DISCUSSION

Dissolution testing

Although atenolol has been well-known and widely used for a long time, the standard procedure to determine its dissolution has not been reported in the individual monograph. Therefore, routine dissolution procedure following the USP regulation was conducted in this study. By the general USP requirement, not less than 75% of the active ingredient dissolved in 0.1 N HCl at 37 °C in 45 minutes in the official paddle apparatus operated at 50 rpm [27,28]. The dissolution of 50 and 100 mg tablets of Tenolol® at 10 minutes was more variable and dissoluted less than those Tenormin® and Prenolol®, however, the overall dissolution profiles after 20 minutes were comparable. Both dosage forms of the three brands dissoluted more than 90% at 30 minutes and essentially completed at 45 minutes, therefore, their dissolution complied with the USP dissolution requirement.

The disolution testing is usually regarded as a screening test for bioequivalence study since it can predict the extent and rate of absorption reasonably well, nevertheless, exception also exists. In the present study, the extent of absorption ($AUC_{0-\infty}$) of all tested products corresponded well to their dissolution profiles. However, the rate of absorption (T_{max}) of the tested products deviated slightly from that predicted by the dissolution characteristics of each products. The dissolution of Prenolol® was more rapid and greater than that of Tenormin® and Tenolol®,

however, its T_{max} was longer than the other two preparations. The reason behide this is currently unknown.

Pharmacokinetics and Bioequivalence Testing

The average plasma concentration-time profiles of 50 and 100 mg dosage forms of Tenormin®, Prenolol® and Tenolol® were comparable. Although the profiles of atenolol in each dosage form of different brand varied considerably between subjects, it is relatively consistent in each individual subject. The plasma concentration-time profile of atenolol in the present study exhibited biphasic peak concentrations in some subjects. This might be due to low water solubility characteristic of this drug [4, 5]. Inadequate fluid intake concurrently with drug administration after an overnight fast led to partial dissolution and absorption of atenolol and hence the first peak, subsequent fluid intake 2 hours after dosing might lead to the second peak.

In this study, the AUC_{0-24} and AUC_{0-30} were not reported since only the AUC-extrapolation to infinity ($AUC_{0-\infty}$) serves better as a characteristic of the extent of absorption in single-dose studies [1, 30, 31]. The reason is based on the pharmacokinetic relationship; F x Dose = Clearance x $AUC_{0-\infty}$ (F = bioavailability). Therefore, the fraction of the ultimately absorbed dose is proportional to $AUC_{0-\infty}$ and clearance is the proportionality factor. It is important that the extrapolation fraction should not exceed 20% of the total AUC [1, 31] and in this study, the average extrapolated portions were less than 10% of the total AUC.

Since the duration of blood samplings was greater than 3 times of the terminal half life [1] and the analytical technique was fairly sensitive, thus, the $AUC_{0-\infty}$ following a single dose in this study could represent the extent of absorption.

The average half-life ($T_{1/2}$), plasma clearance (Cl) and volume of distribution (V_d) were comparable among all tested preparations. The average $T_{1/2}$ was 5-7 hours which were consistent with those values reported in the literatures (Table 30) while the average V_d and Cl were 85-120 L and 170-210 ml/min, respectively which were higher than other reported values (V_d = 50-75 L, and Cl = 154±28 ml/min). The reason being is because the V_d and Cl in this study were calculated based on oral administration of the drug while those values reported from the literature were calculated based on parenteral or intravenous route, therefore, the amount of the drug in the body in this study should be corrected corresponding to the bioavailability values. Since approximately 50% of the oral dose is absorbed, the corrected values of V_d/F and Cl/F in this study would be 42-60 L and 85-110 ml/min, respectively, which are close to the values previously reported.

The results of bioeqivalence testing for both dosage forms of the three brands demonstrated that of the mean ratios of Test/Reference of $AUC_{0-\infty}$ and C_{max} were close to 1 and 90% CI were within the bioequivalence range of 0.8-1.25 for AUC and of 0.7-1.43 for C_{max} [1]. Although 90% CI of the mean $AUC_{0-\infty}$ ratio of 50 mg Prenolol®/ Tenormin® (1.05-1.27) indicated significant difference but it overlapped markedly with the acceptable range, therefore, it is considered acceptable to be bioequivalent (as mentioned in part of statistical analysis, page 32).

The results implied that the two generic preparations were bioequivalent to the innovator in the same dosage form for the extent of absorption, as stated by the US Food and Drug Administration (1985, 1993) [34]. Bioequivalence based on the rate of absorption is stated by the the EU guidelines that the T_{max} will be used as an index of rate of absorption, unless there is a clinical relevant claim for rapid release or action signs for a relation to adverse events [34]. In this study, the blood pressure and heart rate of the volunteers were observed and compared. The result showed no significant differences of the blood pressure and heart rate at any time point, between the three preparations (data not shown). It can be concluded that the differnces of T_{max} between the test preparations (Prenolol® and Tenolol®) were within the ± 20% of mean T_{max} of the reference preparation (Tenormin®) and that there were not clinical differences among them. Therefore, the test preparations (Prenolol® and Tenolol®) are bioequivalent to the reference (Tenormin®) concerning the rate of absorption.

Table 30. Mean (±SD) pharmacokinetic parameters of atenolol following a single oral administration of 50 and 100 mg Tenormin®, Prenolol®,Tenolol® and previous studies.

Parameters	Tenormin®		Prenolol®		Tenolol®		Other studies[a]
	50 mg	100 mg	50 mg	100 mg	50 mg	100 mg	
T_{max} (h)	2.88 ±1.23	3.58 ±1.47	3.25 ±0.87	3.92 ±1.14	2.54 ±1.08	3.53 ±1.93	3.20±1.50[35] 3.30±1.12[18] 2-4[4, 5]
$T_{1/2}$ (h)	6.21 ±1.05	6.47 ±0.90	5.62 ±0.80	6.34 ±0.66	5.93 ±0.71	6.08 ±0.75	6.1± 2.0[3] 8.10±1.40[35] 6.7±2.60[18] 6-7[4] , 5-7[5]
V_d (L)	113.4 ±40.28	120.4 ±70.58	85.40 ±23.44	96.60 ±17.73	95.9 ±18.77	107.80 ±30.98	57±9.0[3] 95.3±40.4[18] 50-75[5]
Cl (ml/min)	204.40 ±52.44	211.40 ±110.16	174.30 ±48.73	179.20 ±39.78	187.60 ±38.63	206.50 ±58.69	144±12.0[3] 154.50±28.0[18] 173.00±31.2[21] 100[5]

[a] The values from various studies [3, 4, 5, 18, 21, 35].