In Vitro and In Vivo Evaluation of Single-Unit Commercial Conventional Tablet and Sustained-Release Capsules Compared With Multiple-Unit Polystyrene Microparticle Dosage Forms of Ibuprofen

Submitted: January 23, 2006; Accepted: May 20, 2006; Published: September 1, 2006

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ABSTRACT

The major aims of the present study were (1) to select a multiple-unit formulation that matched the in vitro dissolution profile of single-unit sustained-release commercial capsules, (2) to compare the sustaining/controlling efficacy of the selected multiple-unit formulation with that of the single-unit commercial conventional tablet and sustained-release capsules, and (3) to determine whether an in vitro–in vivo correlation exists for single- and multiple-unit formulations. Ibuprofen (20%-60% wt/wt)–loaded multiple-unit polystyrene microparticles were prepared by an emulsion-solvent evaporation method from an aqueous system. The in vitro release profiles obtained in phosphate buffer of pH 6.8 for drug-loaded polystyrene microparticles and for commercial sustained-release capsules (Fenlong-SR, 400 mg) were compared. Since the microparticles with 30% ibuprofen load showed a release profile comparable to that of the Fenlong-SR release profile, the microparticles with this drug load were considered to be the optimized/selected formulation and, therefore, were subjected to stability study and in vivo study in human volunteers. A single-dose oral bioavailability study revealed significant differences in C_{max}, T_{max}, $t^{1/2a}$, $t^{1/2e}$, K_a, K_e, and AUC between the conventional tablet and optimized or Fenlong-SR capsule dosage forms. However, all the parameters, with the exception of K_a along with relative bioavailability (F) and retard quotient (R_Δ), obtained from the optimized ibuprofen-loaded microparticles were lower than that obtained from the commercial Fenlong-SR formulation. Furthermore, linear relationship obtained between the percentages dissolved and absorbed suggests a means to predict in vivo absorption by measuring in vitro dissolution.

KEYWORDS: ibuprofen, polystyrene microparticles, in vitro, in vivo, evaluation.

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INTRODUCTION

Following oral administration, conventional drug delivery systems like tablets and capsules often give rise to inordinately high drug concentrations in plasma, which, in turn, can lead to the emergence of adverse drug reactions. Moreover, if the biological half-life of a drug is short, it requires repeated administration, which leads to patient noncompliance. This is particularly true for chronic dosing, especially in the management of rheumatoid arthritis. Sustained-release dosage forms, single-unit or multiple-unit doses, help physicians to provide optimum treatment by better patient compliance and safer systems with steady-state plasma drug concentrations for the desired period of time. However, multiple-unit formulations like microparticles for oral use allow the administration of much smaller drug amounts than single-unit doses do, by modifying the rate of dissolution of drug and providing a method of releasing the active ingredients at a desired rate.[1] In addition, it has been reported that microparticulate oral dosage forms diffuse rapidly, avoiding the vagaries of gastric emptying throughout the gastrointestinal tract,[2] and thus prevent the exposure of the absorbing mucosa to high drug concentrations during chronic dosing[3] and improve gastric tolerability.[4] Furthermore, local unwanted effects are reduced or eliminated when a gastroresistant polymer is used for microparticle preparation. Ibuprofen was selected as a model drug in this study because reduction of side effects, notably gastrointestinal problems,[5] and prolongation of action of this compound have been desired.

In this study, ibuprofen (20%-60% wt/wt)–loaded multiple-unit polystyrene microparticles were prepared by an emulsion-solvent evaporation method from an aqueous system, which was found to be simple and reproducible.[6] The major aims of the study were (1) to select a multiple-unit formulation with an in vitro dissolution profile that matched that of single-unit sustained-release commercial capsules, (2) to compare the sustaining/controlling efficacy of the selected multiple-unit formulation with that of the single-unit commercial conventional tablet and sustained-release capsules, and (3) to determine whether an in vitro–in vivo correlation (IVIVC) exists for single-and multiple-unit formulations.

MATERIALS AND METHODS

Materials

Ibuprofen Indian Pharmacopoeia (M/S Albert-David Ltd, Kolkata, India) and polystyrene (Grade McG-100, general purpose) (Hindustan Polymers, Kolkata, India) were obtained as a sample gift. Conventional tablets of Brufen 400 mg (Boots Pharmaceuticals, Goa, India) and sustained-release capsules of Fenlong-SR 400 mg (SOL Pharmaceuticals, New Delhi, India) and all other chemicals were obtained commercially and used as received.

Methods

Development of Multiple-Unit Dosage Form

Preparation of ibuprofen-loaded polystyrene microparticles by an emulsion-solvent evaporation method from an aqueous system containing methylcellulose as the emulsion stabilizer was reported previously.[6] Briefly, ibuprofen (20%-60% wt/wt) was dissolved in a dichloromethane (5 mL) solution of polystyrene at 15°C and was emulsified at 400 rpm in 150 mL of methylcellulose solution (0.10% wt/vol) (pH 1.4) and stirred for 2 hours. The resulting microparticles were poured into 600 mL of cold distilled water, and the stirring was continued for a further 2 hours. The microparticles were filtered, washed with water, and vacuum-dried.

Sizing of the Microparticles

Microparticles were separated into different size fractions by sieving for 15 minutes on a mechanical shaker using a nest of standard sieves (Endecotts Ltd, London, UK) stacked from bottom to top in ascending order of aperture sizes ranging from 177 to 600 μm. In the current study, microparticles with a diameter of 275 μm were used for further investigations.

Ibuprofen Content Determinations in Various Formulations

For single-unit tablet and sustained-release capsule formulations, the drug content determination was done using the method described in USP,[7] whereas for multiple-unit formulations, the drug content determination was performed by an extraction method reported previously.[6]

Thin-Layer Chromatography

Qualitative thin-layer chromatography (TLC) was performed using 10 × 10 cm precoated silica gel 60 aluminum-backed TLC sheets with layer thickness of 0.25 mm. A dichloromethane solution of an accurately weighed amount of ibuprofen and an equivalent amount of ibuprofen present in single-unit and multiple-unit formulations was applied, using a sample applicator (Camag Nanomet 11 with 1-μL capillary and holder, CAMAG, Berlin, Germany), directly onto the TLC sheet, leaving 2 cm between this area and the edge. The sheet was developed with a benzene–ether–glacial acetic acid–methanol (120 + 60 + 18 + 1)[8] system in a Camag chamber for 20 minutes. After development, the sheet was air-dried and placed in a UV cabinet. The spots were inspected against short-wave UV light (254 nm) in daylight using a glass filter for protection of the eyes against reflected short-wave UV light. From the following relationship, the R_f value was calculated:

$$R_f = \frac{\text{distance traveled by samples (substance)}}{\text{distance traveled by solvent front}} \quad (1)$$

The experiment was duplicated under the identical conditions.

In Vitro Dissolution

The dissolution study was conducted following the USP paddle method Apparatus 2 in a USP XXI dissolution rate test apparatus (Campbell Electronics, Mumbai, India). The dosage forms, ibuprofen conventional tablet (400 mg), sustained-release ibuprofen (Fenlong-SR) capsules (400 mg), or ibuprofen-loaded polystyrene microparticles equivalent to 400 mg of the drug, were placed in a dissolution flask containing 900 mL of USP phosphate buffer solution of pH 6.8 at 37 ± 1°C and stirred with a paddle at 75 rpm. Samples were withdrawn (10 mL) at predetermined time intervals, and sink conditions were maintained by constantly replenishing with the same volume of fresh buffer solution. After suitable dilution, samples were analyzed in a double-beam spectrophotometer (Model 200-20, Hitachi, Japan) at 220 nm using the same buffer solution of pH 6.8 as blank.

Kinetics of Drug Release

In spite of significant compositional and structural differences between the single-unit and multiple-unit dosage forms, the in vitro dissolution data obtained from these studied formulations were fitted in various model equations for assessing the kinetics of ibuprofen release. The model for diffusion-controlled release given by Higuchi[9] is $100 - M = Kt^{1/2}$, where M is the percentage of drug undissolved, K the dissolution rate constant, and t the time of dissolution. The equation proposed by Bamba et al,[10] $\ln M = Kt$, assumes that the drug molecules diffuse out through a dissolving gel-like layer formed around the drug during the dissolution process. The variables M, K, and t in the equation refer, respectively, to the percentage of drug undissolved, the dissolution rate, and the time of

dissolution. The equation $m_0^{1/3} - m^{1/3} = Kt$, proposed by Hixson and Crowell[11] for the dissolution of powder, assumes that the dissolution of powders is independent of the initial particle diameter (where m_o in the equation is the initial drug concentration, m is the amount of drug left undissolved at time t, and K is the dissolution rate constant). The first-order model as adopted by Shah et al[12] is given by $F = 1 - e^{-Kt}$, where F is the fraction of the drug dissolved at time t and K is the dissolution rate constant. The percent ibuprofen released from single-unit and multiple-unit formulations was plotted against time on a log-log scale and analyzed for linearity using the least-squares method. The correlation coefficients were calculated and used to find the fitness of the data.

Stability Studies

Stability studies were conducted on polystyrene microparticles containing 30% wt/wt ibuprofen to assess drug stability with respect to drug content and drug release characteristics after storing the multiple-unit formulation in drug stability testing chambers (Campbell Electronics, Mumbai, India) at 2 different conditions for up to 6 months. Typical stresses are 25°C at 75% relative humidity to represent temperate conditions and 38°C at 90% relative humidity to represent tropical conditions.[13] Drug stability testing chambers containing a saturated aqueous solution in contact with an excess of a definite solid phase at a given temperature to maintain constant humidity in an enclosed space were used. The saturated salt solutions and temperatures used in this study were NaCl at 25°C and $ZnSO_4$. $7H_2O$ at 38°C to represent 75% and 90 ± 5% relative humidity, respectively.

In Vivo Study

The oral bioavailability studies were performed on volunteers in a single-dose crossover design. Four healthy human volunteers (2 males and 2 females, age 22.75 ± 1.50 years, weight 50.75 ± 4.87 kg), who were fully informed of the purpose and the procedure of this study, gave their consent to participate. The study protocol, which complied with the recommendations of the Helsinki Declaration, was fully approved by the institutional review board committee prior to the start of work with the human volunteers. For ethical reasons, the number of subjects was limited to 4. The biochemical examination of the volunteers revealed normal function of the kidney and liver. Use of other medication was not allowed before or during the study, to reduce intra- or intersubject variability. On 3 different occasions, the subjects were separately allocated single oral doses of ibuprofen conventional tablet, Fenlong-SR capsule, or optimized ibuprofen (30% wt/wt)–loaded polystyrene microparticles equivalent to 400 mg of ibuprofen. Each of the 3 occasions was separated by a washout period of at least 10 days. To minimize gastric irritation, the subjects were provided a light breakfast (3 pieces of butter toast, 1 banana, and 50 mL milk) 30 minutes before each dosing, followed by a morning snack (2 crackers and 1 banana) 2.5 hours after dosing and a standard vegetarian lunch 4.5 hours after dosing. Blood samples (3 mL), withdrawn from a cubital vein at 0, 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours, were collected in centrifuge tubes containing 0.1 mL of 50% (wt/vol) sodium citrate solution. The samples were centrifuged and the separated plasma samples were stored at –40°C until analysis by high-performance liquid chromatography (HPLC).

Estimation of Ibuprofen in the Plasma of Human Volunteers

In the present study, plasma ibuprofen concentration in human volunteers was determined by an HPLC method of Adeyeye and Price[14] with a derivation as adopted by Lamprecht et al.[15] The Kontron HPLC system consisted of a Kontron 420 pump, a UV detector 332, and an autosampler 360 (Kontron Instruments, Zurich, Switzerland) equipped with a Rheodyne sample injector with a 50-µL sample loop. A reversed-phase 12.5 cm × 4.6 mm LiChrospher 100 RP-18 (5 µm) column furnished by Merck Co (Darmstadt, Germany) was used. The mobile phase consisted of acetonitrile: water:acetic acid 500:477:3 (premixed). The solvent flow rate was 0.8 mL/min. The analytical column and the guard column were kept inside a column heater held at 50°C.

A 0.3-mL volume of plasma was diluted with 1 mL of 0.2M phosphate buffer (pH 2.0), and 5 mL of diethyl ether was added. The mixture was shaken for 3 minutes and centrifuged at 15 000 rpm for 15 minutes. The ether layer was collected, and the aqueous layer was again extracted with 5 mL of ether. The ether layer was added to that obtained previously. The ether phase was evaporated to dryness, the residue was dissolved in the mobile phase, and 50-µL aliquots were injected into the HPLC system. The eluent was detected by the UV detector at 220 nm, and the sensitivity range of the detector was set at 0.0001 AUFS (absorption units full scale). The calibration curve equation was set up by spiking the drug-free plasma (derived from the blood collected at time 0) with varying amounts of ibuprofen (10-200 µg/mL) and a fixed quantity of internal standard (1 µg) and treating the plasma as described above. The peak area ratio of ibuprofen to internal standard (flurbiprofen) was obtained for each calibration standard. Ratios were fitted by least-squares regression to a linear calibration model. A good linear relationship (r^2 = 0.9996) was observed between the peak area ratio and the plasma concentration of ibuprofen in the range of 20 to 200 µg/mL. The lower detection limit was determined to be 10 µg/mL. The

interday and intraday variation was found to be less than 2.8% coefficient of variation for the HPLC method. Recovery of ibuprofen was found to be 96.8% to 99.3%.

Pharmacokinetic Parameters

Estimates of pharmacokinetic parameters were obtained from the plasma concentration versus time data. The maximum concentration (C_{max}) and the time to reach the maximum concentration (T_{max}) were directly read from the plasma concentration versus time data as a measure of the rate of absorption. The apparent terminal elimination rate constant (K_e) was calculated using the least-squares regression analysis of the terminal portion of the log plasma concentration versus time profile, and the absorption rate constant (K_a) was calculated from the same plot by the method of residuals.[16] The absorption and elimination half-lives ($t^{1/2a}$ and $t^{1/2e}$) were calculated by dividing $0.693/K_a$ and $0.693/K_e$, respectively. The area under the concentration-time curve (AUC) up to the last sampling point was determined by the trapezoidal method,[17] and the AUC beyond the last observed plasma concentration (C_n) was extrapolated to C_n/K_e.

Moment Analysis Parameters

The area under the first moment curve, the mean residence time (MRT), and the mean absorption time (MAT) were calculated by means of moment analysis.[18]

In Vitro–In Vivo Modeling

Ibuprofen plasma levels were converted to percentage ibuprofen absorbed by the use of the modified Wagner-Nelson equation for the single compartment model[19]:

$$\% \text{ absorbed} = \frac{\frac{C_{(t)}}{K_e} + AUC_{0\rightarrow t}}{AUC_{0\rightarrow\infty}} \times 100 \qquad (2)$$

where $C_{(t)}$ is the plasma concentration at time t, K_e is the elimination rate constant, $AUC_{0\rightarrow t}$ is the area under the curve from 0 to time t, and $AUC_{0\rightarrow\infty}$ is the area under the curve from 0 to infinity, $\propto$. The in vivo absorption values were directly related to the in vitro dissolution data to complete the IVIVC.

Statistical Analysis

The student's *t* test procedure was employed to determine the variability of each parameter, as well as any differences existing between reference and test formulations. A *P* value of < .001 was considered statistically significant.

RESULTS AND DISCUSSION

Optimization of Polystyrene Microparticles

Figure 1 shows the release behavior of 20% to 60% wt/wt ibuprofen-loaded polystyrene microparticles together with a conventional tablet formulation in phosphate buffer solution of pH 6.8. While 100% dissolution of the conventional tablet formulation occurred within 20 minutes, release of the drug from the microparticles extended over different periods of time depending on the initial drug loading. However, among the different formulations, 30% wt/wt drug-loaded microparticles appeared to be equivalent in vitro to the Fenlong-SR formulation ($r^2 = 0.9916$) (Figure 2).

The R_f value of the drug obtained from the single-unit and multiple-unit dosage forms was the same as that of the pure drug (data not shown). The qualitative TLC results thus revealed that the drug was compatible with the formulation excipients, and neither decomposition of the drug nor drug-excipient interaction occurred in any tested formulation.

The drug release kinetics, assessed by 4 different model equations, were also found to vary depending on ibuprofen load in polystyrene microparticles (Table 1). From 20% wt/wt to 50% wt/wt drug load, the release rates determined by Higuchi's square root model showed higher correlation coefficient values than the correlation coefficient values of other models. A similar observation was seen for the Fenlong-SR capsules. This indicates that ibuprofen release from 20% to 50% drug-loaded microparticles and from Fenlong-SR capsules best followed a diffusion-controlled mechanism. However, when the drug load in the microparticles was 60% wt/wt, the release rates calculated by Hixon-Crowell's cube root model showed higher correlation coefficient values compared with the correlation coefficient

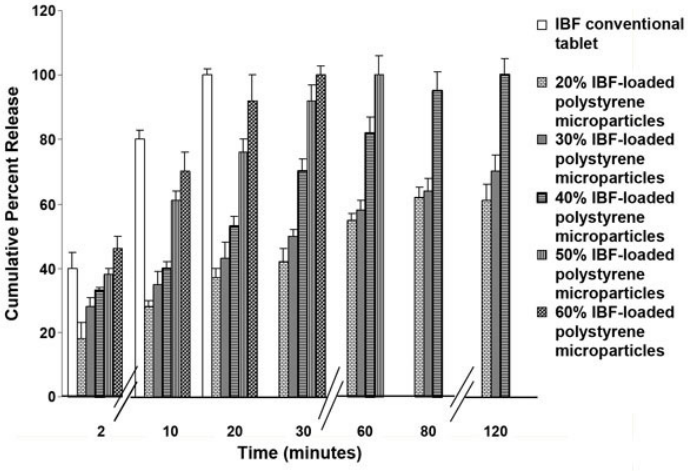

Figure 1. Effect of initial drug loading on IBF release in pH 6.8 from polystyrene microparticles with a 275-μm diameter in conjunction with IBF conventional tablet formulation. IBF indicates ibuprofen.

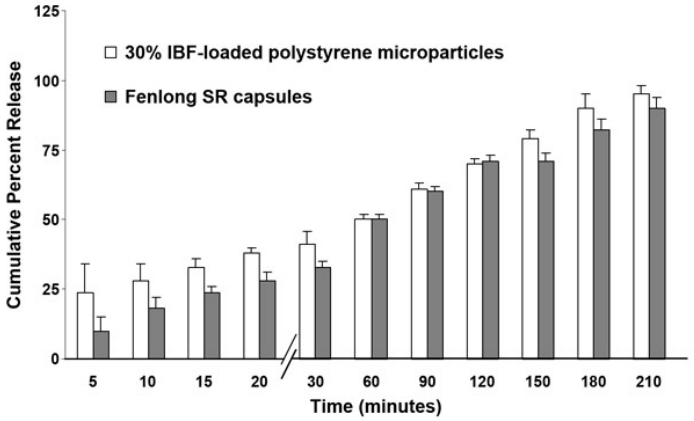

Figure 2. Comparison of IBF release from 30% wt/wt drug-loaded polystyrene microparticles and from Fenlong-SR capsules in phosphate buffer (pH 6.8). IBF indicates ibuprofen.

Table 2. Statistical Moment Parameters and Retard Quotients (R_Δ) Calculated From Plasma IBF Profiles of Different IBF Formulations*

Parameters	IBF Conventional Tablet	Fenlong-SR Capsule	30% IBF-Loaded Polystyrene Microparticles
$MRT_{in\ vitro}$ (h)†	—	1.93 ± 0.11	1.74 ± 0.18
$MRT_{in\ vivo}$ (h)†	5.15 ± 0.76	12.72 ± 0.55	9.75 ± 0.76
MDT (h)‡	2.52 ± 0.76	10.09 ± 0.55	7.12 ± 0.76
MAT (h)‡	2.18 ± 0.81	4.01 ± 0.45	3.32 ± 0.71
R_Δ‡	—	3.74 ± 0.36	2.79 ± 0.45

*IBF indicates ibuprofen; MRT, mean residence time; MDT, mean dissolution time; MAT, mean absorption time.
†Values represent mean ± SD, n = 3.
‡Values represent mean ± SD, n = 4.

values of other models. The same observation was made for the conventional tablet formulation. It is known that there was no release-retarding barrier effect due to the excipients used in the manufacture of conventional tablets. Although a polymeric matrix was available to control the drug release, the amount of drug per unit polymer matrix was high in the case of 60% wt/wt ibuprofen-loaded polystyrene microparticles, as reported in our previous study. In that study, we showed through scanning electron microscopy that microparticles containing more than 50% drug were collapsed in nature and the polymeric film around the microparticles appeared to be discontinuous, exposing the drug particles directly to the dissolution medium.[20] Therefore, these last 2 formulations followed a simple powder mechanism over the time period of the dissolution study (Table 1).

To further investigate whether 30% drug-loaded microparticles were equivalent in vitro to the Fenlong-SR, the $MRT_{in\ vitro}$ values, estimates of statistical mean of the times in which the mass of the drug remains as such in the formulation without undergoing dissolution,[21] were calculated and are given in Table 2. Since the calculated values of $MRT_{in\ vitro}$ of both the formulations were almost the same, the 30% ibuprofen-loaded microparticles could be considered an optimized formulation. Therefore, that formulation was subjected to stability study and in vivo study in human volunteers.

Stability Study

The actual drug content in 30% wt/wt drug-loaded polystyrene microparticles stored in stability test chambers over a period of 6 months at 2 different storage conditions (25°C at 75% relative humidity and 38°C at 90% relative humidity) did not vary significantly. No significant variation was observed in the time required for 50% drug release ($t_{50\%}$), in minutes, from 30% drug-loaded polystyrene microparticles stored in identical storage conditions (data not shown).

Table 1. IBF Release Rates, Assessed by 4 Different Model Equations*

Formulations	Higuchi's Square Root Model $min^{-1/2}$	Bamba's Model min^{-1}	First-Order Model min^{-1}	Hixon-Crowell Cube Root min^{-1}
20% IBF-loaded polystyrene microparticles	33.13 ± 0.20 (0.9474)	0.33 ± 0.03 (0.9087)	0.15 ± 0.04 (0.9086)	0.41 ± 0.02 (0.8991)
30% IBF-loaded polystyrene microparticles	35.44 ± 0.08 (0.9910)	0.40 ± 0.05 (0.9823)	0.17 ± 0.01 (0.9823)	0.46 ± 0.03 (0.9755)
40% IBF-loaded polystyrene microparticles	69.87 ± 0.22 (0.9965)	1.95 ± 0.07 (0.9907)	0.85 ± 0.04 (0.9907)	1.72 ± 0.05 (0.9932)
50% IBF-loaded polystyrene microparticles	124.6 ± 0.10 (0.9910)	4.95 ± 0.02 (0.9740)	2.15 ± 0.05 (0.9740)	4.65 ± 0.06 (0.9895)
60% IBF-loaded polystyrene microparticles	166.8 ± 0.07 (0.9956)	8.45 ± 0.08 (0.9952)	3.67 ± 0.10 (0.9952)	7.69 ± 0.07 (0.9999)
400 mg conventional IBF tablet	226.1 ± 0.12 (0.9923)	15.57 ± 0.10 (0.8850)	6.76 ± 0.12 (0.9885)	12.96 ± 0.09 (0.9996)
400 mg Fenlong-SR capsules	36.44 ± 0.05 (0.9945)	0.48 ± 0.08 (0.9725)	0.20 ± 0.04 (0.9792)	0.52 ± 0.09 (0.9715)

*All values are mean ± SD, n = 3. Figures in parentheses indicate correlation coefficients (r^2). IBF indicates ibuprofen.

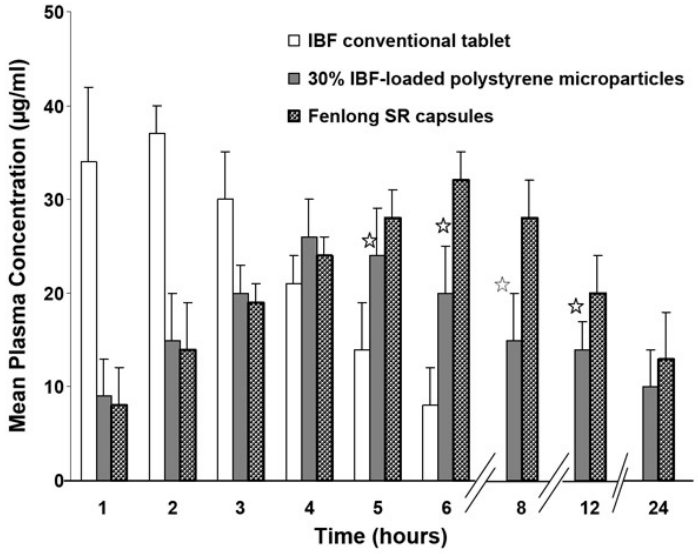

Figure 3. Mean plasma concentrations of IBF in human volunteers following single oral administration of 400 mg or equivalent to 400 mg of various formulations. The vertical bars represent ± SD (n = 4), ☆ indicates $P < .05$ compared with the Fenlong-SR formulation and IBF indicates ibuprofen.

In Vivo Study

Figure 3 shows the mean plasma concentrations of ibuprofen attained following oral administration of conventional tablets, Fenlong-SR capsules, and optimized ibuprofen-loaded microparticles. While the mean plasma concentration value for the conventional tablet formulation was quick to reach a maximum, then fell rapidly, the Fenlong-SR capsules and optimized microparticles were slow to attain a maximum and slow to fall. Furthermore, Fenlong-SR and optimized microparticles maintained the minimum effective concentration, 10 µg/mL,[22] of ibuprofen throughout the study period. This indicates the continuing therapeutic equivalency of these formulations.

Pharmacokinetic parameters derived from the plasma ibuprofen data are summarized in Table 3. Significantly higher C_{max} ($P < .001$), K_a ($.01 < P < .05$), and K_e ($P < .001$) and lower T_{max} ($P < .001$), $t^{1/2a}$ ($.001 < P < .10$), $t^{1/2e}$ ($P < .001$), and $AUC_{0\rightarrow\infty}$ ($.001 < P < .01$) were noted with the conventional tablet formulation. With the exception of K_a, all the parameters of optimized ibuprofen-loaded microparticles were significantly lower than those obtained from the Fenlong-SR formulation (analysis of variance). The extent of absorption (bioavailability) was significantly higher ($P < .01$) with the Fenlong-SR formulation, as seen from the $AUC_{0\rightarrow\infty}$ (491.2 µg.h.mL^{-1}), followed by the optimized formulation (311.3 µg.h.mL^{-1}) and the conventional tablet formulation (160.7 µg.h.mL^{-1}). When the AUCs obtained from the Fenlong-SR or optimized formulations were divided by the AUC obtained from the conventional formulation, the relative bioavailability (F) values for both the formulations were obtained (Table 3). The relative bioavailability (F) value of the optimized ibuprofen-loaded microparticles was low when compared with that of the Fenlong-SR formulation but was high when compared with that of the conventional formulation. The mean dissolution time (MDT) in vivo, an estimate of the mean time during which a drug molecule remains as a solid in the gastrointestinal tract, was calculated following the equation described by Riegelman and Collier[23]:

$$MDT = MRT_{solid} - MRT_{solution} \quad (3)$$

where $MRT_{solution}$ for ibuprofen (solution) is 2.63 hours.[24] The MDT in vivo obtained for the optimized formulation (Table 2) also showed a lower value than that obtained for the Fenlong-SR formulation. Similarly, the MAT calculated for the optimized formulation was low compared with the calculated value for the Fenlong-SR formulation but high compared with that calculated for the conventional

Table 3. Summary of Pharmacokinetic Parameters of Orally Administered IBF Formulations*

Parameters	IBF Conventional Tablet	Fenlong-SR Capsule	30% IBF-Loaded Polystyrene Microparticles
C_{max} (µg/mL)	37.96 ± 1.10	31.98 ± 0.74	27.15 ± 1.80
T_{max} (h)	1.75 ± 0.40	5.88 ± 0.10	4.25 ± 0.40
$t^{1/2a}$ (h)	1.51 ± 0.56	2.78 ± 0.28	2.33 ± 0.51
$t^{1/2e}$ (h)	2.08 ± 0.08	6.06 ± 0.06	4.39 ± 0.48
K_a (µg/h)	0.51 ± 0.13	0.25 ± 0.03	0.31 ± 0.05
K_e (µg/h)	0.34 ± 0.01	0.12 ± 0.01	0.16 ± 0.02
$AUC_{(0\rightarrow 12\,hr)}$(µg.h.mL^{-1})	140.00 ± 13.14	258.22 ± 7.00	190.63 ± 13.33
$AUC_{(0\rightarrow 24\,hr)}$(µg.h.mL^{-1})	—	413.47 ± 22.26	301.97 ± 20.66
$AUC_{(0\rightarrow\infty\,hr)}$(µg.h.mL^{-1})	160.72 ± 13.39	491.23 ± 32.42	311.30 ± 50.67
Bioavailability (F)†	1.00	3.09 ± 0.38	1.94 ± 0.30

*Values represent mean ± SD, n = 4. IBF indicates ibuprofen; AUC, area under the concentration-time curve.

†Relative bioavailability when compared with conventional formulation.

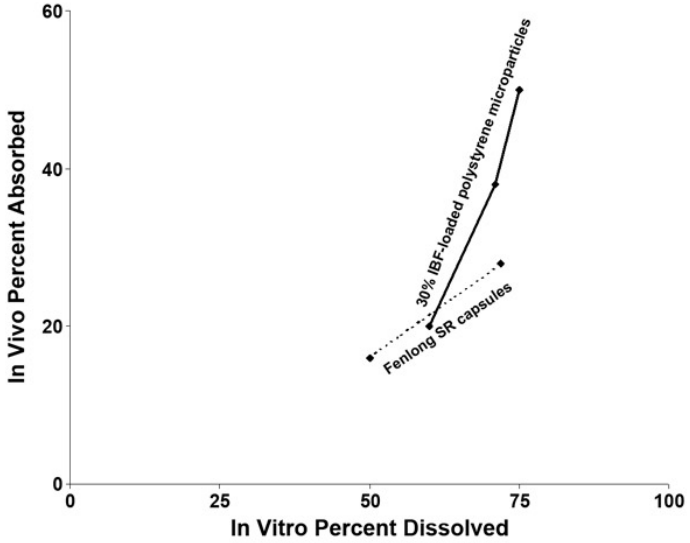

Figure 4. Correlation between percentage dissolved in vitro and percentage absorbed in vivo for 30% wt/wt IBF-loaded polystyrene microparticles and for Fenlong-SR capsules. IBF indicates ibuprofen.

formation (Table 2). Furthermore, the retard quotient (R_Δ) values, which measure the sustaining/controlling efficacy of the formulation, were calculated for the microparticles and the Fenlong-SR formulations from half-value duration (HVD) analysis[25] and are shown in Table 2. A higher R_Δ value represents more retardation, whereas a lower R_Δ value indicates less retardation. However, in this study, the R_Δ value obtained for optimized and Fenlong-SR formulations was significantly different at the *P* level of .05 and was insignificant at the *P* level of .01. In summary, after thorough interpretation of $AUC_{0\rightarrow\infty}$, F, MAT, MDT, R_Δ, and pharmacokinetic parameters, with the exception of K_a, it was apparent that the optimized ibuprofen-loaded microparticles showed lesser values to those of corresponding values of the Fenlong-SR formulation. The lower $AUC_{0\rightarrow\infty}$, F, MAT, MDT, R_Δ, and pharmacokinetic parameters, with the exception of K_a, may be attributed either to lower sustaining/controlling efficacy of the optimized formulation or to the variations among the physiological parameters (eg, food, gastric pH, gastric emptying time, gastric motility, rate of blood flow, rate of metabolism)[26] of the selected volunteers. A third alternative could be considered as the probability that the in vitro dissolution match, using the method selected, is not a good indicator of bioavailability in vivo for these particular formulations, it means that the selected dissolution method is probably not sensitive enough to indicate differences in mechanism of release between the tested formulations. Also, study power (by the total number of participants and by involving different sexes) may have been too low to detect reasons for differences.

IVIVC

Over the past decade, the Biopharmaceutics Classification System (BCS) approach, a regulatory guidance for conventional immediate-release products, is increasingly becoming an integral part of the development of bioequivalence studies, with special interest for BCS Class I and II drugs/their products. Since this study focuses on ibuprofen, a BCS Class II drug,[27] dissolution is the rate-limiting step in the drug absorption and consequent bioavailability. In other words, if the product's rate of dissolution is the limiting factor in drug absorption, rate of dissolution should serve as a true predictor of the product's bioavailability. To assess the viability and the validity of the controlling nature of polystyrene microparticles in comparison to Fenlong-SR, an IVIVC study is essential since prolonged-release products may be especially suited for this kind of study.[28] Furthermore, the low aqueous solubility and the poor wettability of ibuprofen[29] may lead to bioavailability problems; bioavailability is likely to be rate-limited by the product's dissolution. By developing and evaluating an IVIVC study,

Table 4. Summary of In Vitro–In Vivo Correlations (r^2) for IBF Formulations*

	Fenlong-SR Capsule		30% IBF-Loaded Polystyrene Microparticles	
In Vitro Versus In Vivo Parameters	r^2	Significance Level	r^2	Significance Level
$MRT_{in\ vitro}$ versus $MRT_{in\ vivo}$	0.9689	$P < .001$	−0.9856	$P < .001$
$MRT_{in\ vitro}$ versus $MDT_{in\ vivo}$	0.9689	$P < .001$	−0.9953	$P < .001$
$MRT_{in\ vitro}$ versus T_{max}	0.9357	$P < .001$	0.9843	$P < .001$
$T_{50\%}$ versus MAT	−0.9962	$P < .001$	−0.9449	$P < .001$
$T_{50\%}$ versus T_{max}	−0.9078	$P < .001$	0.9449	$P < .001$
$T_{50\%}$ versus $t^{1/2a}$	0.9608	$P < .001$	−0.9449	$P < .001$
$T_{60\%}$ versus C_{max}	0.9991	$P < .001$	0.9138	$P < .001$
$T_{90\%}$ versus MAT	−0.9742	$.001 < P < .01$	−0.9449	$P < .001$
$T_{90\%}$ versus C_{max}	−0.9975	$P < .001$	−0.9052	$P < .001$
$T_{90\%}$ versus $AUC_{(0\rightarrow 12hr)}$	0.9999	$P < .001$	0.9878	$P < .001$

*IBF indicates ibuprofen; MRT, mean residence time; MDT, mean dissolution time; MAT, mean absorption time; AUC, area under the concentration-time curve.

one may be able to establish the dissolution test as a surrogate for human bioequivalence studies. In addition, one may reduce the number of bioequivalence studies performed during the initial US Food and Drug Administration approval process as well as reducing certain scaleup and postapproval changes (eg, formulation, equipment, process, manufacturing site changes).[30]

When the percentage of ibuprofen released in pH 6.8 from optimized or Fenlong-SR formulations using the USP paddle method was plotted against the percentage of ibuprofen absorbed, calculated from Equation 2, a linear correlation was obtained (Figure 4). The regression line was calculated without an intercept by using linear regression analysis: $y = (1.8409)x$, for the optimized formulation ($r^2 = 0.9668$); and $y = (0.5162)x$, for the Fenlong-SR formulation ($r^2 = 0.9999$). This study indicates the correlation between the percentages dissolved in vitro and absorbed in vivo. A similar result has been reported for ibuprofen capsules in a dissolution medium of pH 6.6 using the JP XII paddle method versus absorption in dog.[31] However, the current study shows that the slope for the optimized microparticles formulation appears to be 3 times that of the Fenlong-SR formulation, so while there may be correlations in vivo to in vitro within a single dosage form, it seems that the 2 dosage forms are not equivalent in rates of absorption. To substantiate further the IVIVC, the following in vitro and in vivo parameters were considered to correlate. Time to dissolve 50% and 90% are correlated better with T_{max} and C_{max}, respectively, which corresponds to the rate of absorption, and time to dissolve 90% is better correlated with $AUC_{0\rightarrow\infty}$, which reflects the extent of absorption.[32] Table 4 shows the comprehensive list of these correlations along with correlations of other in vitro and in vivo parameters that were done by linear regression analysis. Since all the selected parameters, including $MRT_{in\ vitro}$ and $MRT_{in\ vivo}$, showed statistically significant correlations ($r^2 > 0.9$), the relatively simple procedure of monitoring the dissolution profile should allow the prediction of in vivo bioavailability,[21] although IVIVC could be improved by exploring a wider variety of dissolution conditions.[33]

CONCLUSION

This work revealed that ibuprofen-loaded polystyrene microparticles prepared by the emulsion-solvent evaporation method provided a new prolonged-release dosage form with improved bioavailability in comparison to that of a conventional tablet formulation. While the duration and intensity of ibuprofen released, in vitro, from the optimized and Fenlong-SR formulations were almost identical in the dissolution apparatus used, the rate and extent of drug absorption following single-dose oral administration of the optimized ibuprofen-loaded polystyrene microparticles appeared to be lower than that of the Fenlong-SR formulation.

ACKNOWLEDGMENTS

S. Tamilvanan received a Senior Research Fellowship from the Council of Scientific and Industrial Research, Ministry of Human Resource Development, Government of India (Grant No. 9/96(281)/96−EMR−I). We are grateful to the 2003-2004 undergraduates of Jadavpur University for their help in performing the in vivo study.

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