

Effect of Granules Properties on the In-vitro and In-vivo Performance of Ibuprofen Sustained Release Matrix Tablets

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Abstract

The impact of variations in the wet granulation step during the manufacturing process on the in-vitro and in-vivo performance of ibuprofen sustained release matrix tablets was investigated. Two batches were produced under different wet granulation conditions. The granules of the first batch (T1) were characterized by having a lower bulk density (0.56 g/ml), a higher percentage of fines (56.7% w/w) and a smaller geometric mean diameter (dg), 600 μm . While the granules of batch (T2) were characterized by having a more coherent properties, a higher bulk density (0.66 g/ml), a lower percentage of fines (36.9% w/w) and a larger dg, 720 μm . Three large scale production batches (B1, B2, B3) were manufactured similarly to T2 and found to have granules possessing similar properties. In-vitro tests showed that tablets of T1 had a statistically significant higher release rate constant than tablets of either T2, B1, B2 or B3. In-vivo tests were done using T1 and T2 tablets. Although T1 and T2 were bioequivalent with respect to C_{max} and AUC, T2 exhibited a statistically significant longer sustained release characteristics than T1 ($P < 0.05$).

Keywords

Ibuprofen, Sustained release tablets, Granulation variables, Matrix tablets, In-vitro and In-vivo studies.

Introduction

Ibuprofen (IB) is a propionic acid derivative of a non-steroidal antiinflammatory drug (NSAID) widely used for the treatment of rheumatoid arthritis and as an analgesic and antipyretic agent [1]. For a short biological half life NSAIDs, a sustained release dosage forms are desirable in order to allow twice or once daily administration of the drug to reduce side effects due to high plasma

concentration and to improve patient compliance. Different sustained release dosage forms for ibuprofen were proposed [2-7]. One of the designs, which was successful in the formulation of sustained release IB dosage form, was the bimodal drug release pattern [8, 9]. The bimodal design aimed at delivering a proportion of IB at colon, and consequently a high morning drug plasma concentration might be achieved [8]. The benefit of a high early morning levels of drug in plasma is to overcome morning stiffness symptom of rheumatoid disease. It was found that the choice of matrix material, amount of drug incorporated in matrix, additives type and amounts, the hardness of the tablet, density variation and tablet shape could affect the release rate and the mechanism of release of the drug [10]. The aim of this study was to investigate the effect of variation in granules properties on the in-vitro and in-vivo performance of IB sustained release matrix tablets.

Results and Discussion

All tablet products were found complying with the required specifications of assay, weight variation, thickness and hardness. The results of the physical properties of T1, T2, B1, B2 and B3 tablets are shown in **tab.1** which indicated reproducibility of the tableting process.

	T1	T2	B1	B2	B3
Granules :					
dg (μm)	600	720	710	740	700
σg (μm)	20.84	21.53	21.23	20.94	17.80
% fraction < 600 μm	56.7	36.9	41.0	35.8	30.0
Bulk density (g/ml)	0.56	0.66	0.66	0.71	0.64
Tablets :					
Weight (mg)	1096.0	1093.3	1097.0	1099.0	1100.0
	± 29.56	± 10.38	± 10.46	± 9.45	± 12.00
Hardness (Kp)	19.3	20.3	19.7	20.0	18.7
	± 0.79	± 1.15	± 2.30	± 1.05	± 2.21
Thickness (mm)	7.32	7.30	7.33	7.28	7.34
	± 0.096	± 0.051	± 0.034	± 0.043	± 0.049

(mean + SD, n = 10)

Tab. 1. Physical properties of granules and tablets.

Granules properties

Microsomical and Density Properties of granules

Microscopical examination showed that T1 granules were more irregular in shape than T2 granules. Visual inspection of granules indicated that T2 granules were more coherent than T1 granules and indicated also from the bulk density of 0.56 and 0.66 g/ml for T1 and T2 respectively. The bulk density of the granules of B1, B2, or B3 (production batches) was similar to T2 (**tab.1**). T1 granules exhibited the highest percentage of fines (< 600 μ m). B1, B2 and B3 granules had similar physical properties to T2 which indicated a reproducible granulation process was attained with acceptable batch to batch variation. This was not the case with T1 as the wet granulation process was different which resulted in production of granules possessing different physical properties as shown in **tab.1**.

Dissolution properties of granules

The dissolution results of T1 and T2 granules showed T1 releasing the drug faster than T2 due to the presence of higher percentage of fines, where 71.7% ($\pm 1.96\%$) and 55.2% ($\pm 0.25\%$) of IB were released after 15 minutes of dissolution for T1 and T2 respectively. After 60 minutes of dissolution T1 released 94.2% ($\pm 0.54\%$) of IB, while T2 released 86.1% ($\pm 0.35\%$) of IB.

Dissolution of the dosage forms

In-vitro dissolution profiles of IB from 6 different products are shown in **fig.1**.

Dissolution Models

The reference product showed the highest dissolution rate. **Tab. 2** shows the mathematical modeling parameters and regression data of the dissolution results. It was noticed that the dissolution data did not fit neither the zero-order nor the first-order kinetics ($r^2 < 0.99$). Furthermore, it was notable that the dissolution profiles fitted the Higuchi model ($r^2 > 0.99$) indicating that within the limitation of the model, the dissolution data were consistent with a diffusional mechanism of release.

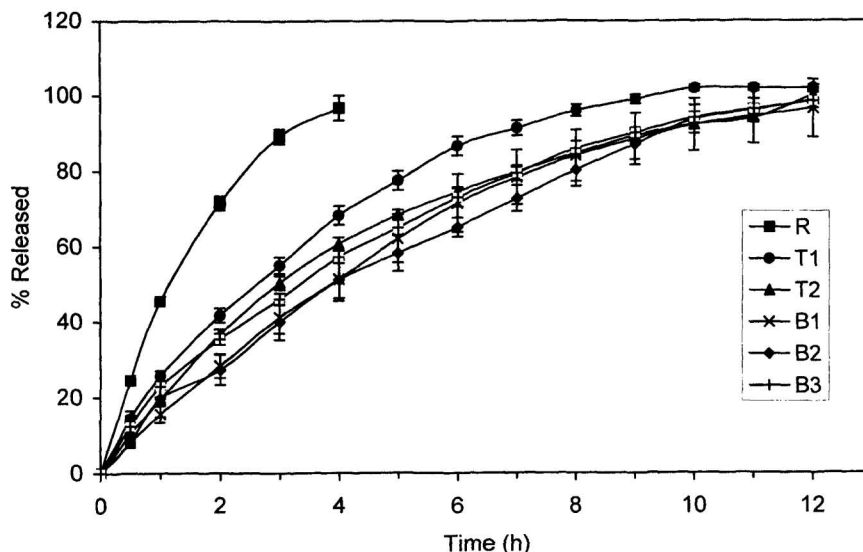


Fig.1. Dissolution of ibuprofen from: Fenbid[®] capsules (reference, R) and test sustained release tablets (T1 and T2 as pilot batches; B1, B2 and B3 as production batches), mean % released \pm SD, n= 6.

However, matrix dissolution or erosion, which is an important characteristic of swellable and erodible systems is not considered in Higuchi model kinetics. Therefore, additional analysis was done using Korsmeyer-Peppas and Hixson-Crowell models to make more definitive conclusions. According to the Korsmeyer-Peppas semi-empirical exponential equation, the best overall function was an anomalous non-Fickian transport mechanism ($0.5 < n < 1.0$) as shown for all dissolution profiles in **tab. 2** which means more than one type of release mechanisms could be involved. Furthermore, it appears that Hixson-Crowell model resulted in a good fit ($r^2 > 0.99$). Consequently, erosion of the matrix contributed to the release of the drug along with the diffusional mechanism.

Release	R	T1	T2	B1	B2	B3
Zero Order :						
r^2	0.9378	0.9331	0.9295	0.9465	0.9703	0.9440
K	0.341	0.156	0.125	0.137	0.132	0.126
First Order :						
r^2	0.8215	0.9331	0.7631	0.7960	0.8070	0.8014
K	0.0026	0.0013	0.0012	0.0014	0.00134	0.00114
Hixson-Crowell:						
r^2	0.9994	0.9992	0.9963	0.9992	0.9959	0.9980
K	0.0131	0.0062	0.0044	0.0044	0.0039	0.0046
Korsmeyer- Peppas:						
r^2	0.9916	0.9982	0.9924	0.9944	0.9785	0.9954
n	0.7726	0.7434	0.8340	0.8741	0.8059	0.6528
Higuchi Model :						
r^2	0.9979	0.9958	0.9901	0.9908	0.9953	0.9938
K	8.150	5.146	4.296	4.446	4.367	4.199
Intercept	-19.00	-10.34	-10.97	-17.34	-16.48	-9.30
Lag time (min)	2.3	2.0	2.6	3.9	3.8	2.2

r^2 , correlation coefficient; K, release rate constant and n, diffusional exponent.

Tab. 2. Mathematical model parameters and regression data of the dissolution results.

In-vitro Evaluation

The similarity factor (f_2) showed significant deviations from the acceptance limits for the comparison of T1 and T2 products with the reference products (R). These results indicated T1 and T2 products were not similar to R. The dissolution profiles of B1, B2 and B3 were found to be similar to that of T2. f_2 values were 65.1, 60.3 and 80.3 for B1, B2 and B3 respectively which indicated an acceptable batch to batch variation. However, this was not the case with T1 as the metric value

was found outside the recommended limits of similarity, 47.1% (acceptance criteria is 50% or more).

The difference between T1 and other test products (T2, B1, B2 and B3) with regard to the time required for 100% release of IB was found to be significant ($P < 0.05$).

The rate constant of Higuchi's model for T1 was higher than that of either T2, B1, B2 or B3 as shown in **tab. 2** indicating a faster diffusion rate for T1 tablets.

Furthermore, it was observed visually that upon dissolution T1 tablets eroded faster than T2. The rate constants of Hixson-Crowell model showed T1 had K_p value 1.5 times of either T2, B1, B2 or B3, an indication of faster erosion. A faster diffusion and erosion of T1 tablets could be related to the physical properties of their granules as shown previously.

In-vivo study: Bioavailability of R, T1 and T2

Fig. 2 shows the mean (\pm SD) plasma concentration-time profiles of IB after 600mg single-dose administration of R, T1 and T2 products.

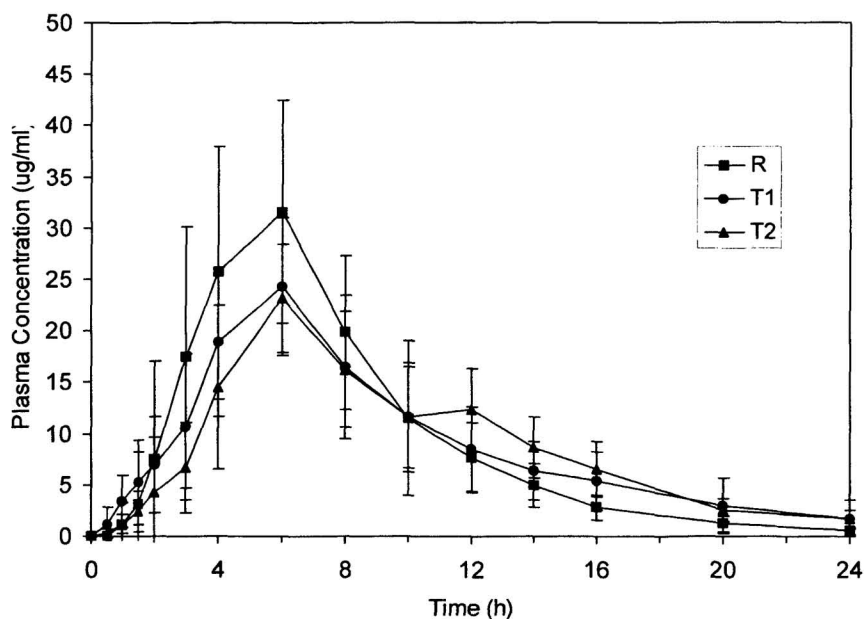


Fig. 2. Bioavailability of ibuprofen from 2x 300 mg Fenbid® capsules (reference, R) and test 600 mg sustained release tablets (T1 and T2).

Pharmacokinetic parameters derived from the plasma drug data are summarized in **tab. 3**.

Parameter	R Capsules 2 x 300 mg	T1 Tablets 600 mg	T2 Tablets 600 mg
C_{max} $\mu\text{g/ml}$	35.1 \pm 10.26	26.1 \pm 6.82	24.2 \pm 5.53
t_{max} (h)	5.7 \pm 1.34	5.6 \pm 1.27	6.2 \pm 1.14
AUC_{0-12} $\mu\text{g.h/ml}$	198.9 \pm 54.58	162 \pm 40.79	147.7 \pm 38.58
AUC_{0-24} $\mu\text{g.h/ml}$	230.1 \pm 62.31	215.1 \pm 58.25	210.6 \pm 53.70
$AUC_{0-\infty}$ $\mu\text{g.h/ml}$	232.4 \pm 62.32	222.0 \pm 61.92	221.7 \pm 62.55
AUC_{12-24} $\mu\text{g.h/ml}$	31.5 \pm 14.56	52.9 \pm 25.93	62.9 \pm 21.81
K_e (h^{-1})	0.222 \pm 0.900	0.222 \pm 0.044	0.158 \pm 0.060
$t_{1/2}$ (h)	3.17 \pm 0.136	3.80 \pm 0.403	4.45 \pm 0.191
$MRT_{in-vivo}$ (h)	7.83 \pm 0.350	8.96 \pm 0.520	10.55 \pm 0.380
$MRT_{in-vitro}$ (h)	0.413 \pm 0.0177	0.460 \pm 0.0234	0.558 \pm 0.0293
$MDT_{in-vivo}$ (h)	5.20 \pm 0.346	6.33 \pm 1.646	7.91 \pm 1.139
C_{12} $\mu\text{g/ml}$	7.6 \pm 3.42	8.6 \pm 4.14	12.3 \pm 4.00
$HVD_{t50\% C_{max}}$ (h)	5.4 \pm 0.91	6.2 \pm 1.57	7.9 \pm 2.36
$\% C_{12} / C_{max}$	23.2 \pm 11.21	32.9 \pm 14.33	53.1 \pm 19.84

AUC_{0-12} , AUC_{0-24} and $AUC_{0-\infty}$: area under the plasma concentration-time curve for 12, 24 hours and to the infinity respectively; C_{max} : mean maximum plasma drug concentration; C_{12} : mean plasma drug concentration 12 hours after drug administration; t_{max} : time to maximum concentration; K_e : elimination rate constant; $t_{1/2}$: elimination half life; $MRT_{in-vivo}$: mean residence time in-vivo; $MRT_{in-vitro}$: mean residence time in-vitro; $MDT_{in-vivo}$: the mean dissolution time in-vivo = $MRT_{in-vivo}$ (tablets) – 2.63 ($MRT_{in-vivo}$ for ibuprofen solution according to reference 17); $HVD_{t50\% C_{max}}$: half value duration, the time range which 50% of the observed maximum plasma concentration is attained; AUC_{12-24} : area under the plasma concentration-time curve from 12-24 hours after drug administration.

Tab. 3. Pharmacokinetic parameters (mean \pm SD, n=10) obtained from concentration-time data for reference (R) and two test Products (T1 and T2) after a single dose of 600 mg ibuprofen as a sustained release dosage form.

Test products versus Reference product

Peak plasma concentration attained by the products T1 and T2 are significantly lower than the reference R ($P < 0.05$). No significant difference was observed for the values of t_{max} within the three products ($P > 0.05$). The extent of absorptions (AUC_{0-24} and $AUC_{0-\infty}$, $\mu\text{g.h./ml}$) for R when compared with T1 and T2 were found not statistically significantly different ($P > 0.05$). Elimination rate constant (k_e) and elimination half life ($t_{1/2}$) values for R and T1 showed a difference that was not statistically significant. k_e and $t_{1/2}$ were significantly different for T2 which clearly reflected product-related differences in drug release as shown by its dissimilar in-vivo profiles (fig. 2). The 90% confidence intervals based on parametric testing of the log-transformed data of the ratio T/R for the C_{max} were 0.67-0.84 for T1 and 0.60-0.82 for T2. They were outside the generally used acceptance criteria for bioequivalence (0.70 - 1.43). Furthermore, the corresponding values of the extent of absorption (bioavailability) represented by AUC_{0-24} were 0.85-1.02 for T1 and 0.83-1.03 for T2 which were within the generally used acceptance criteria for bioequivalence (0.80 - 1.25). Evaluation of $AUC_{0-\infty}$ for T1 and T2 showed similar results.

Test product T1 versus test product T2

For C_{max} and AUC parameters T1 was found bioequivalent to T2 where the 90% confidence intervals for the geometric mean ratio (T1/T2) were within the acceptance range of bioequivalence requirements, C_{max} (1.01-1.04), AUC_{0-24} (1.00-1.07) and $AUC_{0-\infty}$ (0.99-1.01).

In-vivo study: Sustained release characteristics of R, T1 and T2

In-vitro data showed T2 releasing the drug in a rate significantly slower than T1 (tab. 2). Despite the slower release rate of T2, the bioavailability data indicated that its extent of absorption represented by AUC_{0-24} and $AUC_{0-\infty}$ were not significantly different from those values of T1 or R and were within the acceptance range of bioequivalence requirements as described in the previous section. In order to describe the sustained release characteristics of the products $MRT_{in-vitro}$, $MRT_{in-vivo}$, $MDT_{in-vivo}$, $HVD_{15\%}$, C_{max} , C_{12} , $\% C_{12}/C_{max}$ and AUC_{12-24} were determined as shown in tab. 3. It is known that the higher values of these parameters represent greater sustained release performance. The mean dissolution time ($MDT_{in-vivo}$) for T2 was greater than $MDT_{in-vivo}$ of either R or T1 and showed a difference that was statistically significant ($P < 0.05$). Furthermore, $MRT_{in-vitro}$ and $MRT_{in-vivo}$ values of T2

were significantly higher than the corresponding values of either R or T1 products ($P < 0.05$). C_{12} , $\%C_{12}/C_{max}$ and $HVD_{t50\%} C_{max}$ values were significantly higher ($p < 0.05$) for T2 than R or T1. The C_{12} value of T1 was not significantly higher than the C_{12} value of R ($P > 0.05$) although the values of $HVD_{t50\%} C_{max}$ and $\% C_{12}/C_{max}$ were marginally significant ($P < 0.05$). The difference in these parameters between T2 and R or T1 explained the differences in the residual AUC represented by AUC_{12-24} . The value of AUC_{12-24} in case of T2 was significantly higher than the corresponding value of R ($P < 0.05$) or T1 ($P < 0.025$). The higher values of C_{12} , $\% C_{12}/C_{max}$, $HVD_{t50\%} C_{max}$ and AUC_{12-24} could be due to the arrival of a portion of the tablet in the colon, where it was then disintegrated and ibuprofen was dissolved and absorbed as previously pointed out [9]. However, this characteristic was lost in the case of T1 tablets. T1 product was matrix tablet prepared from smaller particle size and less coherent granules which produced higher dissolution rate (**tab. 2**) and smaller $MRT_{in-vitro}$ whereas T2 matrix tablets were made from larger particle size and more coherent granules, showed slower dissolution rate (**tab. 2**) and higher $MRT_{in-vitro}$. Thus T1 tablets were expected to erode or disintegrate faster in the gastrointestinal tract with larger proportion in the small intestinal region and allowing minimum proportion to reach the ascending colon. From the results described above, T2 appeared to have a more prolonged in-vivo delivery of IB than R and T1.

In-vivo study: Steady state performance

The advantage of T2 over R was shown by reporting that the morning steady-state mean plasma concentrations after administration of T2 tablets was significantly higher than that for R capsules, being 18.0 and 10.5 $\mu\text{g/ml}$, respectively. This was interpreted as being a result of higher C_{12} for T2 tablets [8]. A high morning drug plasma concentration is considered as an advantage because it is useful to overcome morning stiffness, which is characteristic symptoms of many rheumatic conditions [11]. R and T2 products are administered twice daily, so C_{12} as IB plasma concentration is an important pharmacokinetic parameter to be determined. In this investigation as shown in **tab. 3**, the C_{12} of T2 was significantly higher ($P < 0.05$) than C_{12} of either R or T1. However, R and T1 products did not show significant difference for their C_{12} values ($P > 0.05$). When $MDT_{in-vivo}$ or $MRT_{in-vivo}$ was plotted versus C_{12} values of R, T1 and T2 a linear relationship was obtained ($0.90 < r^2 < 0.99$). Thus, it could be predicted that T1 would produce C_{12} at steady-

state conditions significantly lower than C_{12} of T2. Consequently, the advantages of lower fluctuation of the steady state concentrations and higher C_{12} value attained by T2 tablets will not be achieved by the administration of T1 tablets.

In conclusion, variations in the wet granulation process were reflected on the in-vitro and in-vivo sustained release characteristics of ibuprofen sustained release matrix tablets. In-vitro, T1 showed a significant higher diffusion and erosion rates than T2 ($P < 0.05$). Although T1 and T2 were bioequivalent with respect to C_{max} , AUC_{0-24} and $AUC_{0-\infty}$, T2 exhibited a statistically significant longer sustained release characteristics than T1 ($P < 0.05$) as represented by the parameters C_{12} , $MRT_{in-vivo}$, $MRT_{in-vitro}$, $MDT_{in-vivo}$, $HVD_{t50\% C_{max}}$, C_{12}/C_{max} and AUC_{12-24} .

Experimental

Materials

Ibuprofen; lactose monohydrate; maize starch; magnesium stearate; titanium dioxide; polysorbate 80; and talc were materials of pharmaceutical grade and supplied by the Arab Pharmaceutical Manufacturing Co., Sult, Jordan. Ammonio methacrylate copolymer, Type B, NF (Eudragit RS) granules were supplied by Rohm Pharma Polymers, Degussa, Darmstadt, Germany. Hypromellose 2910 (hydroxypropyl methylcellulose), Methocel E15 Premium- 29% methoxyl and 8.5% hydroxypropoxyl content and viscosity grade 15 cP was supplied by Colorcon, Kent, UK. Colloidal silicon dioxide (Aerosil 200, Degussa, Germany) and Sodium starch glycolate (Primojel, Avebe America Inc., NJ, USA) were used. All chemicals and solvents were of analytical grade and supplied by E. Merck, Germany. Distilled water was used to prepare aqueous solutions and granulating agents. Fenbid® 300 mg ibuprofen sustained release (SR) spansules in capsules (Smithkline Beecham, UK) were purchased locally and used as reference product (R).

Production of tablets

600 mg IB sustained release tablets were produced according to the general formula as reported in **tab. 4**. Five different batches were prepared, T1 and T2 as pilot batches; and B1, B2 and B3 as large scale production batches. The powder mixture was prepared by mixing together IB, half amount of lactose powder and hypromellose in Gral mixer and granulator (Collette, Belgium) for 10 minutes with the mixer adjusted at low speed and the chopper at high speed. T1 was wet granulated with aqueous dispersion of Eudragit RS (20% w/w) by adding the

Ingredients	mg/tablet
Core :	
Ibuprofen	600.0
Lactose monohydrate	111.34
Maize Starch	33.40
Hypromellose	167.11
Eudragit RS	111.34
Sodium Starch glycolate	22.27
Talc	11.13
Colloidal silicon dioxide	2.83
Magnesium Stearate	5.57
Core Weight	1065
Film Coating :	
Hypromellose	24.0
Talc	8.0
Titanium dioxide	2.8
Polysorbate 80	0.2
Distilled water	300
Total Weight	1100

Tab. 4. Formulation composition.

required amount of the dispersion gradually in five portions to the powder mixture and mixed for 3 minutes after each addition. The speed of either mixer or chopper was adjusted at low speed setting. The other batches T2, B1, B2 and B3 were wet granulated similarly using a more diluted Eudragit RS dispersion (15% w/w) allowing more water to be incorporated into the wet mass. Addition was performed in 6 portions allowing mixing for 5 minutes after each addition. For all batches wet granules were then dried and milled using standard processes. Particle size analysis was done in duplicate on 100 gm of screened granules through sieves 2000, 1250, 1000, 800, 600 μm and receiver. Shaking was conducted for 15 minutes. Diluent granules made from lactose powder and starch and granulated with hypromellose 5% aqueous solution were prepared using the same equipment.

Final powder mix was then prepared by mixing drug granules with diluent granules, Primojel and talc for 15 minutes. Aerosil was then added and mixing was performed for another 5 minutes. At the end of mixing operation magnesium stearate was added and mixed for 5 minutes. The final powder mix was compressed into tablets (oblong, 19 mm x 9 mm) using 22 station rotary tableting machine (Perfecta –5, Fette, Germany) under controlled hardness ($20 \text{ Kp} \pm 10\%$). Film coating was done using Accela cota (Manesty, UK). Physical characteristics like tablet weight, thickness and hardness (Core) were controlled.

Quality control tests

Assay of IB tablets and capsules was done according to the USP 24 monograph. The dissolution profile of each dosage form was obtained using Erweka dissolution apparatus (Hensenstamm, Germany) with paddles rotating at 75 rpm and 900 ml of USP phosphate buffer solution (pH 7.2) heated at 37C° . For dissolution of granules, paddles were allowed to rotate at 50 rpm instead of 75 rpm and the dissolution medium was diluted with distilled water (2:1) while the pH was kept at 7.2. Such conditions allowed 100% of IB to be released in more than 60 minutes.. The drug concentration was determined spectrophotometrically versus a standard solution (DU-7 Spectrophotometer, Beckman, USA) at 275 nm.

In-vivo tests

Randomized, single dose crossover studies were performed on 10 healthy male volunteers aged between 18 and 40 years over 3 treatment periods with one week washout phase after each period according to a previously published method and followed ICH guidelines [8]. The dose of 600 mg IB (one tablet of either T1 or T2, 2 capsules of Fenbid[®] as a reference) was given orally with 250 ml of orange juice after having a light breakfast. Withdrawal of blood samples (7ml) via a cannula inserted into a forearm vein was done immediately before the dose (0 time) and then at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20 and 24 hours post administration. Blood samples were drawn into heparinised tubes, centrifuged at 3000 rpm for 5 minutes, and the plasma was stored frozen at -20C° until the day of analysis. Plasma analysis for IB concentrations was carried out using a validated HPLC method [8].

In-vitro data analysis

Drug dissolution from solid dosage forms has been described by different kinetic models like zero order, first order, Higuchi square root of time model,

Korsmeyer-Peppas semi-empirical exponential equation model and Hixson-Crowell cubic root of the unreleased fraction of drug versus time model [12,13].

Evaluation of similarity

Comparison of dissolution profiles were done using the similarity factor (f_2) as adopted by FDA and EMEA (European Agency for the Evaluation of Medicinal Products) as a criterion for the assessment of the similarity between two in-vitro dissolution profiles [14, 15]. FDA and EMEA suggest that two dissolution profiles are considered similar if f_2 value is between 50 and 100. The test is sensitive to measurements obtained after either test or reference batch are dissolved more than 85%. Shah et al [14] recommended that, the number of sample points be limited not more than one, once any of the product reaches 85% dissolution.

In-vivo data analysis

The bioavailability parameters of the three products were determined by a standard non-compartmental method and ANALYSIS OF VARIANCE (ANOVA) statistics were used for bioequivalence evaluations. Pharmacokinetic parameters were calculated. The maximum IB plasma concentration (C_{max} , $\mu\text{g}/\text{ml}$) and the corresponding peak time (t_{max} , h) were determined by the examination of the individual drug plasma concentration-time profiles. The area under the curve to the last measurable concentration (AUC_{0-24} , $\mu\text{g}\cdot\text{h}/\text{ml}$) and the area under the curve from 0 to 12 hours (AUC_{0-12} , $\mu\text{g}\cdot\text{h}/\text{ml}$) or from 12 to 24 hours after administration (AUC_{12-24} , $\mu\text{g}\cdot\text{h}/\text{ml}$) were calculated by the linear trapezoidal rule. $AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h}/\text{ml}$) was calculated as: $[(AUC_{0-24}) + (C_t / K_e)]$ where C_t is the last detectable plasma concentration and K_e is the elimination rate constant (h^{-1}). Half Value Duration ($HVDt_{50\% C_{max}}$, h) analysis was used to evaluate the sustained release nature of the product [5]. It is the time range which 50% of the observed maximum plasma level concentration is attained. $\% C_{12} / C_{max}$, the percentage of the ratio of C_{12} (the plasma concentration at the end of the intended dose interval) and C_{max} . This ratio provides an indicator of the peak-trough fluctuation to be expected after steady-state administration. A higher percentage also indicates a better performance as a sustained release dosage forms that are given twice daily. In-vivo mean residence time ($MRT_{in-vivo}$, h), in-vitro mean residence time ($MRT_{in-vitro}$, h) and in-vivo mean dissolution time of the product (MDT in-vivo) were calculated according to Banaker [16] and Shargel and Yu [17]. The pharmacokinetic parameters AUC and C_{max} were assumed to be log-normally distributed. Log-transformed values of these

pharmacokinetic parameters were analyzed by performing ANOVA analyses using SAS statistical program. A 5% level of significance was used for all comparisons. The two one-sided tests for bioequivalence and 90% confidence intervals for the ratios of the geometric means were calculated. The recommended range of bioequivalence was 80-125% for AUC and 70-143% for C_{max} .

Acknowledgement

I would like to express my gratitude to Dr. T. Arafat (University of Petra), Dr. N. Idkaidek (JUST), Dr. A. Sallam (APM.Co.) for their cooperation and useful discussion and also to Miss Muna Al-Resheq for her excellent secretarial work in preparing this manuscript.

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Received July 1st, 2004
Accepted December 3rd, 2004