified limit

Table 9: ANOVA

ANOVA						
Test		**Sum of Squares**	**df**	**Mean Square**	**F**	**Sig.**
Wt. Variation	Between Groups	2842.600	3	947.533	1647.884	.000
	Within Groups	9.200	16	.575		
	Total	2851.800	19			
Thickness	Between Groups	.069	3	.023	463.333	.000
	Within Groups	.001	16	.000		
	Total	.070	19			
Hardness	Between Groups	22.244	3	7.415	61787.708	.000
	Within Groups	.002	16	.000		
	Total	22.245	19			
Friability	Between Groups	.642	3	.214	3569.111	.000
	Within Groups	.001	16	.000		
	Total	.643	19			
Disintegration	Between Groups	26250.000	3	8750.000	17500.000	.000
	Within Groups	8.000	16	.500		
	Total	26258.000	19			
Dissolution	Between Groups	209.722	3	69.907	558.576	.000
	Within Groups	2.002	16	.125		
	Total	211.724	19			

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