Stereoselective Disposition of Suspensions of Conventional and Wax-matrix Sustained Release Ibuprofen Microspheres in Rats

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Purpose. The aim of the study is to evaluate stereoselective *in vivo* disposition of suspensions of conventional and wax-matrix sustained release ibuprofen microspheres in rats.

Methods. Male wistar rats were dosed IV with 20 mg/kg, or orally with conventional suspension, and three suspension formulations of sustained release microspheres (having three different particle sizes) of racemic ibuprofen. Blood samples were analyzed stereoselectively by reverse phase HPLC.

Results. The mean C_{max} for (S)- and (R)- ibuprofen decreased with increased particle size of the drug or microspheres in the suspension dosage forms, while the T_{max} increased with increased particle size. The mean S/R ratio (AUC_{0-48}) of the suspensions decreased with increase in particle size of the drug or microspheres and these ratios (for both conventional and sustained formulations) were higher than that of the IV, an indication of presystemic inversion. Decrease in the ratios with increased particle size is suggestive of formulation dependent inversion. The plasma concentration-time data of the sustained release formulations showed bimodal profiles, irrespective of the particle size of the microspheres. The second peak observed after 8 hours is indicative of colonic absorption.

Conclusions. Stereoselective disposition of ibuprofen microspheres showed higher bioavailability compared to the conventional suspension. Bimodal disposition is influenced by dosage form while presystemic inversion is both site-specific, and dosage form dependent.

KEY WORDS: stereoselective disposition; microspheres; ibuprofen; particle size.

INTRODUCTION

The importance of stereospecific formulation of ibuprofen or related non-steroidal antiinflammatory drugs (NSAIDs) and their disposition has been raised in recent literature due to the fact that regulatory bodies in Europe and USA already recommended the use of stereoselective assay when a racemate is formulated (1,2). It is one of the most widely discussed topics in pharmaceutical forums today in the USA and at international levels.

Many authors have reported that the R- isomer is inverted to the S- isomer (3,4,5) and that the inversion may be presystemic, i.e. in the GIT tract. Jamali *et al* (3) reported that the presystemic inversion or S:R concentration ratio increased until 4 to 6 hours and then leveled off. They argued that if the inversion is systemic, a continuous process will proceed until the entire circulating R- isomer is eliminated. However, in a more recent study, Avgerinos *et al* (6) reported a progressive increase in the plasma S/R ratio in humans, which would indicate a systemic contribution to the inversion of the isomers. Ahn *et al* (7) also reported significant systemic inversion of R- isomer to S- isomer upon bolus intravenous administration of the enantiomers and their admixtures to beagle dogs. Cox *et al* (8) reported that the presystemic inversion in rats was negligible, but contrary to this finding, Simmonds *et al* (9), in earlier investigation, reported substantial inversion of the R-isomer to the S- isomer when benoxaprofen was exposed to everted rat gut. Recent studies by Sattari and Jamali (10), in which eroding sustained release ibuprofen granules were used, supported the report that rats are a good model for studying intestinal presystemic inversion of ibuprofen.

Presystemic inversion has also been linked with the residence time in the GIT, in which case, prolonging the residence time of the racemate (via sustained release formulation) should favor the inversion of R- form to the S- form compared to conventional release formulation (3). Therefore, the S/R plasma ratio of the conventional suspension should be lower than the sustained release formulation, post single dose administration. In the studies of Sattari and Jamali where eroding granules were used, the presystemic inversion observed will not only depend on the residence time, but on the dosage form device. In a report by Parr *et al* (11), in which eroding ibuprofen tablets were evaluated for their disposition in humans, non-stereoselectively, they concluded that there were differences in absorption in the different segments of the colon. In all the studies discussed above, a solution, conventional release suspension or eroding sustained release oral tablets or granules were used. The blood sampling had also been limited to a maximum of 24 hours. Since the sustained release dosage form unit or device does affect GI motility or residence time, which can in turn affect presystemic inversion, it is important to know how other dosage forms, non-eroding multi units such as microspheres, can affect the stereoselective disposition. Moreover, considering the ubiquitous use of NSAIDs, especially ibuprofen, as anti-inflammatory drugs, and the use of the suspensions among the geriatric and pediatric population, the need to know more about its disposition, especially of the sustained release dosage form, becomes crucial. Therefore, the project focussed on investigating stereoselectively, the plasma concentration-time profiles of conventional suspension and suspensions of sustained release, non-eroding ibuprofen microspheres. The aim is to establish the possible site-specific and dosage form dependence on stereoselective disposition of the drug.

MATERIALS AND METHODS

Materials

Ibuprofen was obtained from Albemarle Corporation (Baton Rogue, LA). The ceresine wax was donated by Frank B. Ross Co., Inc. (Jersey City, NJ). All other chemicals were of analytical grade.

Methods

Preparation of Microspheres and Dosage Forms

The microspheres were prepared by the congealable disperse microencapsulation process in which the drug particles

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were coated with paraffin wax (12). The amount of drug corresponding to microspheres used in the formulation is 172 mg/g of microspheres. The microspheres (96, 130.5 and 165 m) were suspended in 1% methylcellulose (MC) solution containing 1% surfactant (Tween 80) in three separate formulations. The uncoated conventional release (48 μm size) suspension was similarly prepared using MC solution. The IV solution was prepared by dissolving an appropriate amount of ibuprofen in a mixture of deionized water and 0.1N sodium hydroxide, and adjusting the pH to 7.4.

In Vivo Disposition Studies

Dosing and Sampling. Three groups of precannulated male Wistar rats, 6 rats/group, were used in a two-way cross-over fashion to study the disposition of ibuprofen for each of the five dosage forms [intravenous solution, conventional release and the three sustained release (i.e. microsphere) oral suspensions].

The rats (average weight of 350 g) were fasted overnight and dosed orally (20 mg drug/kg) by gavage with respective formulation. Blood samples (250 μl) were obtained using the cannulated jugular vein at 0, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 24, 36 and 48 hours after drug administration. An equal volume of sterilized normal saline was used to replace the withdrawn blood to maintain homeostasis. Blood samples were centrifuged and the plasma obtained was frozen at −20°C until assayed. A washout period of 5–7 days was allowed between doses.

Stereospecific HPLC Assay. The assay procedure (13) was modified with derivatizing agent of Lemko *et al.* (14). Moreover, the concentration range for the standards (0.5–20 μg/ml) and the mobile phase flow rate were also modified as stated below.

The standards were prepared by spiking blank plasma samples with ibuprofen to give different concentrations ranging from 0.5–20 μg/ml. The plasma samples were acidified with 200 μl of 0.6M sulfuric acid and extracted by vortex-mixing with 3 ml of a mixture of isooctane-isopropanolol (95:5% v/v) using fenoprofen as internal standard. This constitutes the first extraction process. The organic layer was evaporated and the resulting residue was reconstituted with 300 μl triethylamine in acetonitrile (50 mM/L) and derivatized with 50 μl S-(-)-1(1-naphthyl)ethylamine (S-NEA, 1ml/L), after addition of 50 μl ethylchloroformate (60 mM/L) as the coupling reagent. The mixture was vortexed for 30 sec, and after 3 minutes, the reaction was stopped by the addition of 1 ml of 0.25N HCl. The sample was then extracted by vortex-mixing with 3 ml chloroform and the organic layer was collected in clean tubes, evaporated and reconstituted with 0.5 ml mobile phase (pH 5). The resultant diastereomers corresponding to ibuprofen and fenoprofen were injected onto an IB-SIL C 18 column, 100 × 4.6 mm, 5 μm (Phenomenex, Torrance CA) on a Shimadzu HPLC system (Shimadzu Scientific Instruments,Columbia MD), with a mobile phase that consisted of acetonitrile:water:triethylamine:glacial acetic acid (60:40:0.02:0.1). The flow rate was 1 ml/min and the UV absorbance was measured at 225 nm. The data was acquired and processed using Shimadzu EzChrom software.

Accuracy and Precision. Standard solutions to yield concentrations of 0.5, 1, 2, 5, 10 and 20 μg/ml were prepared and analyzed as described under stereospecific HPLC assay. Each solution was prepared in triplicate on three consecutive days. Accuracy was calculated as mean percentage error which is [{(mean measured concentration—expected concentration) / expected concentration} × 100], while precision was determined from the inter-day coefficients of variation (CV).

Data Analysis. The maximum plasma concentration of the enantiomers (Cmax) and the time taken to attain them (Tmax) were obtained from an examination of the individual data following the single dose. The areas under the plasma concentration time curves (AUC_{0-8} and AUC_{0-48}) were estimated by the linear trapezoidal rule as a result of the prolonged and bimodal distribution. Segmented AUCs were used to determine percent drug absorbed at the two time intervals. The extent of inversion was similarly determined by calculating the S/R ratio of the AUCs.

The ratio of mean AUC_{0-8} values of the sustained release suspension to that of AUC_{0-48} of conventional suspension (relative bioavailability) was calculated to assess the extent of absorption from each of the suspensions of sustained release microspheres. Absolute bioavailability was determined from the ratio of the mean AUC_{0-48} of the total drug (S + R) for the conventional or microsphere suspension to that of the IV.

The significance of differences among the mean observations in Cmax, Tmax, and AUCs for conventional formulation and suspensions of microspheres (96 μm, 130.5 μm, and 165 μm) was determined using two-way ANOVA tests ($\alpha = 0.05$). The S:R ratios of AUCs after different dosage forms were compared using one-way ANOVA. Differences between means were analyzed by Tukey-Kramer multiple comparison of means test (statistical software, JMP version 3.0, SAS Institute, Cary, North Carolina).

RESULTS

Assay Procedure. The retention times for R and S ibuprofen were 13 min and 14 min, while those of R and S fenoprofen were 9 min and 10 min respectively. There was linearity between the peak area ratios and corresponding concentrations (0.5, 1, 2, 5,10 and 20 μg/ml) with a r^2 of 0.999 (n = 3). The method was precise and accurate with an inter-day CV of 2.87–15.08%; the accuracy was 92.58–103.1%. The CVs were reasonable, less than 10% for all the concentrations, except for 2 and 5 μg/ml that had 11.82 and 15.08% CV respectively.

Disposition and Inversion Parameters

Mean C_{max}, T_{max} and AUC. The plasma concentrations of (S)-ibuprofen were significantly greater than those of (R)-ibuprofen as shown for the suspensions, in Figure 1 ($\alpha = 0.05$). No systemic inversion was observed in the IV dose because the AUC_{0-8} or AUC_{0-48} for (S)- was not significantly different from (R)-. For the suspensions, the mean C_{max}; for (S)- and (R)- ibuprofen generally decreased with increased particle size of the drug or microspheres (Table IA). Tukey-Kramer test showed no significant difference between the C_{max} values of 130.5 and 165 μm sizes, relative to the 96 μm size. The mean T_{max} values increased with increased particle size. For (S)-enantiomer, there was significant difference between means of the three different microsphere sizes while for the (R)- enantiomer, the T_{max} for the 165 μm size was significantly different compared with the other two sizes.

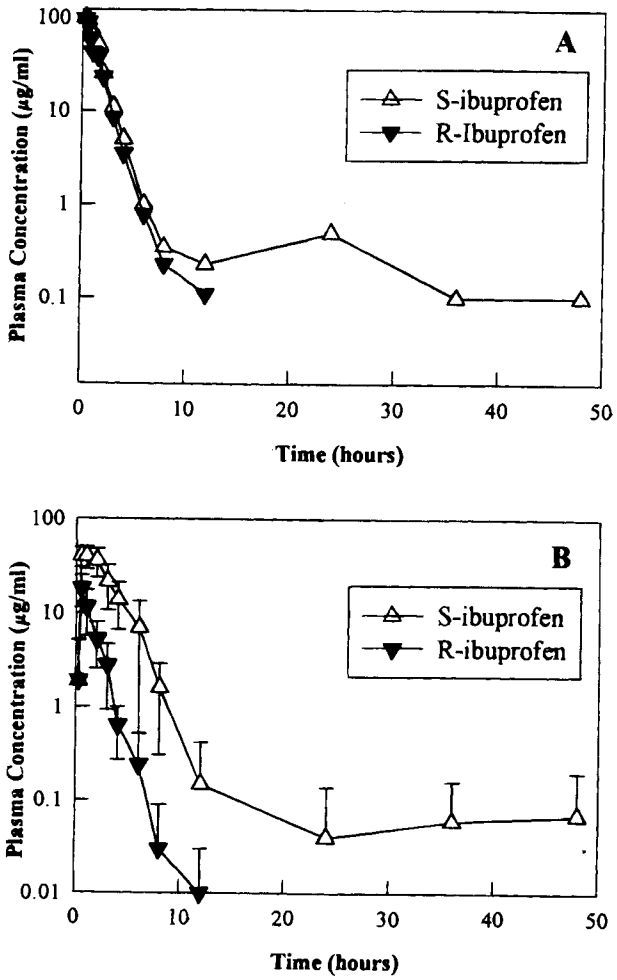

Fig. 1. Plasma concentration-time profiles of ibuprofen following IV administration (A), conventional oral suspension formulation (B); sustained release suspensions containing 96 μm size microspheres (C), 130.5 μm size microspheres (D) and 165 μm size microspheres (E). Dose = 20 mg/kg, n = 4 for IV and 6 for the suspensions.

The mean AUC_{0-48} for the (S)- ibuprofen sustained release suspensions increased relative to that of the conventional release suspension (having 48 μm size). Two way ANOVA test revealed significant differences between the mean AUCs for the conventional and sustained release suspensions ($\alpha = 0.05$) as shown in Table IB. Using Tukey test, no significant difference was found between the means of the AUC_{0-48} values of (S)- isomer from the three microsphere formulations. In contrast, the means of the AUC_{0-48} values of (R)- ibuprofen were relatively small compared to those of (S)- ibuprofen and there was significant difference between the means. A consistent increase in the AUC_{0-48} values was observed for the (R)- ibuprofen as the particle size of the drug or microspheres increased (Table IB).

S/R Ratios. The (AUC_{0-48}) S/R ratio for the conventional suspension (48 μm) was higher than those of the suspensions of the microspheres (Table IIA). The mean S/R ratio (AUC_{0-48}) of the suspensions decreased with increase in particle size of the microspheres. In contrast, the mean S/R (AUC_{0-8}) ratio for all the sustained release suspensions were similar except for the 130.5 μm size microsphere formulation in which a slight decrease in the ratio was observed Table IIA). Tukey-Kramer

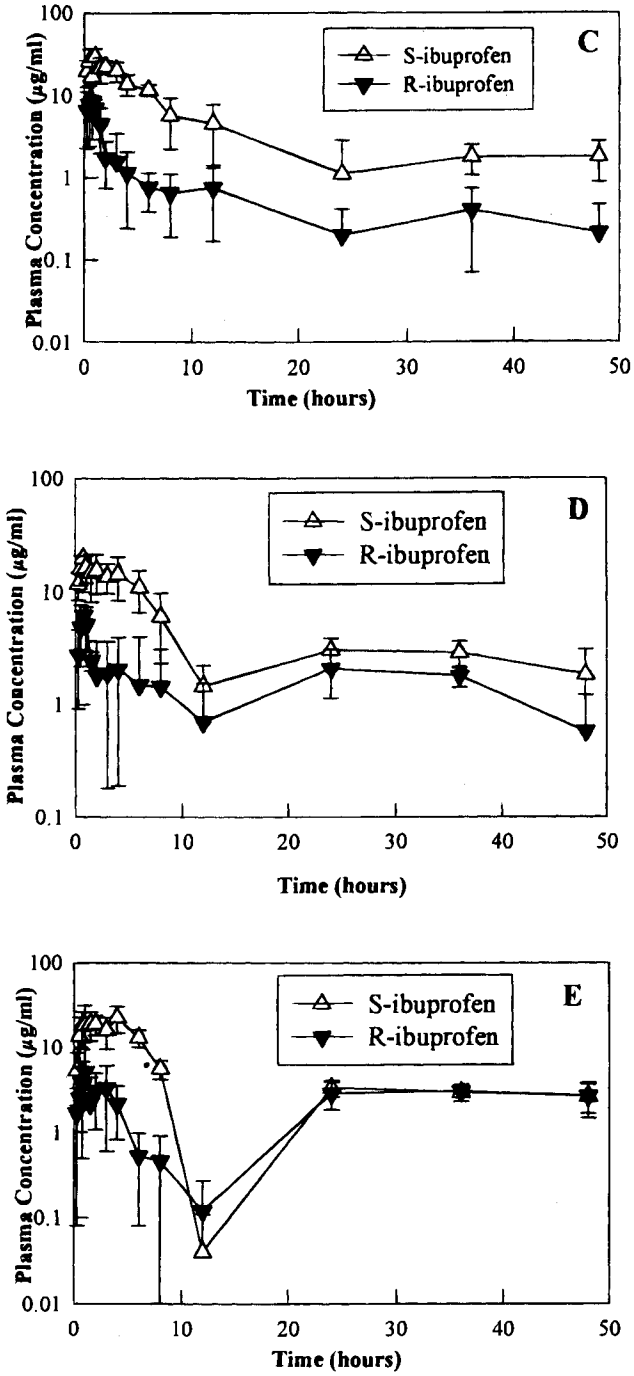

Fig. 1. Continued.

Table 1A. Mean Values of Disposition Parameters of Rats Dosed with Racemic Ibuprofen

Dosage Form	Cmax (μg/ml)		Tmax (hours)	
	S-	R-	S-	R-
IV	98.00(15.8)	95.00(9.6)	0.25	0.25
CS	42.24(10.1)	17.7 (5.19)	0.33(0.13)	0.29(0.1)
96 μm	31.07(6.5)	12.54(3.4)	0.83(0.2)	0.75(0.22)
130.5 μm	18.66(5.11)	7.1 (0.94)	2.17(1.5)	1.2(1.38)
165 μm	23.95(9.54)	9.77(5.9)	3.67(0.51)	3.5(0.51)

Table 1B.

Dosage Form	AUC (0–8) (μg.h/ml)		AUC (0–48) (μ.h/ml)	
	S-	R-	S-[a]	R-
IV	155.85	128.04	166.51	129.38
CS	110.83(46.52)	17.71(5.24)	117.08(45.6)	17.86(5.29)
96 μm	113.81(23.52)	14.89(3.69)	200.74(37.26)	31.44(8.24)[b]
130.5 μm	93.64(29.08)	15.74(9.97)	201.61(32.16)	76.26(20.66)[b]
165 μm	113.84(29.82)	13.95(4.63)	200.47(32.49)	86.35(12.51)[b]

ANOVA, Tukey- Kramer test $\alpha=0.05$.

[a] Significant differences between the means of the $AUC_{(0-48)}$ of conventional and sustained release microsphere suspensions.

[b] Significant differences between the means of R-isomer $AUC_{(0-48)}$ values for sustained release microsphere.

test indicated no significant difference between the different formulations. The S/R ratio of the IV dose was the least because there was no systemic inversion. From the plot of S/R ratios of the individual data points it was observed that the highest ratios were obtained within the first 8 hours post administration of the suspensions, with the maximum ratios observed at between 6–8 hours (Figure II).

Thereafter, the ratios fell and then leveled off. There was no change in the S/R ratios over the 48-hour interval for IV dose.

Bimodal Absorption and Site-specific Inversion. The absorption was bimodal with the troughs shown at 8 hours for 96 μm and 12 hours for 130.5 or 165 μm sizes respectively (Figure 1C, 1D and 1E). Ninety five percent of drug was absorbed from the eroding (conventional) suspension in 8 hours from the upper GIT (Table IIA). In contrast, significant absorption of drug from the microspheres formulation took place in the lower GIT. For example, for the 130.5 and 165 μm microspheres, only 39.63 and 44.55% of the drug were absorbed

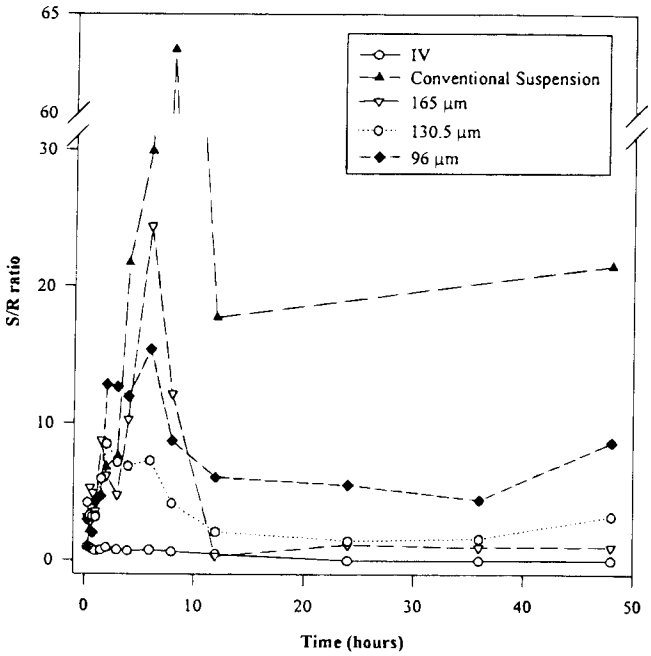

Fig. 2. Mean S/R ratios versus time of ibuprofen suspension formulations showing the extent of inversion.

in 8 hours respectively. The site specific absorption was calculated using the ratio of the AUC_{0-8} to AUC_{0-48}. The S/R ratio (AUC_{0-48}) were 2.64 and 2.32 respectively (Table IIB), an indication that the chiral inversion is minimal in lower intestine (the main site of ibuprofen release from the microspheres). The S/R ratio AUC_{0-48} decreased with increase in particle size. That of the conventional suspension of eroding particles (48 μm) was approximately 7 while those of the non-eroding micro-

Table 2A. Mean AUCs and S/R Ratios of Disposition Parameters of Rats Dosed with Racemic Ibuprofen

Dosage form	Mean AUC (S+R) (μg.h/ml)			S/R (AUC) ratios		
			AUC(0–8)×100%			(0–8)×100%
	AUC (0–8)	AUC (0–48)	AUC (0–48)	(0–8hr)	(0–48hr)	(0–48)
IV	283.89	285.89	99.30	1.22	1.29	94.57
CS	128.54(51.76)	134.94(50.89)	95.26	6.26	6.56	95.42
96 μm	128.70(27.21)	232.18 (45.5)	55.43	7.64	6.38	119.75
130.5 μm	109.38(39.05)	277.87(52.82)	39.63	5.95	2.64	225.38
165 μm	127.79(34.45)	286.82(44.99)	44.55	8.16	2.32	351.72

ANOVA, Tukey- Kramer test $\alpha=0.05$

Table 2B. Bioavailability Values for Different Ibuprofen Suspensions in Rats

Dosage form	Absolute bioavailability(%)		Relative bioavailability(%)	
	(0–8)hr	(0–48)hr	(0–8)hr	(0–48)hr
Conventional suspension (48 μm)	45.28	45.60	—	—
Microsphere suspension (96 μm)	45.33	78.47	100.12	172.06
Microsphere suspension (130.5 μm)	38.53	93.91	85.09	205.92
Microsphere suspension (165 μm)	45.01	96.93	99.42	212.56

spheres (96 μm, 130.50 μm and 165 μm) were approximately 6, 3 and 2 respectively. The extent of inversion calculated using the segmented S/R AUC ratios increased with increase in particle size. This showed that most of the inversion took place in the upper GIT and it is dosage form dependent.

Extent of Absorption. The plasma concentration-time profiles showed that drug release from the sustained release formulations (96 μm, 130.5 μm, and 165 μm) was prolonged compared to the conventional suspension (Figure 1C, D and E).

The absolute bioavailabilities (0–48) for the conventional suspension was 45.60%, and those of the different sustained release suspensions of microspheres, i.e., 96, 130.5 and 165 μm, were 78.50, 93.90 and 96.93% respectively (Table II B). The relative bioavailabilities (0–48) of the sustained release suspensions for the respective microsphere sizes were 172.06%, 205.92% and 212.56%. The low bioavailability for the conventional suspension may be due to high hepatic extraction ratio that may be peculiar to rat model.

DISCUSSION

The stereoselective disposition or presystemic inversion for sustained release dosage form was affected by the dosage form unit or device, residence time or site of absorption. Considering the dosage form device, the extent of absorption over the 48-hour period showed that the gastrointestinal mucosa was exposed to less drug per unit time with the sustained release suspensions due to the longer T_{max} and lower C_{max}. This is consistent with an earlier report (15) in which the sustained release multiple units (microspheres) significantly reduced GIT irritation in male Wistar rats consequent to less exposure of the mucosa to the drug.

The structural integrity of the microspheres prepared with ceresine wax was such that they are non-eroding and have a tendency to float (another variable for a sustained release effect). The *in vitro* T_{50} (time taken for 50% of the drug to be released) ranged from 2 hours to over 6 hours, depending on the size and the type of wax used (16), whereas in the conventional suspension of eroding particles, 85% of the drug dissolved within 1 hour.The microspheres were also recovered intact after *in vitro* dissolution and 7 hours post administration in rats (15). Moreover, in a 3-month stability study, the microsphere structure was preserved at room temperature (17).

The particle size-dependence or site specific absorption was probably due to the shorter residence time of the bigger particles in the upper GIT compared to the smaller size particles. In the studies of Parr *et al* (11), in which the movement of ibuprofen sustained release tablets along the bowel was followed using gamma scintigraphy for 24 hours in humans, the mean residence time in the large intestine was 10.3 hours. They concluded that the large intestine was a major site of absorption of ibuprofen. In our study, the residence time may be longer considering the multiple units microspheres, therefore, longer sampling period (48 hours) was used. Wilson *et al* (18) had reported that the ascending colon represents an important site of absorption for sustained release formulations of NSAIDs. Washington *et al* (19), using a simulation model, recently reported that the colonic absorption of ibuprofen observed by the Wilson *et al* may be due to the higher pH (pH 6.5) in the colon compared to other segments of the GIT.

The troughs between the two peaks observed in our study showed that there is a region of poor absorption, reported to be the cecum by Washington *et al* (19), where the pH is low (pH 5.5). The differences in the time to reach the trough in the bimodal profiles of the bigger microspheres was a reflection of the relatively faster GI motility of the bigger particles compared to the smallest 96 μm size microspheres. Based on the report of these authors and that of Parr *et al* (11), the second peak shown for the sustained release formulations in the present study is due to colonic absorption. Enterohepatic circulation is unlikely because in an ongoing study in our lab, in which rats with ligated bile ducts were dosed with the microsphere formulation, the bimodal disposition profile was still observed.

The increase in S/R AUC_{0-8} of the conventional and sustained release suspensions compared with that of the IV showed that there was presystemic inversion. The observation is consistent with the theory that the inversion of ibuprofen includes a presystemic path. The decrease in S/R ratio (AUC_{0-48}) for the microspheres with increase in particle size indicated that inversion was minimal in the lower intestine, i.e., GIT site-specific. It is been reported that inversion of (R)- ibuprofen to (S)-ibuprofen in the distal GIT is less compared to the upper GI (10). The high S/R ratios observed up to 8 hours for the suspensions is an indication that there was presystemic inversion up to 8 hours (i.e in the upper GIT) and thereafter, inversion rate fell and then leveled off. Lack of systemic inversion was shown in the constant values of the S/R ratios for the IV dose. In a past study by Hall *et al* (20), in which a rapidly absorbed oral suspension was compared to an IV dose in humans, they concluded that there is no presystemic inversion, but that with sustained release delivery system, presystemic inversion is possible. In another study by Jamali *et al* (3), the S/R ratio was higher for sustained release compared to conventional dosage form. However, AUC_{0-48} was not evaluated and since transit time is dependent on the entire GI motility and on the type of dosage form device, their observation may not apply to other multiple units such as non-eroding wax-matrix microspheres used in our study.

The absolute and relative bioavailabilities, calculated using the combined AUC, (AUC_{0-48}), indicated that the sustained release formulations were highly bioavailable. This is an indication that the longer residence time of the sustained release formulations and nature of the multiple units themselves allowed for more of the drug to be absorbed over a prolonged period with consequent higher AUC.

CONCLUSIONS

Drug release from the multi-particulate non-eroding microspheres was prolonged and particle size-dependent. Presystemic inversion of R to S ibuprofen in suspensions of the non-eroding multiparticulates was GIT-site specific, and formulation dependent. The bimodal absorption profile was suggestive of colonic absorption, although it was also formulation dependent. Subsequently, disposition studies of similar chiral drugs should be extended for up to 48 hours or longer, post-dosing. Multiparticulate sustained release NSAIDs delivery systems have different absorption profiles compared with single unit systems. Granting the complexity of stereoselective disposition of ibuprofen and its formulation dependency, further research is needed in this area.

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