Drug Development and Industrial Pharmacy, 24(11), 995–1005 (1998)

RESEARCH PAPER

Assessment of Pharmaceutical Quality of Furosemide Tablets from Multinational Markets*

S. A. Qureshi and I. J. McGilveray

Therapeutic Products Directorate, Health Protection Branch (PL #2202C1), Health Canada, Ottawa, K1A 0L2, Canada

ABSTRACT

*This report describes results of a collaborative study in which samples of the 40-mg strength of furosemide tablets were evaluated following a common protocol based on British (BP), European (Ph. Eur.), and US Pharmacopoeial (USP) specifications. Several tests, including identification, uniformity of mass, and dissolution, were performed. In total, excluding Lasix lots, results for 162 lots obtained from 115 manufacturers or suppliers were submitted. Also, 23 laboratories identified and submitted data for 34 lots of Lasix products available in their countries. There were no reported abnormalities in the physical test requirements of the products analyzed. The summaries (*n*, mean, and 95% CI) of the assay results for the "standard sample" (a common sample), Lasix lots from participating countries, and for all other furosemide products, respectively, are as follows: 30, 99.8%, 96–104; 33, 100.0%, 94–106; and 162, 99.6, 94–105. About half (~62%) of the reported uniformity of mass results based on tablet weights were in the range 150–175 mg/tablet. However, there appears to be a notable variability in tablet weights that would result in significant differences in the ratios (0.14 to 0.40) of active ingredient to excipient. The reported disintegration times ranged from 0 (instantaneous) to 18 min, with most less than 1 min. The drug dissolution testing was conducted with phosphate buffer at pH 5.8 (USP recommended). Another test was conducted with acetate buffer at pH 4.6 (noncompendial). There appears to be remarkable similarity in overall percentage of drug release from the three types of products (standard sample, Lasix lots, and other products). Although apparently there is a very wide spread in dissolution characteristics of the products tested, the analyses of variance did not detect*

* In collaboration with the study group (see Table 2) of the Official Laboratories and Medicines Control Services (OLMCS) section of the International Pharmaceutical Federation (FIP).

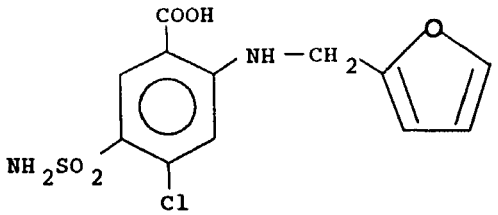
differences among the products tested and, to this extent, would not indicate differences in bioavailability characteristics for most of these products. It is observed that about 20–38% of the variability in dissolution testing is not product related (i.e., it is from the dissolution testing itself), while the remaining 62–80% variability is product related (manufacturing, formulation, etc). The results of this multinational collaborative study showed that most of the furosemide products available in different countries met the required pharmaceutical quality standards, including drug-release characteristics. Based on an extensive statistical analysis, the main concern from the study was that the high variability in drug dissolution testing would require wide tolerance standards (e.g., pharmacopoeial standards). This may result in lack of needed discriminating ability of the test in revealing the impacts of formulation and manufacturing changes on in vitro, and perhaps in vivo, drug-release characteristics.

INTRODUCTION

Furosemide (United States) or frusemide (United Kingdom) (Structure 1) is a sulphonamide-type loop diuretic that occurs as a white to slightly yellow, odorless, crystalline powder with a pK_a of 3.9. The drug is practically insoluble in water, sparingly soluble in alcohol, and freely soluble in alkali hydroxides (1).

Furosemide is commonly available as tablet preparations in strengths of 20, 40, and 80 mg. The tablets are to be stored and dispensed in well-closed, light-resistant containers. Exposure of furosemide tablets to light may cause discoloration. The discolored tablets are not to be dispensed.

When a 40 or 80 mg tablet of furosemide is taken orally by healthy adults during the fasting state, a detectable concentration of drug appears in the serum within 10 min and peaks between 60 and 90 min at a level of 1–3 μg/ml. When furosemide is taken in close proximity to a meal, there is a delay in its appearance in plasma, and a peak concentration of about 1 μg/ml is obtained after approximately 2 hr. However, the total amount of drug absorbed when taken with food is similar despite the difference in peak serum concentrations (2).



Structure 1. Chemical structure of furosemide: formula ($C_{12}H_{11}ClN_2O_5S$) wt = 330.7.

The diuretic effect of orally administered furosemide is apparent within 30 min to 1 hr and is maximal in the first or second hour. From a pharmacodynamic viewpoint, the diuretic activity of furosemide in conventional doses appears to correlate best with the first two exponential components of the plasma concentration-elimination curve. The $t_{1/2\alpha}$ and $t_{1/2\beta}$ are reported to be 6 to 11 min and 19 to 100 min, respectively (2).

The bioavailability of commercially prepared tablets is comparable to an aqueous solution of furosemide. In healthy subjects, the range of oral absorption is 60% to 69%. In patients with end-stage renal disease, absorption is reduced to values between 43% and 46%. Elimination half-lives of 19 to 100 min are reported in healthy subjects, but may extend to 8 to 15 hr in patients with renal disease.

Considering the low aqueous solubility of furosemide, its absorption through the gastrointestinal (GI) tract could be erratic with high inter- and intrasubject variability (e.g., see Ref. 3). The high variability in bioavailability levels could be related to both the drug itself and the type of formulation. Rubinstein and Rughani (4) have reported that differences of excipient (e.g., polyvinylpyrrolidone, methylhydroxyethyl cellulose, stearic acid, or starch mucilage) significantly altered the drug bioavailability in humans, and the observed differences were also reflected in in vitro drug release characteristics.

There are some reports in the literature describing successful in vitro-in vivo correlations for furosemide products (4–9). In contrast, results are also described that show a lack of such correlations (3,10). However, in one

of the studies in which two tablet products and a solution were compared in 21 healthy human volunteers, Waller et al. (3) suggested that the lack of success toward in vitro–in vivo correlation could be attributed to the high variability of the in vivo results with resultant loss of sensitivity to show differences as compared to the in vitro studies. Therefore, it remains likely that in vitro studies can serve as a reliable detector for potential problem drug products. In a retrospective study, scientists at the U.S. Food and Drug Administration (FDA) successfully correlated in vivo drug release characteristics of a problem product with the in vitro release (6).

Presently, there are no compendial requirements for dissolution studies of furosemide products in the British Pharmacopoeia (BP) and European Pharmacopoeia (Ph. Eur). However, the U.S. Pharmacopoeia (USP) requires a dissolution standard. Therefore, products appearing in the different markets would be evaluated using different criteria for product quality assessment.

The aim of the study was to assess the quality of furosemide products (in particular, drug-release characteristics) following a common protocol, as in previously completed studies (11–14), for a more appropriate comparison among products from different markets.

MATERIAL AND METHODS

The study protocol was prepared by Drs. S. A. Qureshi and I. J. McGilveray of the Department of Health, Canada, and was distributed among the potential participating laboratories. The draft was finalized following discussions at the meetings of the Section of Official Laboratories and Medicines Control Services (OLMCS) of the International Pharmaceutical Federation (FIP), Lisbon, Portugal, September 1994. An abbreviated version of the study protocol is described in Table 1.

It was suggested that, if possible, each laboratory should submit results by analyzing two lots of 40-mg strength furosemide tablets marketed in the participant's country. Further, it was recommended that, preferably, one sample should be obtained from the market (i.e., retail pharmacy or wholesaler) and the second sample should be procured directly from the manufacturer.

Each laboratory was also sent a sample of 50 tablets of Lasix product, from a single 40-mg lot, to allow comparison of variability among the laboratories. This common sample is designated as the "standard sample."

It was required that the dissolution apparatus should have been calibrated following the *USP Dissolution Apparatus Suitability Test* using disintegrating-type calibrator tablets (prednisone) as described under the general chapter on dissolution in the USP XXII.

Data Presentation and Analysis

All participating laboratories were asked to submit data in a suggested common table format. The results received were collated and analyzed using SAS software (SAS Institute, Cary, NC).

Table 1

Protocol Requirements for the Collaborative Study

Test[a]	Description
Identification (USP)	IR spectrum and color test
Amines test (BP)	Free primary aromatic amines
Uniformity of mass (Ph. Eur)	Weight variation of 20 tablets
Assay (USP)	Using HPLC method
Disintegration (BP)	Run for a set of six tablets
Dissolution (USP)	USP Apparatus 2 (paddle method at 50 rpm) Medium: 1. Phosphate bufffer pH 5.8 (900 ml) 2. Acetate buffer pH 4.6 (900 ml) Detection: UV (274 nm) Sample: 6 tablets Sampling times (5.0 ml at 10, 20, 30, 60, 90, and 120 min); solvent replacement by test medium or correction for volume removed

[a]Pharmacopeial reference in parentheses.

The variance components (i.e., contribution in variability as percentage of total due to different factors such as laboratories [within and between], product types, lots, etc.) were determined using the SAS procedure for "nested designs" with a random effects model (15). From the resulting total variance, output from the SAS procedure, 95% confidence intervals (CI) were calculated around the mean (i.e., grand mean ± 2 * SD).

RESULTS AND DISCUSSION

For the study, 33 laboratories representing 30 countries participated by submitting results. Table 2 provides the names of participating institutions and the investigators.

In total results for 162 lots, excluding Lasix lots, obtained from 115 manufacturers or supplier were submitted. Except for the laboratory from China, which submitted data for 20-mg strength product, all participants provided results for 40-mg strength tablets, mostly for multiple products and lots. Also, 23 laboratories identified and submitted data for 34 lots of Lasix lots available in their countries. Details of the products tested are summarized in the Table 3.

There were no reported abnormalities in the physical test requirements of the products analyzed. Therefore, all preparations investigated in this study fulfilled the requirements of USP XXII for identification tests.

The summary (n, mean, and 95% CI, respectively) of the assay results is as follows: 30, 99.8%, 96–104 for the standard sample; 33, 100.0% 94–106 for Lasix products from participating countries; and 162, 99.6%, 94–105 for all other furosemide products. Except for one extreme value of 80.3%, all products would comply with the USP *Acceptable Range* of 90–110%.

About half (~62%) of the reported uniformity of mass results based on tablet weights were in the range 150–175 mg/tablet for the standard sample, Lasix products, and most of the locally available products. However, a significant variability in tablet weights was reported that would result in significant differences in the ratios (0.14 to 0.40) of active ingredient to excipient. This variation in weights is illustrated in Fig. 1. Within-lot variability (%CV) ranged from 0.5 to 5.0 for Lasix and the standard product; however, for the other products, it was reported to be high, up to 8.0.

The reported disintegration times ranged from 0 (instantaneous) to 18 min. For Lasix lots and the standard sample, the mean disintegration time was less than 1 min (Fig. 2). The reported mean disintegration times for other products were as follows: less than 1 min (40%), between 1 and 4 min (46%), and within 4 to 18 min (22%).

In Vitro Dissolution

Except for one laboratory, which submitted data for the system suitability test at 50 rpm only, all participating laboratories submitted data for the USP prednisone calibrator tablets dissolution results for both 50 and 100 rpm rotation speeds as requested in the study protocol. The total number of calibrator tablet sets reported was 67 (35 at 50 rpm and 32 at 100 rpm). The prednisone calibrator tablets from lots F and H (1 lab each), J (17 labs), and K (14 labs) were analyzed by different laboratories. The reported results from 10 laboratories (15 sets using lots J and K) were outside the *USP Dissolution Apparatus Acceptance Ranges*. The 95% CI calculated were 43–65 and 37–62 at 50 rpm and 53–74 and 52–72 at 100 rpm for lots J and K, respectively. These ranges are slightly wider than, but similar to, those of *USP Dissolution Apparatus Acceptance Ranges*. The reason for these wider ranges may be due to the fact that, when the USP develops its ranges, it uses a statistical approach to eliminate potential outliers, which was not applied in this study (e.g., 16). However, there was no apparent reason to consider that data from any of the laboratories were skewed; thus it was considered that all apparatuses employed were of acceptable specifications.

The drug dissolution tests were conducted using phosphate buffer at pH 5.8 (compendial method) with paddle method (at 50 rpm). Another set of tests using acetate buffer at pH 4.6 (nearer to the pK_a of furosemide) were conducted to evaluate if potential slower dissolution (low solubility) may provide better product discriminating ability.

Except for three laboratories, which analyzed the standard sample in phosphate medium only, all laboratories reported dissolution data for the standard furosemide sample using both media, the phosphate buffer (pH 5.8) and acetate buffer (pH 4.6).

Mean (n = 6) percentage drug-release profiles for the standard sample, Lasix lots, and all other products are shown in Fig. 3. For comparison, the overall percentage drug-release values (mean ±SD) for different types of products (standard sample, Lasix, and all other products) are given in Table 4. There appears to be remarkable similarity in overall percentage of drug release from the three types of products. Due to the relatively lower solubility of furosemide at pH 4.6, as expected, a slight lag time in drug release in acetate buffer was observed. However, these differences do not appear to have a great impact on

Table 2

Institutions and Investigators Participating in the Study

COUNTRY	PARTICIPANTS AND THEIR AFFILIATIONS
Argentina	C. Bregni, University of Buenos Aires
Austria	H. Viernstein, Universitat Wien
Brazil	F. Rosenberg, Fundacao Oswaldo Cruz
Canada	S.A. Qureshi and I.J. McGilveray, Health Canada
China	Yu Ru-Yin, Nat. Institute for the Control of Pharmaceutical and Biological Products
Cyprus	M. Aletrari and E. Dragou, Pharmaceutical Dept, State General Lab.
Denmark	M. Handlos, National Board of Health
Egypt	L.k. El-Khordagui, U of Alexandria
Finland	E. Totterman, Lääkelaitos, National Agency for Medicines
France	J-M. Aiache, Laboratoire De Biopharmacie, Clermont-Ferrand
Germany	H. Blume, B. Marx and S.L. Ali, ZL Deutscher Apotheker
Greece	M. Georgarakis, University of Thessaloniki
Hungary	I. Torok, National Institute of Pharmacy
Luxembourg	J.I. Robert, Laboratory of National Health
Mexico	H. Jung C, Facultad De Quimica, Division De Estudios De Posgrado, Unam
Netherlands	J.W. Van Duijn and J.C. Van Der Steen, Rigo F.J. Van De Vaart & O.S.N.M Smeets, Lab. Der Nederlandse Apotheker and O.M. Van Berkel-Geldof, Farmanalyse
New Zealand	R.A. Richardson, Institute of Environmental Science and Research (ESR)
Poland	A.P. Mazurek and L. Fijeteli, Drug Institute, Warsaw
Portugal	A.R. Farinha & M.G. Paulo, Laboratório De Estudos Farmacêuticos
Singapore	Woo Soo On, Institute of Science & Forensic Medicine
South Africa	B. Boneschans, MCC Laboratory, Potchefstroom University
Spain	A. Velazquez, Centro National Pharmacobiologia, Ctra Majadahonda
Sweden	H. Selander, M.E. Johansson, and E. Sjoberg, Apoteksboleget
	J.O. Walterson, M. Karlsson & M. Tyden, Medical Products Agency
Switzerland	S. Steiner, Intercantonal Office for the Control of Medicines
Syria	H. Abboud, Ministry of Health
Tunisia	H. Trabelsi, Ministry of Public Health
Turkey	T. Burat and M. Yalin, Refik Saydam Central Institute of Hygiene
UK	A.G. Davidson, Medicines Testing Laboratory
Uruguay	E. Frugoni, Jefe Del Laboratorio De Biofarmacia
USA	V.P. Shah and G. Shiu, Office of Generic Drugs, FDA

the total percentage of drug release. Therefore, it may be said that both media can be used as acceptable dissolution media for evaluating drug-release characteristics of these products. However, as reported in the literature (6,9), a dissolution medium with a lower pH (4.6 vs. 5.8) offers better representation of in vivo release; thus, testing of these products using phosphate buffer of pH 4.6 may be more appropriate.

To determine quality of a drug product with respect to its drug-release characteristics, one needs to assess the results as described under the *Tolerance Criteria* for the USP furosemide tablet monograph. The Q-value for furo-

Table 3

Details of the Tablet Preparations Analyzed

COUNTRY	MANUFACTURER [PRODUCT NAME (BATCH #s)]
Argentina	FECOFAR [FURSEMA (087594)], DEVEGE S.R.L. [FURSEMIDA (196074)], SINTESINA [FURSEMIDA (40503-1)], HOECHST [LASIX (145302/DHB)]
Austria	MERCKLE [FURON (36 32 T 4)], GENERICON [FUROSEMID (0 31 424)], HOECHST [LASIX (12D140)]
Brazil	INST. QUIMICO DE COMPINAS [FUROSEMIDE (M4042)], HOECHST [LASIX (D013 & D014)
Canada	APOTEX [APO-FUROSEMIDE (WH461 & YB393)], HOECHST [LASIX (9694A)], NOVOPHARM [NOVO-SEMIDE (3801740 & 4636540)]
China	NO 3 [FUROSEMIDE (921001)], TANG SHAN BO HAI [FUROSEMIDE (940601)], CHO YANG [FUROSEMIDE (940606)]
Cyprus	HOESHST-GREECE [LASIX (40915)], REMEDICA [SALUREX (5203)]
Denmark	A.L PHARMA [DIVRAL (802251)], DURASCAN [FURESE (7066603)], NYCOMED BENZON [FURIX (F662550)], NETTO PHARMA [FURONET (1B0722-1)], DUMEX [FURONET (523343-1)],NM GERARD [FUROSEMID (81115 02)], NYCOMED [FUROSEMID (A609450)], HOECHST [LASIX (040559)]
Egypt	HOECHST [LASIX (498 & 580)]
Finland	LAAKEFARMOS [FURESIS (UHA64C)], MERCKLE [FUROMIN (1766T3)], HOECHST [LAISX (03D541 & 336L525)], BENZON PHARMA [VESIX (082638)]
France	COX [FRUSEMIDE (953285 & FD 227)], LAFRAN [FUROSEMIDE (93167A)], HOECHST [LASILIX (485 & 475)]
Germany	[1(A & B)], [2(A)], [3(A & B)], [4(A)], [5(A & B)], [6(A & B)], [7(A & B)], [8(A & B)], [9(A)], [10(A & B)], [11(A & B)], [12(A)], [13(A & B)], [14(A & B)], [15(A & B)], [16(A & B)], [17(A & B)], [18(A)], [19(A & B)], [20(A & B)], [21(A & B)], [22(A & B)], [23(A & B)], [24(A & B)], [25(A)], [26(A & B)], [27(A & B)]
Greece	HOCHST-HELLAS [LASSIX (missing, 40916)], ERFAR [SEMID (930632 & 953285)]
Hungary	CHINON [FUROSEMID, (7680594, 7690594)]
Luxembourg	HEXAL [FURORESE (119001 & 9122889)], RATIOPHARM [FUROSEMIDE (1072T3, 1282T3 & 2225T4)], EUROGENERICS [FUROSEMIDE (93C25.B & 93K17.F)], HOECHST [LASIX (02D549, 02D549 & 02D554)]
Mexico	HOECHST [LASIX, (94H1232 & 94H1233)]
Netherlands	BENZON PHARMA [VESIX (81058)], CENTRAFARM [FUROSEMIDUM (94J27B)], DAGRA [FUROSEMIDE (941114)], DUMEX [FUROSEMIDE-DUMEX (519687)], HOESHST [LASIX (91D17431)], ICN [FUSID (94D24)], KATWIJK [FUROSEMIDE (94/15G)], LAGAP [FUROSEMIDE (940220A)], MEDICALEX [FUROSEMIDE (441EL)], MULTIPHARMA [MP-FUROSEMIDE (940519/733)], NEDCOX [FUROSEMIDE (94G11/0017)], PHARBITA [FUROSEMIDUM (V01234)], PHARMACHEMIE [FUROSEMIDUM (94D05KB)], RHONE-POULENC RORER [FUROSEMIDE (4P37DW)], STEPHIM [FUROSEMIDE (931210)], SUDCO [FUROSEMIDE (94A20 1 S)], TEEVA [FUROSEMIDE (94B09328046)]
New Zealand	APOTEX [APO-FRUSEMIDE(40122)], DOUGLAS [FRUSID(9451540)], HOECHST [LASIX(29746/2)], PACIFIC [DIURIN(950101)]
Poland	[FUROSEMIDUM(1011194 & 1040894)]
Portugal	HOECHST [LASIX(242472 & 242492)], SOFARIMEX [AQUEDUX(105625 & 42403)]
Singapore	[FRUSEMIDE(UNKNOWN)]

Table 3 Continued

COUNTRY	MANUFACTURER [PRODUCT NAME (BATCH #s)]
South Africa	ARCANA [ARCANAMIDE(9308167 & MG74830)], HOECHST [LASIX(0421B & 1906A)], LENNON [PURESIS(MH72830 & MH85000)] QUICK MED/PREMIER [UREMIDE(1100)], ROLAB [HYDREX(94G107B & 94JU7)]
Spain	[A(I-14 & I-3)]
Sweden	BENZON PHARMA [FURIX(F613920 & 587860)], DUMEX [IMPUGAN(519778-2 & 519692)], HOECHST [LASIX(01D550 & 03D541)], MERCKLE [FUROSEMID(0261T4 & FUROSEMID FERMENTA(0644F0)], NM PHARMA [FUROSEMID(P4H003 & PHD004)]
Switzerland	BOSS [DIURESAL(65758 & 65767/A)], BOSS [FUROSIFAR(65869 & 65873)], CENTRAPHARM [DIURIX(92I01.8 &93K17.6)], DUMEX [IMPUGAN(517716 & 519989)], HOECHST [LASIX(01D553 & 01D554)], MEPHA [OEDEMEX(94151 & 94195)], SAGITTA [FURO-BASAN(BC0210 & BI0780)]
Syria	[LAZILEX(2111 & 22)], [OBARSIX(212 & 213)]
Tunisia	[LASILIX(004)]
Turkey	[DE-BI(941108)], [FU-DE(4020410 & 4061149)], [HO-LA(HLD & HLL)]
UK	A [FRUSEMIDE TABLETS(33008)], B [FRUSEMIDE TABLETS(33003 & 33011)], C [FRUSEMIDE TABLETS(33005 & 33010)], D [FRUSEMIDE TABLETS(33007)], E [FRUSEMIDE TABLETS(33012)], F [FRUSEMIDE TABLETS(33009)], G [FRUSEMIDE TABLETS(33006)]
Uruguay	ASTER [FUROASTER(8)], BIOS [BIOSEMIDE(90111)], CELSIUS [FISHERMIDE(347)], DNSFFAA [FUROSEMIDE(2058)], FARMACO URUGUAY [FUROSEMIDE(15V397)], HOECHST [LASIX(DHD)], LAB BOME [DIUSEMIDE(21239)]
USA	[MYLAN(Z029D)], HOECHST [LASIX(0600484)]

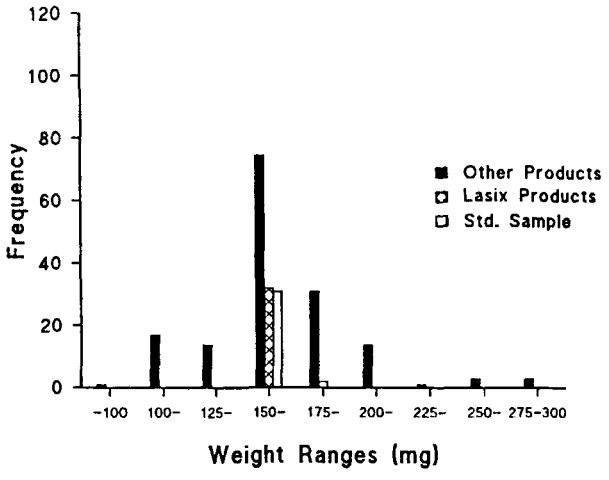


Figure 1. Frequency of mean ($n = 20$) tablet weights reported for all products analyzed.

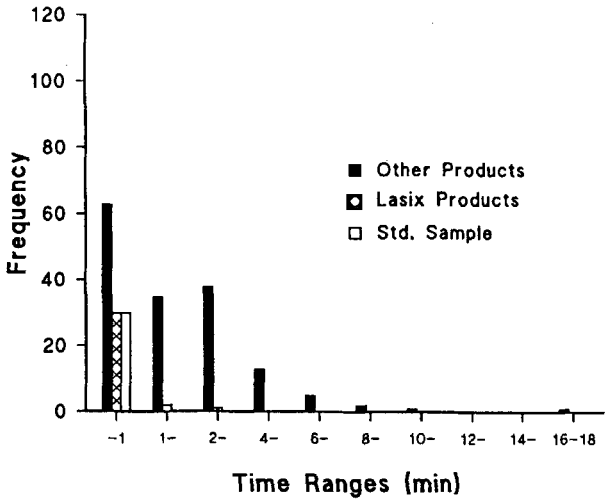


Figure 2. Frequency of mean ($n = 6$) disintegration times reported for all products analyzed.

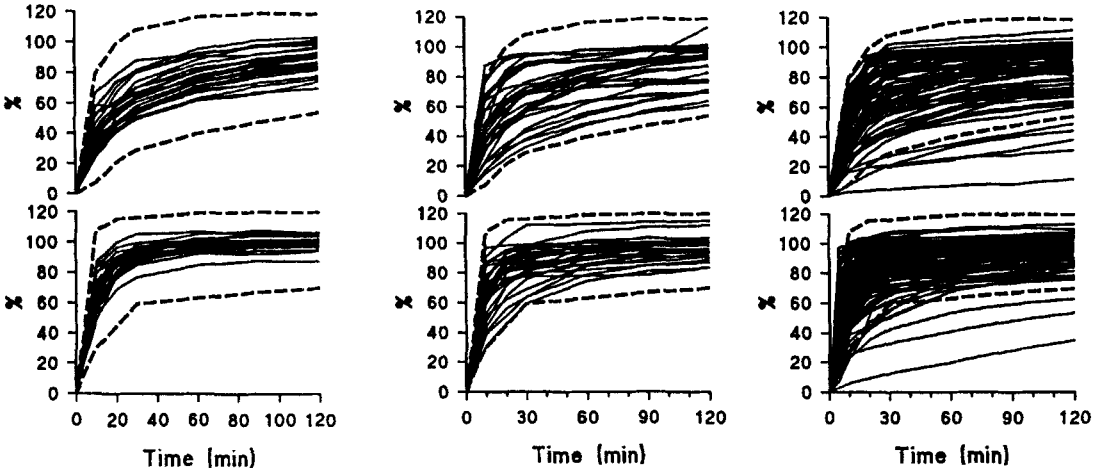


Figure 3. Mean percentage drug release profiles for furosemide products: standard sample (left), Lasix (middle), and all other products (right). The drug release was evaluated using two separate media: acetate buffer, pH 4.6 (top profiles); and phosphate buffer, pH 5.8 (bottom profiles). The experiments were conducted using USP Apparatus 2 (50 rpm). The dashed lines represent a 95% CI for individual tablet results obtained by pooling data separately from each testing medium and sampling time.

semide tablet is 80% at 60 min, which means that, to meet the *USP Acceptance Criteria*, the products have to meet one of the following three conditions:

1. *Stage 1.* Of 6 tablets, no tablets should result in less than 85% drug release.
2. *Stage 2.* Based on a 12-tablet run, including the first set of 6, the mean drug release should not be less than 80%, and no tablets should provide less than 65% drug release.
3. *Stage 3.* Of a 24-tablet run, including the previous 12 tablets, mean drug release should be not less than 80%, with no more than 2 tablets showing drug release of less than 65%, and not more than 1 tablet should show drug release of less than 55%.

In this study, the protocol required testing of only 6 tablets per product; therefore, the results can only show which lot or product would not meet the USP first-stage criterion and would have to be tested at least a second time to meet the *Acceptance Criterion.*

On the other hand, if a product shows more than two

Table 4

Mean (± SD) Percentage Drug Release from Furosemide Tablets in Acetate (A) and Phosphate (B) Buffers Using Paddle Method (rpm = 50)

	Sampling Times	Standard Sample	Lasix Lots	Other Products
A	10	39.6 ± 11.7	45.0 ± 19.7	43.9 ± 16.7
	20	54.5 ± 10.9	60.4 ± 19.7	61.4 ± 19.9
	30	64.3 ± 10.9	68.7 ± 18.4	69.5 ± 20.3
	40	77.8 ± 9.5	78.2 ± 14.4	78.2 ± 19.0
	50	84.9 ± 9.4	83.0 ± 13.0	82.5 ± 18.0
	60	88.5 ± 9.7	88.0 ± 12.9	85.1 ± 17.1
B	10	67.5 ± 10.1	68.1 ± 16.8	69.7 ± 18.6
	20	84.7 ± 6.7	80.2 ± 13.6	78.8 ± 17.3
	30	92.2 ± 5.4	85.9 ± 11.8	87.2 ± 14.5
	40	97.6 ± 4.4	93.1 ± 9.7	88.6 ± 13.6
	50	99.1 ± 4.3	95.7 ± 7.7	91.1 ± 12.2
	60	99.4 ± 4.2	96.7 ± 6.9	92.7 ± 11.0

tablets with less than 65% drug release or any tablet with less than 55% drug release, that product should be considered a substandard product as the products cannot meet the stage 2 or 3 criterion even though these results are obtained from the first run of six tablets. Considering the above criteria, the results from this study were analyzed. Furthermore, according to the USP monograph, only those values were analyzed that were obtained at the sampling time of 60 min using phosphate buffer as the medium.

The results from five laboratories show that dissolution testing of the standard sample would have to be conducted at least twice to provide acceptable results according to *USP Acceptance Criteria*. However, it is reasonable to assume that all laboratories may show the standard product to be of acceptable quality as no tablets showed a percentage drug-release value of less than 55%. The lowest reported from one laboratory for one tablet was 66%.

The results from 11 laboratories reported that Lasix products from their countries were outside the stage 1 acceptance criteria. However, based on the submitted data, it is reasonable to assume that all Lasix lots tested may be of acceptable quality (stages 2 and 3) as the lowest percentage drug release at 60 min was 63%.

With respect to the results for all other products, 40 lots did not meet the USP stage 1 criterion. However, results from 4 laboratories showed that 5 lots of these products would fail the stage 3 criterion as the percentage drug-release values were less than 55% at 60 min. The drug-release characteristics of the 5 substandard lots are shown in Fig. 4.

From Fig. 3 and Table 4, it is apparent that the overall drug-release pattern for the standard sample, Lasix lots, and other products is as expected. That is, the standard sample shows a narrower spread, followed by the Lasix lots, which include variability due to lot-to-lot differences and different manufacturing sites, in addition to within- and between-laboratory variability. Obviously, higher variability among different products would be expected as this also includes formulation differences.

To assess contributions to total variability due to different components, an analysis of variance (ANOVA) was conducted based on a nested design approach. The nested design was defined as lots within manufacturers, manufacturers within product types, and product types within laboratories. In this regard, all the results from dissolution testing, using each medium and sampling time, were pooled separately. The ANOVA was conducted, and total variances along with percentage contributions from different effects were obtained as an output

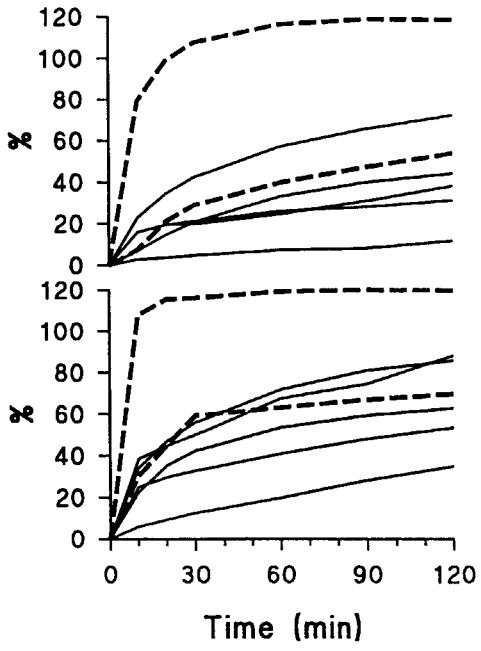


Figure 4. Mean percentage drug profiles for those furosemide products that would fail to meet the USP *Tolerance Criteria*. Further details are the same as given in Fig. 3.

from an SAS software procedure. The results are summarized in Table 5. From the total variance values, 95% CI for each sampling time were calculated, shown as thick dashed lines in Fig. 3. It is important to note that, in this analysis, Lasix tablets were assumed to be products from different manufacturers rather than different lots as it was not possible to establish manufacturing sites for these products. Therefore, it may be possible that the resulting variances due to manufacturers may very well include variability due to different lots.

In the second column of Table 5 are reported mean percentage drug-release values, along with %CV value calculated from total variance values.

The variances are somewhat lower for the phosphate buffer, but the overall patterns are the same as for the acetate buffer. The reason for the smaller variances for the phosphate buffer may be that the drug is dissolved relatively faster (higher solubility) in the phosphate buffer. Thus, once the maximum drug release is attained, the variability is influenced only by those tablets that still have to reach the limit of maximum drug release.

Examining Table 5, it is evident that about 20–38% of the variability in dissolution testing comes from the testing itself (between and within laboratory). In absolute terms, this observed variability (variance) is in line with

Table 5

Mean Percentage Release from Furosemide Products and Total Variance Values with Percentage Contributions Due to Different Factors[a]

	Time (min)	Mean (%CV)	Total Variance	Contributions as % of Total Variances by Different Factors				
				Interlaboratory	Product Type	Manufacturers	Lots	Error Term (Within Run)
A	10	43.4 (41.4)	321.9	5.0	6.4	53.3	18.2	17.1
	20	59.9 (32.4)	377.4	11.4	3.2	55.0	21.5	8.9
	30	68.3 (28.9)	390.2	18.4	0.0	56.4	18.1	7.1
	60	78.1 (24.6)	367.9	26.1	0.0	51.6	14.6	7.7
	90	83.2 (21.6)	322.3	25.4	0.0	54.5	12.9	7.2
	120	86.3 (18.8)	263.7	22.7	0.0	53.3	13.5	10.6
B	10	69.1 (28.0)	374.5	11.8	0.0	47.9	15.0	14.9
	20	80.2 (22.0)	311.7	14.8	0.0	58.6	14.6	11.6
	30	87.7 (16.2)	201.8	18.1	10.2	44.6	14.6	12.5
	60	91.2 (15.4)	197.0	17.9	0.0	55.3	14.6	12.2
	90	93.5 (14.2)	175.4	25.0	0.0	52.8	10.3	12.0
	120	94.7 (13.2)	156.7	26.1	0.0	52.6	9.3	11.9

[a]Using acetate (A) and phosphate (B) buffers at different sampling times; calculated by pooling results from all products (standard sample, Lasix, and other products).

those obtained in other studies (17) in which a single drug product was analyzed by different laboratories. Therefore, 62–80% of observed variability in dissolution testing comes from product variation related to manufacturing, formulation, and so on.

As stated above, there was a wide spread in tablet weights from product to product, and thus in ratios of active ingredient to excipient, along with spread in disintegration times. However, data analysis did not reveal any particular pattern of dissolution release characteristics with different tablet weights or disintegration times. Therefore, it appears that the reported wide differences in formulations and manufacturing sites do not appear to relate to the in vitro drug-release characteristics and may indicate similarity in bioavailability characteristics for most of these products.

Another important observation from this study is that, although there appears to be a very wide spread in dissolution characteristics of products, the ANOVA results (Table 5) and the summary results (Table 4) show a practical similarity in drug-release characteristics among the product categories (standard sample, Lasix products, and other products). Therefore, one may infer that the dissolution test may not be a discriminatory test to detect differences in formulation and manufacturing changes. The second possibility is that the dissolution test itself may be highly variable, and thus the observed high variability in results may be just due to the testing itself and not because of the products. The last observation is similar to the one suggested by Qureshi and McGilveray (17) that the dissolution test itself may be highly variable in detecting formulation and manufacturing changes, especially for slower dissolving products.

Based on the *USP Acceptance Criteria* and the 95% CI approach, both approaches suggest that three products would be considered of substandard drug-release quality. Two of the five lots for which percentage drug release for one of the six tablets tested for each lot show less than less 55% and thus would mot meet the USP criteria even at stage 3.

The drug-release profiles of the two products that did not meet the *USP Acceptance Criteria* (stage 3) showed drug-release characteristics within the 95% CI. Therefore, there is a possibility that these products may be of acceptable quality (Fig. 4).

To summarize, a large number of furosemide products were evaluated for their pharmaceutical quality in comparison with an innovator product. The results show that, based on the identification and impurity, disintegration, assay, and uniformity of mass tests, all products show acceptable quality.

Drug-release characteristics of most of the products tested based on the dissolution test as described in the USP using phosphate buffer medium, as well as in acetate buffer, would show an acceptable quality of release characteristics. Of the 162 lots of product tested, 5 would not

meet the USP criteria. However, using 95% CI criteria, only 3 lots of 2 products would be of substandard quality.

Aside from acceptable quality of drug-release characteristics of the tested products, there appears to be significantly high variability with the products of this drug that would require wide acceptance criteria. A quarter to about half of the variability in dissolution testing appears to come from dissolution testing itself (i.e., is not product related). It is of concern that, with the wide tolerance standards, detection of the impact of formulation and manufacturing changes on drug-release characteristics may not be possible.

ACKNOWLEDGMENT

Our thanks to Dr. Martin Siewert of Hoechst Marion Roussel AG, Germany, for providing furosemide tablets and Mr. Eric Ormsby of Therapeutic Products Directorate for assistance in statistical analysis.

REFERENCES

1. *AHFS Drug Information '94*, American Society of Hospital Pharmacists, pp. 1709–1713.
2. R. E. Cutler and A. D. Blair, Clin. Pharmacokin., 4, 279–296 (1979).
3. E. S. Waller, M. L. Crismon, R. V. Smith, M. T. Bauza, and J. T. Doluisio, Biopharm. Drug Dispos., 9, 211–218 (1988).
4. M. H. Rubinstein and J. M. Rughani, Drug Dev. Ind. Pharm., 4, 541–553 (1978).
5. W. Stüber, E. Mutschler, and D. Steinbach, Drug Res., 32, 693–697 (1982).
6. V. K. Prasad, R. S. Rapaka, P. W. Knight, and B. E. Cabana, Int. J. Pharmaceutics, 11, 81–90 (1982).
7. M. Kingsford, N. J. Eggers, G. Soteros, T. J. B. Maling, and R. J. Shirkey, J. Pharm. Pharmacol., 36, 536–538 (1984).
8. P. J. McNamara, T. S. Foster, G. A. Digenis, R. B. Patel, W. A. Craig, P. G. Welling, R. S. Rapaka, V. K. Prasad, and V. P. Shah, Pharm. Res., 4, 150–153 (1987).
9. P. L. Fagiolino, J. M. Aiache, R. Camacho, S. Aiache, and R. Renoux, Cienc. Ind. Farm., 4, 311–319 (1985).
10. M. H. Rubinstein, Drug Dev. Ind. Pharm., 6, 105–119 (1980).
11. H. Blume, S. L. Ali, and M. Siewert, Drug Dev. Ind. Pharm., 19, 2713 (1993).
12. H. Blume, S. A. Qureshi, S. L. Ali, and I. J. McGilveray, Drug Dev. Ind. Pharm., 21, 925 (1995).
13. A. G. Davidson, Drug Dev. Ind. Pharm., 21, 2167 (1995).
14. A. Farinha, S. D. Nóbrega and M. G. Paulo, Drug Dev. Ind. Pharm., 23, 47 (1997).
15. SAS Institute, *SAS/STAT User Guide*, Version 6, 4th ed., vol. 2, SAS Institute, Cary, NC, 1989, p. 1127.
16. *Pharmacopeial Forum, 23*, 4198–4237 (1997).
17. S. A. Qureshi and I. J. McGilveray, submitted for publication.