COMPARATIVE QUALITY EVALUATION OF DIFFERENT BRANDS OF FRUSEMIDE TABLETS AVAILABLE IN BANGLADESHI MARKET

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Abstract: *Frusemide is a widely produced and marketed drug by many Pharmaceutical companies in Bangladesh. The performance evaluation (Namely, some physical parameters, potency, disintegration and dissolution profile), of Frusemide tablets from six different pharmaceutical companies was carried out in order to find out whether they really complied the required standards. As a part of evaluation of physical parameters, the size and shape, specially, thickness of representative samples of each pharmaceutical companies were evaluated and they were found to be uniform. The tablets from all the companies successfully passed the friability test as the % of friability of all of them were found to be way below one. Out of the tablets of six evaluated pharmaceutical companies, the potency of Frusemide tablets from five companies was found to be satisfactory and one was poor. The disintegration time of tablets from all the companies were found to be satisfactory. The minimum disintegration time was found to be 2.50 minute and the maximum disintegration was found to be 5 minutes. The dissolution profile of the representative sample was determined. The profiles for all the companies were satisfactory. The best profile was showed 90.42% at 45 minutes and 92.50% at 50 minutes.*

Keywords: *Frusemide, Diuretics, Weight variation, Disintegration, Dissolution.*

Introduction

Diuretics are drugs which increase the excretion of salt (NaCl, Na_2CO_3) and water. This can be achieved by a direct action on the cells of the nephron and indirectly modifying the content of the filtrate. Normally (i.e. in the absence of diuretics), less than 1% of filtered sodium is excreted. The main diuretics are the loop diuretics and the thiazide diuretics. Loop diuretics (e.g. Frusemide) cause up to 15-20% of filtered Na^+ to be excreted, with copious urine production. They act by inhibiting the $Na^+/K^+/Cl^-$ co-transporter in the thick ascending loop. They increase K^+ and Ca^{2+} loss. Frusemide is 4-chloro-N-furfuryl-5-sulphamoyl anthranilic acid with molecular weight 330.74 and categorized as a potent high ceiling loop diuretic agent commonly indicated for acute or chronic renal failure. In low dose it is also used for the treatment of chronic hypertension. [1] It shows a prompt onset of action and produces a peak diuresis far greater than that observed with other diuretic agents.[2] Bangladesh with a high population is one of the developing countries of South Asia and is actively involved in the Action Programmed of

Essential Drugs proposed by WHO. Through a developing country, over the last few years, Bangladesh has shown commendable development in the pharmaceutical sector. Almost all major companies are trying to make their drugs ethically, try to improve standard of GMP. A medicinal product must satisfy certain standards to claim it to be a quality drug. The principal criteria for a Quality drug product are safety, potency, efficacy, stability and market acceptability.[3] The major purpose of this work is to find out the current status of the quality of the marketed Frusemide preparations available in Bangladesh. This work makes awareness among the peoples health, health practitioners and drug control authority so that pharmaceutical manufacturers produce quality medicine. It provides a comprehensive knowledge about the hardness, friability, weight variation, disintegration, dissolution, percentage of potencies of Frusemide market preparations and compares these values with their official specifications.

Materials and Methods

Six brands of Furosemide tablets, manufactured by different manufacturer with labeled contents of 100 mg each, were obtained from local market. All tablets were of same manufacturing year. All other reagents were of analytical grade.

Appearance test of tablets: The tablets were tested visually at day light under a white background. Color of the tablets was determined. In this way color of the 6 different brands of tablets were determined and observed result for each sample was recorded. Shape and surface texture were also observed (Table 1).

Weight Variation Determination: 20 tablets from each generic brand products were weighted individually in a weighing balance (Ohaus CP213 China). The average weights of the tablet as well as their percentage deviation were calculated (Table 2).[4]

$$\% \text{ of weight variation} = \frac{\text{Individual weight} - \text{average weight}}{\text{Average weight}} \times 100$$

Thickness test of tablets: Thickness of 10 tablets of each sample was measured with a slide calipers. The average thickness of the tablets was determined and then thickness variation was calculated. In this way the thickness variation of 6 different brands of tablets was determined and the observed result for each sample was recorded (Table 3).

Diameter tests of tablets: Ten tablets were taken and determined individual diameter, average diameter and standard deviation (Table 4).

Friability Testing: Friability test was conducted by employing a Friability tester USP 23 (Electro lab, Mumbai, India) at 25 rev/ min for 4 minutes. Percent friability was determined by using the following formula(Table 5)[5].

$$\% \text{ of friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

Disintegration Testing: 6 tablets from each generic brand products were employed for the disintegration test in water at 37 ± 2 °C using a disintegration apparatus. The disintegration time was taken to be the time, when no particle remained on the basket (Table 6)[6].

Assay:

Preparation of Standard curve: 20 mg of standard Frusemide was weighed accurately and was taken in a 100-ml volumetric flask. 70 ml of 0.1N NaOH solution was added and shakes mechanically. Then the volume was adjusted to 100 ml by 0.1N NaOH solution and standard stock solution was prepared. Then 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml and 8 ml of stock solutions were taken in a series of separated 100-ml volumetric flask and each of them was diluted up to 100 ml with 0.1N NaOH solution. Thus a series of standard solutions with different concentration of standard Frusemide e.g., 2 mcg/ml, 4 mcg/ml, 6 mcg/ml, 8 mcg/ml, 10 g/ml, 12 mcg/ml, 14 mcg/ml and 16mcg/ml were obtained. Then absorbance were taken at 271 nm against blank for each solution and the average was calculated which has been given in Table-3.3. The measured absorbance were plotted against the respective concentrations of the standard solutions which give a straight line in the concentration range of 2 mcg/ml to 16 mcg/ml (Fig 6).

Preparation of standard solution: 20 mg of standard Frusemide was weighed accurately in an analytical balance and was taken in a 100-ml volumetric flask. 70 ml of 0.1 N NaOH solutions was added and was shaken mechanically. The volume was made upto the mark with the same solvent. 4 ml of the above solution was diluted to 100 ml with the same solvent.

Preparation of assay solution: 20 tablets were weighed and powdered in a mortar with a pestle. An amount of powder equivalent to 20 mg of Frusemide was transferred in a 100-ml volumetric flask. 70 ml of 0.1 N NaOH solutions was added and was shaken for 30 minutes. The volume was made upto the mark with the same solvent and filtered the solution with Whatman filter paper. 4 ml of the filtered solution was diluted to 100 ml with the same solvent.

The absorbance of both standard and sample were measured in a suitable UV-VIS spectrophotometer at 271 nm using 0.1 N NaOH. Each sample was run in triplicate and average of the results was taken in to consideration. Then calculate by the following equation

$$\text{Potency of sample} = \frac{\text{Absorbance of sample} \times \text{Weight of standard}}{\text{Absorbance of standard} \times \text{Weight of sample}} \times \text{Purity of standard}$$

In-vitro **Dissolution Studies:** *In-vitro* dissolution studies were carried out using a dissolution USP apparatus #1. The dissolution medium was 900 ml of Phosphate buffer, pH 5.8, which was maintained at 37 ± 0.5 °C and 50 rpm. In all dissolution experiments, 5 ml of dissolution samples were withdrawn and replaced with equal volume fresh dissolution medium at regular intervals. Collected dissolution samples were used for

determination of released furosemide concentrations by using a UV-VIS spectrophotometer (T60U PG Instruments, England) against a blank. Maximum wavelength obtained by scanning all samples from 200 to 400 nm and this was 271 nm (Table 8).

Result

All the brand of Furosemide tablets used in this investigation were within their shelf life. All tablets obtained from local market were subjected to a number of tests in order to assess quality parameters like assay, weight variation, friability, hardness, and disintegration time. All the tablets of different brand contained Furosemide within 100 ±5 % of the labeled claim. The USP[7]and IP[8] specifications for assay are that the Furosemide content should be less than 95 % and not more than 105 %. Therefore, the assay results ascertain the presence and compendia quality of Furosemide in all the products. Weight variation does serve as a pointer to good manufacturing practices (GMP) maintained by the manufacturers as well as amount of active pharmaceutical ingredient (API) contained in the formulation. The weight variation for all the tablets used in this study showed compliance within the official specifications[7, 9], as none of the products deviated by up to 5 % from their average weight.

Table 1: Appearances of the tablets

Sample code	Shape	Color	Surface texture
FT01	Round	Off white	Smooth
FT02	Round	White	Smooth
FT03	Round convex	White	Smooth
FT04	Round	Off white	Rough
FT05	Round convex	Off white	Smooth
FT06	Round	White	Smooth

Table 2: Weight variation test

Sample code	Number of tablets taken	Average weight per tablet (mg)	Weight variation	
			Number of tablets within BP/USP range	Number of tablets out of BP/USP range
FT01	10	132.0	10	0
FT02	10	153.0	10	0
FT03	10	157.0	10	0
FT04	10	200.0	10	0
FT05	10	136.0	10	0
FT06	10	162.4	10	0

Table 3: Thickness of various brands Frusemide of tablets

Sample code	Number of tablets taken	Average thickness per tablet (mm)	Number of tablets within BP / USP range	Number of tablets out of BP / USP range
FT01	10	2.54	10	0
FT02	10	2.23	10	0
FT03	10	3.48	10	0
FT04	10	3.52	10	0
FT05	10	3.12	10	0
FT06	10	2.64	10	0

Table 4: Diameter of various brands of Frusemide tablets

Sample code	Number of tablets taken	Average diameter per tablet (mm)	Number of tablets within BP / USP range	Number of tablets out of BP / USP range
FT01	10	7.31	10	0
FT02	10	8.10	10	0
FT03	10	7.18	10	0
FT04	10	8.12	10	0
FT05	10	7.12	10	0
FT06	10	8.11	10	0

Table 5: Friability of various brands of Frusemide tablets

Sample code	Number of tablets taken	Total initial weight (mg)	Total final weight (mg)	Observed friability % (w/w)
FT01	5	645.4	641.3	0.64
FT02	5	771.6	765.2	0.83
FT03	5	795.2	791.2	0.50
FT04	5	998.0	996.4	0.16
FT05	5	685.3	682.8	0.36
FT06	5	814.0	810.0	0.49

Table 6 Disintegration time of various brands of Frusemide tablets.

Sample code	No. of tablets	Disintegration time(min)
FT01	6	4.30
FT02	6	3.30
FT03	6	5.00
FT04	6	2.50
FT05	6	3.50
FT06	6	3.35

Figure 1: Standard curve of Frusemide

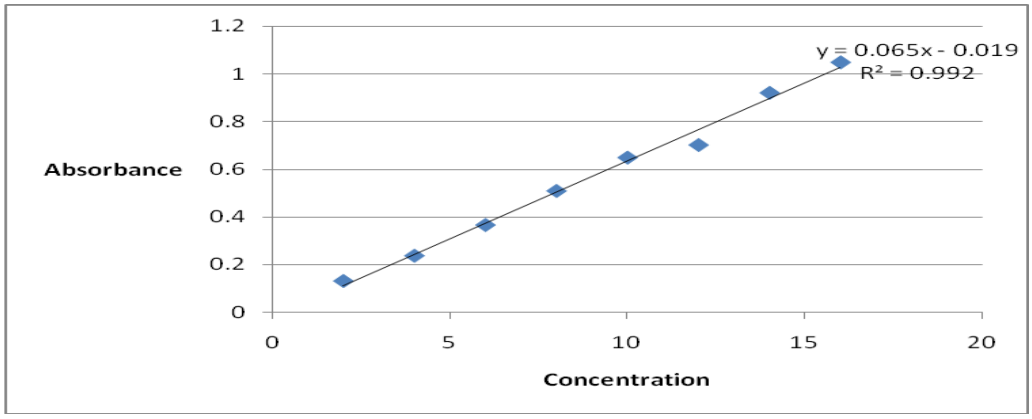

Table 7: Potency of Frusemide Tablet.

Sample code	Potency (% w/w)
FT01	92.36
FT02	99.11
FT03	95.33
FT04	96.93
FT05	96.53
FT06	97.32

Table 8: Dissolution Rate of Various Brands of Frusemide Tablets

Sample code	% of drug release after 45 minutes	%of drug release after 50 minutes
FT01	88.79	90.27
FT02	89.77	91.51
FT03	90.02	91.02
FT04	89.77	90.27
FT05	90.52	92.25
FT06	90.02	92.50

Discussion

USP[7]/BP[9] specifications for weight variation: Allowed range of variation for 0 to 130 mg tablets: ±5% (w/w). It is observed from the above result (Table 2) that all brands complied with the specification.

The weight variation test is a satisfactory method of determining the drug content uniformity of tablets

It may result from, poor granulation flow properties, resulting in uneven die fill. A wide variation in granules particle size which results in a variation in die fill density as a function of particle size distribution at different points in the production run. Differences in lower punch length which result in different size die cavities. Improper incorporation of glidant, granulation flow promoters. Tablet machines in mechanically poor condition or dirty which prevent free punch movement. When the weight variation is within the specifications the tablets are thought to contain uniform active ingredient to give desired therapeutic response. But when the weight variation is out of the specification the tablets are thought to contain less or more active ingredient to give ineffective therapeutic response or toxic effect respectively.

USP[7]/BP[9] specification of diameter variation: ±5%. It is found from the above results (Tables 3) that none of the samples exceeded the specification for diameter variation. Therefore, it can be said that the entire studied sample complied with the official specification for diameter variation. The thickness of a tablet is the only dimensional variable related to the process .At a constant compressive load, tablet thickness varies with changes in die fill, with particle size distribution and packing of the particle mix being compressed, and with tablet weight, while with a constant die fill, thickness varies with variations in compressive load.[10] Tablet thickness may be controlled by –Controlling the physical properties of raw materials. Standardizing the upper and lower punch lengths. Controlling the granulation properties including density particle size, and particle size distribution. Tablet thickness cannot be controlled independently, since it is related to tablet weight compaction, density friability and possibly drug release.[5] In addition, tablet thickness must be controlled to facilitate packaging.

USP[7]/BP[9] Specification for Friability of tablets: Allowed range =1.0% (w/w) .From the above results (Table 5), it is appeared that all brands of Frusemide tablets complied with the specification of friability. Tablet friability may be profoundly affected by the moisture content of the tablet granulation and the finished tablets. Very dry granulation and tablets containing less than 0.5 to 1.0 percent of moisture may be much more friable than tablets contain 2 to 4 % of moisture (Gilbert and Neil, 1991). Friability of tablets is important to determine the loss of weight during packaging and shipment. If the friability is higher (more than 1.0 % w/w), the loss of active ingredient during packaging and transportation will be excessive, and the remaining active ingredient in the tablet will result in the tablet will result in deficient therapeutics effect.[10]

USP[7]/BP[9] specification of disintegration time: Not more than 30 minutes for uncoated tablets. Enteric coated are to show no evidence of disintegration after one hour in simulated gastric fluid and are to disintegrate in two hours plus the time specified in the monograph in the intestinal fluid .To be compliance with USP standards, the tablets must disintegrate, and all particles must pass through the 3 inches long glass tubes and held against a 10-mesh screen in the time specified. [10]The onset of action of a dosage form of a drug depends on the time to be taken by the tablets to release the active ingredients into the digestive fluid. The tablets should be disintegrated in the appropriate time, otherwise the prescribed course will be affected and the drug may not exert its effect properly. It is seen from the above results (Table 6) that none of the samples exceeded the specification for disintegration time. Therefore, it can be said that all the studied samples complied with the specification for tablet disintegration time.

BP[9] Specification of potency: 95-105% for Frusemide tablet. The ingredients of tablets exert the therapeutic effect. The deficient potency will result in less therapeutic response or even the product may be ineffective. From the above result (Table 7), it is observed that all brands of tablets meet the specification of potency. From the above table it is shown that 5 brands meet the BP specification but one brand fails.

BP[9] specification of dissolution percentage: To be compliance with BP standard at least 90% of the tablets must be dissolved within 45 minutes. The rate of dissolution may be directly related to the efficacy of the tablet product, as well as to bioavailability differences between formulations .Therefore, an evaluation as to whether or not a tablet releases its drug contents when placed in the environment of the gastrointestinal tract is often of fundamental concern to the tablet formulator (Table 8). [10]

Conclusion

The findings of the study are assumed that although most of the brands meet with specification, few brands do not satisfy the specification Sub-standard products may cause death of patients. So Drug Administration should be strict to formulate quality product as well as strengthen their visiting team to visit frequently the manufacturing plant and establish more effective analytical measures to analyze the marketed drugs. This work will help both health practitioners and consumers to select quality products. Also this work can provide some information for Drug Control Authority of Bangladesh to evaluate the overall quality status of Frusemide preparations.

References

1. *Indian pharmacopoeia, 4th edition, 1996, volume I, Controller of publication, ministry of human resorce and family welfare, Government of India, Delhi; 333-334.*
2. *P. K. Choudhury, , G. S. Panigrahi, K. K. Pradhan, C. K. Panda , G. S Pasa; Design, development and evaluation of Frusemide loaded micropellets prepared by Ionotropic gelation method;Int.J. PharmTech Res.2010,2(1), 420-426.*
3. *Takagaki T, Matsuda M, Mizuki Y and Terauchi Y., "Quantitative analysis of Chlorpheniramine Maleate", Journal of Chromatogr B Analytical Technology, 2002.*
4. *Murtha JL, Julian TN and Radebaugh GW., "Quantitative analysis of Chlorpheniramine Maleate", Journal of Pharmceutical Science. 1988, Vol. 77(8), pp. 715-8.*
5. *Lewis W.Dittert, Sprawls "American Pharmacy", pp 374-384*
6. *Kirchhoefer RD.,"Quantitative analysis of Chlorpheniramine Maleate", J Assoc Off Anal Chem., 1979, Vol. 62(6), pp. 1197-201.*
7. *US Pharmacopoeia National Formulary, USP 23/NF 18, United States Pharmacopoeia Convention Inc., Rockville, MD, 2000: 1882-1883.*
8. *The Indian Pharmacopoeia, The Controller of Publications, Ministry of Health, Govt. of India, New Delhi, Vol. 1, 1996: 190.*
9. *British Pharmacopoeia, The Pharmaceutical Press, Her Majesty's Office, London, Vol. 1, 1998: 1296.*
10. *Gilbert S. Banker and Neil R. Anderson, Tablets. In L.Lachman, Herbert, Halieberman, Joseph L.Kaing, "The Theory and Practice of Industrial Pharmacy", 4th Edition, 1991, pp 804, 296-303,189.*