Scientific Research and Essay Vol. 2 (8), pp. 348-352, August 2007
Available online at http://www.academicjournals.org/SRE
ISSN 1992-2248 © 2007 Academic Journals

Full Length Research Paper

Quality control assessment and the possibility of interchangeability between multisourced norfloxacin tablets marketed in Nigeria

Ngozi Nwodo, Ikem Uzochukwu and Edwin Ogechukwu Omeje*

Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria.

Accepted 25 July, 2007

Quality control assessment of four brands of norfloxacin tablets marketed in Nigeria was carried out in enzyme-free simulated intestinal fluid (SIF) and simulated gastric fluid (SGF) with the aim of selecting brands that are interchangeable. The possible *in vivo* bioavailabilities of the brands were predicated based on their respective dissolution efficiency (DE) and predicted availability equivalent (PAE). The results of weight uniformity test, disintegration time test and other non-pharmacopoeia tests of all brands were within the acceptable ranges. Predictions from DE indicated that the brands were all bioequivalent and therefore interchangeable with the innovator brand. The concept of dissolution efficiency (DE), *in vitro* dissolution studies could serve as a rapid means of comparing brands of norfloxacin tablets.

Key words: Norfloxacin, interchangeability, quality control, dissolution efficiency, predicted availability equivalent.

INTRODUCTION

Increasing economic activities in many parts of the world has led to proliferation of pharmaceutical manufacturing industries with the attendant introduction of many brands of the same drug into the drug market. The availability of different brands of the same drug places many prescribers in difficult situation over choice of an 'ideal' brand. Notably, the rapid influx of multisourced norfloxacin tablet from different countries into Nigerian market is on the increase. Many of these products are cheap and affordable, but with high uncertainty about their interchangeability with the innovator brand. Interchangeability is the process of dispensing a different brand or unbranded drug product in place of the prescribed drug product (Baba, 2001). Interchangeable products must contain the same amount of the active ingredients and exhibit similar bioavailability profile. Biopharmaceutical studies have shown that the bioavailability and hence the therapeutic efficacy of many drugs are significantly affected by formulation factors, (Ofoefule et al., 1998). These factors have been studied extensively with respect to tablet dosage form (Rubeinsten, 1990). The prediction of *in vivo* bioavailability of most oral drugs depends mostly on the *in vitro* dissolution studies as *in vitro* disintegration tests do not always give good *in vivo* correlation (Olaniyi, 2005). Ideally, dissolution tests should provide data to distinguish good and bad products, formulations, batches especially when operating conditions are optimal (Baba, 2001).

There are reports on similar studies with some other drugs such as metformin (Osadebe and Akabogu, 2004) and ciprofloxacin hydrochloride, (Osadebe et al., 2003). The authors established that the brands evaluated were interchangeable with their respective innovator brand. Generally the quality assurance of tablets would involve these tests; hardness/tensile strength, uniformity of diameter/thickness, weight uniformity/variation, disintegration tests, content uniformity test, friability and dissolution rate tests.

Norfloxacin, a fluoroquinolone antibacterial agent structurally related to nalidixic acid, Merck Index (2001) is used mainly in the treatment of urinary tract infection, gastro-enteritis and peritonitis (United States Pharmaco-

*Corresponding author. E-mail: winnomeje@yahoo.com.

Table 1. Tablet parameters of the different brands of norfloxacin tablets.

Brand	Average weight ± SEM (mg)	Diameter (mm)	Thickness (mm)	Hardness ± SEM (kg/F)	Friability (%)	Disintegration time (min)		Assay (%)
						SGF	SIF	
NBA	656 ± 0.29	8.5	3.0	9.66 ± 0.05	0.00	8.0	5.0	85.0
NBB	655 ± 0.15	8.5	3.0	8.84 ± 0.05	0.06	3.0	6.0	80.0
NBF	589 ± 0.33	8.0	2.5	7.42 ± 0.08	0.00	2.0	15.0	100.0
NBZ	605 ± 0.46	13.0	3.0	4.72 ± 0.04	0.00	2.0	6.0	96.0

poeia, 18th Edition, 1993). These parameters were used to evaluate the four brands of norfloxacin tablets. In the present study, *in vitro* techniques were used to ascertain the bioavailability of four brands of norfloxacin tablet dosage form marketed in Nigeria (coded as NBA, NBB, NBF and NBZ all with label strength of 400 mg) with the aim of establishing their interchangeability with the innovator brand, NBF.

MATERIALS AND METHODS

Apparatus

Apparatus used were UV-Visible PC Spectrophotometer (Model Unico 2120, USA), Mosanto tablet hardness tester, (Mosanto, UK) Erweka disintegrating chamber, Erweka DT-D dissolution test, (Erweka, Uk) Roche friabilator, digital analytical balance (Adventure® Ohaus, China), volumetric flasks, conical flasks, glass funnels, test tubes (Pyrex glass, Scott) and Gallenkamp melting point apparatus.

Solvents

The following solvents were used; concentrated hydrochloric acid, acetic acid, ethyl alcohol (BDH chemical UK) distilled water (obtained from Pharmaceutical Chemistry Laboratory, University of Nigeria Nsukka), methanol (May and Baker UK), simulated gastric fluid (SGF) and simulated intestinal fluid (SIF).

Absolute methanol (85 ml) was mixed with 15 ml of 2 N hydrochloric acid (HCl). The preparation of the dissolution media (SGF and SIF), weight uniformity test, tablet friability test, crushing strength/hardness test, disintegration time test, content of active ingredient test were all carried out using official methods as previously described (Osadebe and Akabogu, 2004; Osadebe et al., 2003). Beer's calibration curve was established with pure norfloxacin sample.

Assay of the various samples of Norfloxacin tablets

Five tablets selected at random from each brand were weighed together, crushed in a mortar with a pestle and the quantity of powder equivalent to the average weight per tablet of each brand was placed in a 100 ml capacity beakers. Freshly prepared methanolic HCl was added with shaking to the flask to make 100 ml. The mixture was filtered and appropriate dilution made with methanolic HCl. The absorbance of the filtered samples was read at 250 nm using a UV-Visible spectrophotometer. The concentration of each brand was determined from the calibration curve previously obtained with a pure sample of norfloxacin.

Dissolution rate test

The dissolution test was done using the modified paddle method in SIF and SGF, with sink conditions maintained and at a temperature of 38 ± 1°C. One tablet chosen at random from each of the 4 brands was placed into the dissolution medium and at various time intervals for a total of 180 min, 2 ml of the solution was withdrawn and replaced with 2 ml of fresh dissolution medium. Each withdrawn sample was filtered and filtrate diluted appropriately. The absorbance of the filtered samples was read at 273 nm using a Uv-Visible spectrophotometer against the blank solution of the appropriate dissolution medium. The concentration of each brand was determined from the calibration curve previously obtained with a pure sample of norfloxacin.

Statistical analysis

The statistical significance between differences amongst brands was analyzed using the student's t – test. $P < 0.2$ was considered significant (Woodson, 1987).

RESULTS AND DISCUSSION

The summary of the weight uniformity test, friability test, crushing strength test, content uniformity test and disintegration time are presented in Table 1. Figures 1 and 2 represent the percentage of the different brands in SGF and SIF release, respectively. The dissolution efficiency (DE) test and the predicted availability equivalent (PAE) test were calculated using the equations below:

DE_X = AUC at time X / AUC over the entire course of release (1)

Where DE_X = dissolution efficiency of brand X, and AUC = area under the dissolution time curve.

DE^B = AUC of innovator brand / AUC over the entire dissolution time curve (2)

$PAE = DE_X / DE^B$ = (AUC / AUC of innovator) x 100 (3)

The result is shown in Table 2. The weight uniformity test indicates that the four brands of norfloxacin tablet had uniform weights with little standard deviation and hence

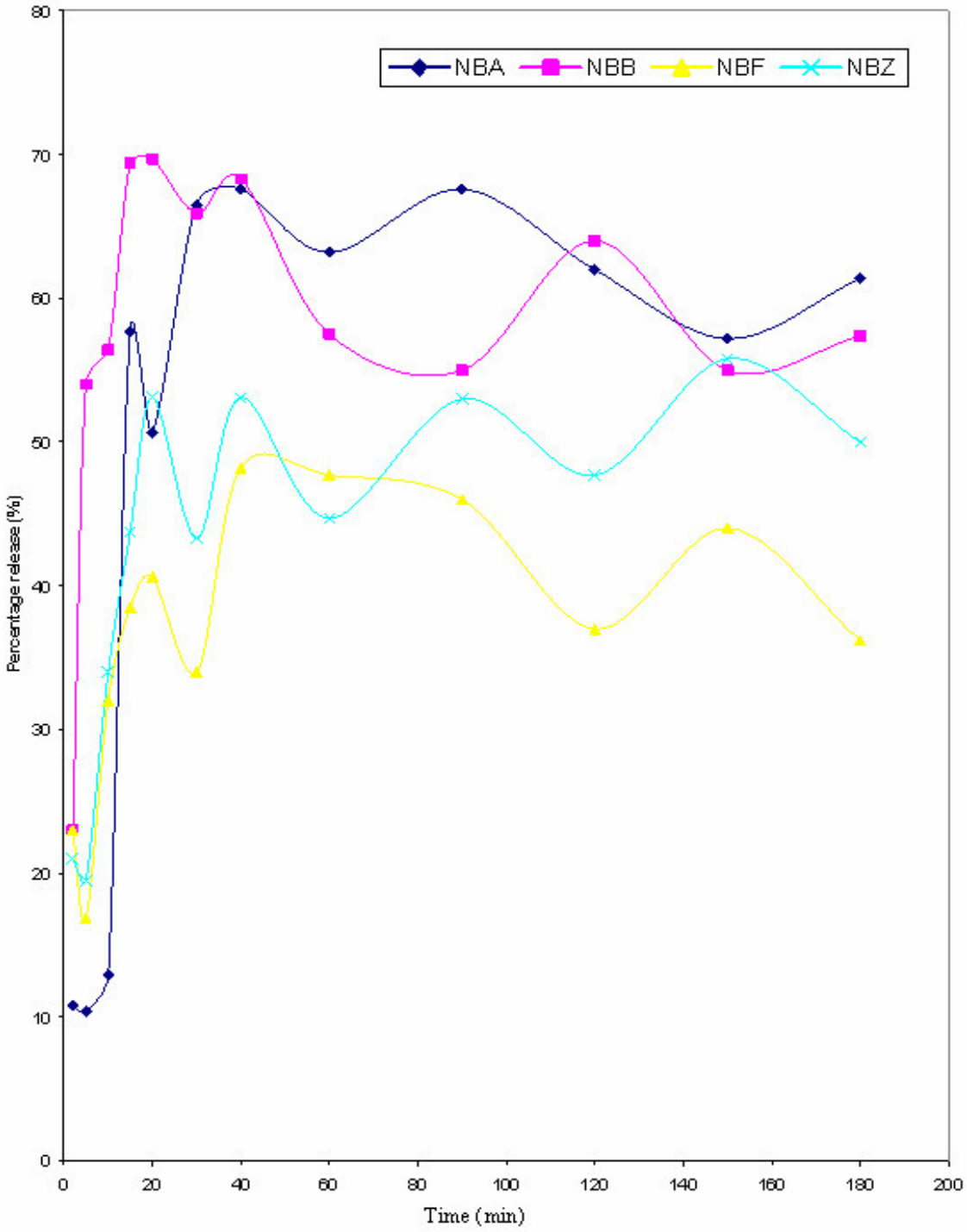

Figure 1. Percentage release of norfloxacin brands in SIF.

conformed to the United States Pharmacopoeias specification of not more than 5% deviation for tablets weights of 250 mg or more (United States Pharmacopoeia, 18th Edition, 1993). However, NBF the innovator brand exhibited excellent weight uniformity. It would be recalled that variation in tablet weight is attributed to various formulation factors, which vary from manufacturer to manufacturer (Ofoefule et al., 1998). Similarly, the four brands of norfloxacin tablets complied with the friability test specification of 0.8 - 1.0% loss in weight and that no tablet caps, laminates or breaks up in the course of the test. This trend was also observed with the non-official hardness test. Uncoated tablets with crushing strength greater than or equal to 5 kgF are considered optimal and accep-

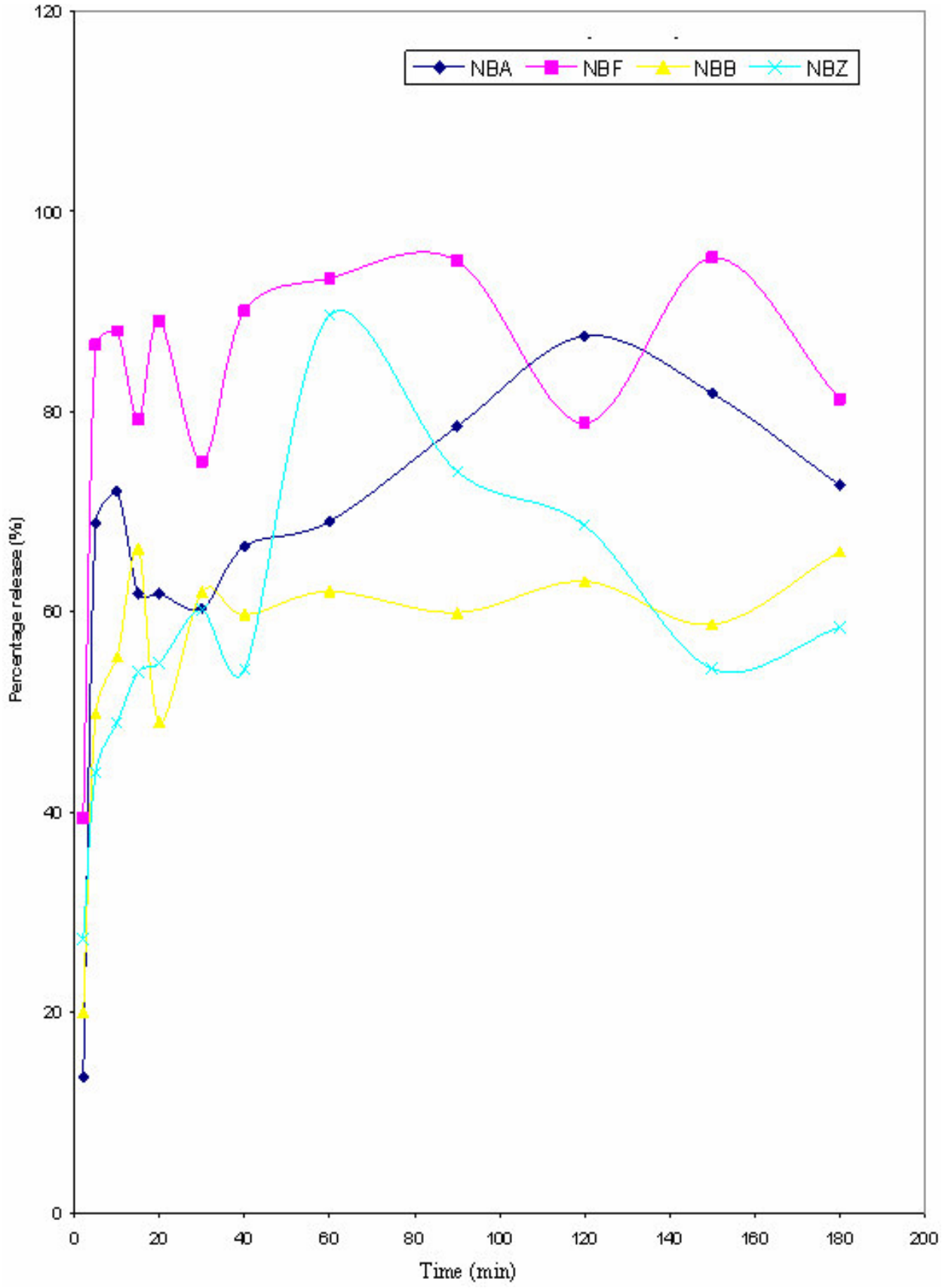

Figure 2. Percentage release of norfloxacin brands in SGF.

Table 2. Area under the curve (AUC); drug concentration in SGF and SIF.

Brand	SGF						SIF					
	AUC	AUC_{40}	DE*	PAE	T_{50}	T_{90}	AUC	AUC_{40}	DE*	PAE	T_{40}	T_{90}
NBA	45180	8033	17.8	89.5	92.0	93.0	34206	6362.3	18.6	90.3	68.0	69.0
NBB	51312	10139	19.8	99.7	84.0	80.0	33974	6237.6	18.4	88.3	63.0	57.0
NBF	42800	8500	19.9	100	67.0	73.0	25689	5343.3	20.8	100	48.0	53.0
NBZ	44454	8401	18.9	95.2	62.0	61.0	33383	4273.0	17.8	98.6	46.0	47.0

*Insignificant differences amongst brands at $P < 0.2$. SGF = simulated gastric fluid; SIF = simulated intestinal fluid. T_{40}, T_{50} and T_{90} are percentage of drug release at 40, 50 and 90 min, respectively

table (Ofoefule et al., 1998). The disintegration time test in both simulated body fluids (SIF and SGF) exhibited interesting observations. Hence, norfloxacin tablets disintegrate faster in the acidic (SGF pH = 2.2) than in the alkaline (SIF pH = 7.4). This observation is in agreement with the predicted solubility of norfloxacin based on its chemical structure. In comparing the bioavailability of the four brands of norfloxacin, the concepts of dissolution efficiency (DE) and predicted availability equivalent (PAE) still showed that they are all similar in SGF as all brands released more than 70% of their active content within 30 min. This supports our expectation that the four brands are really bioequivalent. It is interesting to note that several authors have previously disagreed on the correlation between disintegration time and dissolution time. Some authors maintain that disintegration and dissolution times are correlated (Robinson, 1979; Proudfoot, 1988), while others continue to disagree (Wagner, 1971). From our findings, there seems to be a high correlation between the two variables. In terms of absolute content uniformity, all brands in comparison with the innovator brand (NBF) had active content very near to the specified limit of 99 - 101% (British Pharmacopoeia, 2001). These parameters have indicated close similarity between the four brands, and are therefore bioequivalent. We maintain that the brands could be interchanged with the innovator brand, NBF. It is worthy of note that the present study was carried out in (absolute) methanolic HCl (2 N) in contrast to the conventional 0.I N HCl. The wider polarity range of the solvent combination would afford better results.

In conclusion, this work has shown that the dissolution efficiencies (DE) of the four brands are similar and are thus interchangeable with the innovator brand, NBF. This does not preclude the need for assessment of other brands of norfloxacin not covered in this study. It is also mandatory for manufacturers and all other key players in the drug distribution business to assure their final consumers of high quality and efficacious products. This is only possible in an environment of high ethical and moral standards.

REFERENCES

Baba CP (2001). Bioavailability/Bioequivalence ($^{BA}/_{BE}$) Assessment. In Olaniyi A.A. Babalola, C.P, Oladeinde, F.O. and Adegeko, A.O. (ds) Towards Better quality assurance of Drug in the 3rd Millennium Biopharmaceutical Methods in Drug Quality Assurance 1st Edn. Omoadade Printing Press. Ibadan, Nigeria, p. 79.

British Pharmacopoeia (2001). The Stationery Office, London, p. 1183. Merck Index (2001). Mack Publish Co; Easton London, UK, p. 346.

Ofoefule SO, Orisakwe, Ibezim EC, Esimone CO (1998). Boll. Chim Farmac., 137: 223-227.

Olaniyi AA (2005). Principles of Pharmacokinetics In: Essential Medicinal Chemistry 3rd Edition Hope Publications, Ibadan, Nigeria, pp. 59-79.

Osadebe PO, Akabogu IC (2004). Assessment of quality control parameters and interchangeability of multisourced metformin HCl tablets marketed in Nigeria, Boll. Chim. Farmac., 143 (4): 170-173.

Osadebe PO, Esimone OC, Akabogu IC (2003). An Empirical assessment of the possibility of interchangeability between multisourced Ciprofloxacin hydrochloride tablets marketed in Nigeria Boll. Chim. Farmac., 142 (8): 352-356.

Proudfoot SG (1988). Factors Influencing Bioavailability and Drug Absorption from the gastrointestinal tract. In Aulton Mr. (Ed.) Pharmacokinetics. The Science of dosage forms design 1st Edn. Churchill linguistic London UK. p. 135.

Robinson AP (1979). "The Absorption of amino Penicillin's J. Pharm, Sci. 60: 1168.

Rubeistein MH (1990). Tablets In: Aulton, MR (ed.) Pharmaceutics: The Science of Dosage Form Design 1st Ed; Churchill Livingstone, UK, p. 304.

The United States Pharmacopoeia (18th Rev), (1993). Mack Publishing Co. Easton. pp. 44-45

Wagner PO (1971). Biopharmaceutics and Relevant Pharmacokinetics: Hamilton Press, Hamilton III, p. 28.

Woodson RF (1987). Statistical Methods for the Analysis of Biochemical Data. Probability and Mathematical Sciences. Wiley, Chichester, pp. 315-317.