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RESEARCH PAPER

Peroral Sustained-Release Film-Coated Pellets as a Means to Overcome Physicochemical and Biological Drug-Related Problems. II. Bioavailability and Tolerance Assessment in Dogs

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ABSTRACT

Sustained-release (SR) dosage forms consisting of pellets coated with different pH-sensitive film layers, previously optimized in vitro with regard to pH independence of their durg release characteristics, were evaluated in vivo after single administration to Beagle dogs. In vivo performances were compared to those of a nonoptimized SR matrix tablet and a reference instant release (IR) capsule, in terms of the observed plasma pharmacokinetic profiles for the parent drug (ucb 11056) and its primary metabolite (ucb 26201), the bioavailability results, and the drug tolerance data. All SR dosage forms were seen to be effective in prolonging the relatively short biological half-life of the compound and in reducing the incidence of concentration-related side-effects, e.g., emesis, and of behavioral symptoms, e.g., restlessness, discomfort, and indisposition. The film-coated SR pellets offer a number of advantages over the monolithic SR matrix system in terms of a drug delivery pattern less dependent on pH changes in the gastrointestinal (GI) tract, a higher flexibility for adjusting and controlling the pharmacokinetic profiles, and a consequently more efficient approach for keeping all concentration-related side-effects under control.

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INTRODUCTION

The development of oral sustained release (SR) dosage forms as a means to extend the biological half-life of certain drugs has become very popular in drug therapy, facilitated by the recent progresses in pharmaceutical manufacturing technology.

A sound knowledge of the physicochemical properties of the active substance is in this case, perhaps more than elsewhere, a prerequisite. Drug solubility and/or dissolution rate, among other factors, can for instance greatly influence the release characteristics of the SR formulations and the subsequent achievement of the desired biological performances.

In the first part of this work (1), we reported the in vitro development and evaluation of different SR dosage forms of ucb 11056, a model drug substance showing a marked pH dependence of its solubility and dissolution properties. The use of multiple-unit pellets dosage forms was particularly considered, not only for their potential biopharmaceutical advantages such as more predictable and less variable gastric emptying and intestinal transit in comparison with larger single-unit delivery systems (2), but also for the higher flexibility of release adjustment obtainable because of the great deal of flexibility in formulation and the higher surface area offered for dissolution (3).

Indeed, using a coating technique with different kinds of pH-sensitive film layers, i.e., formulation blends of neutral and anionic acrylic polymers, a quite satisfactory pH independence of the in vitro release characteristics was achievable (1).

Two optimized ucb 11056 SR pellets formulations (batch 11 and 15) were selected in view of the evaluation of their in vivo performances, which is the topic of the present paper. The relative bioavailability and the tolerance of ucb 11056 and its major metabolite were thus investigated for the two SR pellets formulations, after single oral dose administration, in comparison with a standard instant-release (IR) dosage form (IR capsule) taken as a dosing reference, and with a previously developed SR matrix tablet showing a clear pH-dependence of its in vitro release characteristics (1).

Conducting preliminary bioavailability and tolerance studies of oral drug formulations for human use in animals, as an ethical obligation, always entails the problem of choosing the most appropriate animal species. Inherent discrepancies exist because of substantial interspecies differences in the gastrointestinal (GI) physiology, such as for gastric emptying and the duration of the intestinal transit, which are probably the key factors affecting dissolution and absorption of oral drugs. Beagle dogs were selected because they provide a particularly convenient animal model for testing human-scale oral dosage forms and also because they appeared from previous studies to be one of the best compromises among other animal species (3,5). However, bioavailability results in dogs might possibly be underestimated as a result of a faster gastric emptying and a shorter intestinal transit time compared to man (6).

EXPERIMENTAL

Materials and Methods

Study Dosage Forms

The selected study dosage forms were an SR matrix formulation compressed as a 13-mm diameter tablet (batch 74), two different formulations of SR pellets (1 mm diameter) filled into size 1 capsules (batches 11 and 15), and one control IR form (IR capsule batch 910306 containing the test substance alone). The nominal ucb 11056 dose content was 125 mg for all SR dosage forms and 62.5 mg (half-dose) for the IR capsules. Formulations and drug release characteristics were described previously (1).

In Vivo Study Design

Single-dose peroral administration of the four different study treatments to 12 adult Beagle dogs (age 14 ± 2 months, 6 males and 6 females) was realized over four study sessions according to a randomized cross-over design, a wash-out period of at least 1 week being allowed between each session.

The animals were in good health on the basis of normal laboratory findings (blood chemistry, hematology, urine analysis) and clinical examination.

Animal Dosing and Blood Sampling

Following an acclimatization period and an overnight fast of 16 hr in the study unit, the animals were dosed orally and a tap-water chaser volume of about 25 ml was given immediately after dosing. They remained fasting for at least 6 hr post-dose and food (300 g animal diet 125C, Animal Labo UAR, France) as well as drinking water (*ad libitum*) were thereafter made available. The dogs were housed singly in metabolic cages.

Blood (4 ml) was collected in dry Li-heparinized tubes before dosing and at 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 32, and 48 hr post-dosing, and plasma was separated by centrifugation.

In Vivo Study Experimental Evaluations

Analytical Assays and Pharmacokinetic Parameters

Plasma samples were assayed, after appropriate extraction and/or cleaning, for their ucb 11056 levels as well as metabolite (ucb 26201) by means of validated analytical procedures and reversed-phase liquid chromatography assay methods (7). Concentrations of the parent drug and metabolite measured in plasma were used to calculate the standard pharmacokinetic parameters, the latter being expressed, unless otherwise specified, as means ± standard deviation (SD) of all individual results, normalized and submitted to statistical analysis as applicable, e.g., two-tailed Student's *t*-test for small size independent samples. Abbreviations were taken from the American College of Clinical Pharmacy (ACCP) definitions (8), except for the so-called half-value duration (HVD), which is defined as the plateau time during which the plasma drug concentration remains equal to or higher than 50% of the C_{max} value.

Bioavailability Assessments

Relative bioavailability estimation was realized on the basis of the $AUC_{0-48\ hr}$ values, with the normalized results of the ucb 11056 IR capsules taken as reference. The geometric mean ratio of the different treatments was computed from the analysis of logarithmic (neperian) pretransformed values. The difference in the means, together with the 90% confidence limits symmetrical about the difference (significance level $\alpha = 5\%$), was detransformed from logarithms (9,10).

Bioequivalence, with respect to the extent of bioavailability, was concluded if the 90% confidence limits for the ratio of the tests and reference treatment averages were fully contained within the 80–125% acceptance range (11).

Calculation of the pharmacokinetic parameters was also carried out and reported after discarding the results of the animals that vomited a fraction of the dose, where confirmed by the presence of ucb 11056 (>5% of the administered dose) in the regurgitated gastric contents (analytical assay).

Clinical Observations

Clinical examination was performed for each animal for up to 48 hr post-dose. Clinical signs, e.g., emesis, were as far as possible recorded with their time of onset, duration, intensity, and number of animals involved.

Spontaneous activity of the animals was more specifically recorded at time 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 9 hr post-dose and reported as mean scores, individual scores being defined as 0: normal activity, -1: slight activity reduction, -2: marked activity reduction, and -3: severe activity reduction. Other behavioral symptoms with grade of severity ranked as restlessness < discomfort < indisposition were also specifically recorded at time 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, and 9 hr post-dose and reported as the number of dogs affected.

RESULTS AND DISCUSSION

The mean plasma concentration curves obtained in the Beagle dogs with the four different study dosage forms are shown in Fig. 1 for the parent drug ucb 11056 (above) and for the major metabolite ucb 26201 (below). The relating mean and dose-adjusted (normalized) plasma pharmacokinetic parameters are reported in Tables 1 and 2, as calculated with all dogs included and also after rejection of those results is based upon the study population with emesis excluded, because it more adequately reflects the true drug exposure of the animals. Note also that the interest for considering as well the data of the major metabolite in the present study is justified by the very high presystemic clearance of the parent drug, which makes a correct pharmacokinetic assessment difficult, and also because it is known from other studies that ucb 26201 supports to a large extent the pharmacological activity and can thus be considered as an active metabolite.

The pharmacokinetic data are altogether quite representative of the type of dosage forms administered, with the IR capsule showing the shortest t_{max} and the highest C_{max} and k_a values (plasmatic concentrations–time profiles given in Fig. 1, dose-adjusted data in Tables 1 and 2), while all the SR dosage forms exhibit a comparatively lower k_a, a delayed t_{max}, and a lower C_{max}.

More specifically, the SR matrix and SR pellets batch 15 show globally comparable results, with perhaps somewhat higher although not statistically different C_{max} ($p > 0.7$), t_{max} ($p > 0.4$), and $AUC_{0-48\ hr}$) ($p > 0.2$) values for the SR matrix tablet for both the ucb 11056 and ucb 26201 data.

The SR pellets batch 11 demonstrates a definitely distinct pharmacokinetic profile, with a roughly sevenfold slower apparent absorption rate compared to the other SR forms, resulting in the significantly lower plasma C_{max} levels ($p < 0.05$) and the lowest $AUC_{0-48\ hr}$ values ($p < 0.02$) for parent drug. One should nevertheless bear in mind for later discussion that the ucb 26201 C_{max} and $AUC_{0-48\ hr}$ values are, although slightly inferior, no longer statistically different from those of the other SR forms ($p > 0.5$).

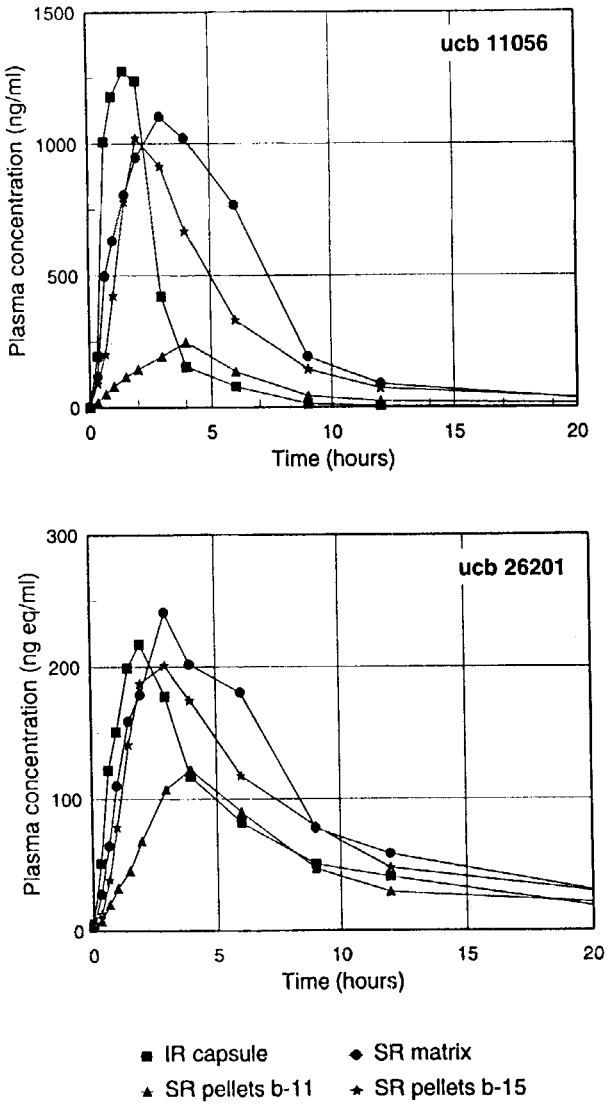

Figure 1. Mean plasma concentration–time profiles in Beagle dogs of ucb 11056 (parent drug) and ucb 26201 (major metabolite) after oral administration of an IR capsule (62.5 mg dose) or three different SR dosage forms (125 mg dose) (animals with emesis excluded from calculation).

For the two types of pellets dosage forms, the observed pharmacokinetic profiles are in agreement with the pH-gradient release curves obtained in vitro (1). The slowest drug delivery formulation (batch 11) is consistently the one providing the lowest k_a, C_{max}, and $AUC_{0\text{-}48\ hr}$ values, and differentiation between the two types is as marked in vivo as in vitro. The coating technique with different kinds of pH-sensitive film layers applied on pellet dosage forms is a very efficient means for adjusting and controlling the pharmacokinetic profile of a drug substance.

For the SR matrix tablet, the in vitro–in vivo correlation is not directly understandable because this form achieves the highest plasma levels and bioavailability data of all SR forms despite an apparently intermediate in vitro dissolution profile. This tablet shows, however, the fastest dissolution characteristics as long as it remains in acidic conditions, i.e., between pH 1.3 and 5.0, and one may therefore assume that the in vivo delivery must presumably also occur in such a favorable pH environment for a longer period of time. This could, for instance, be the case if gastric emptying of this quite large size tablet (diameter 13 mm) is delayed, in comparison with that of the pellets (diameter 1 mm), because it is known from other studies that the cut-off size at the pylorus level (about 2 mm in dogs) plays a predominant role in the gastric emptying process and resulting transit time of indigestible solids (2). A comparable pH-dependent effect is furthermore not expected from, and apparently not observed for, the two SR pellets formulations for which the drug delivery characteristics have been optimized with regard to pH independence; e.g., by slowing the release rate in acidic media and providing an increased film-coating permeability as soon as the form arrives in intestinal pH conditions (1).

Conversely, the in vivo assessment outcome of the study dosage forms appears to be different if one takes into account the parameters expressly describing their SR performances, such as the $C_{12\ hr}/C_{max}$ ratios or the HVD values (SR dosages forms > IR capsule, ucb 11056 and ucb 26201 data).

These data also indicate that the SR pellets batch 11 formulation achieves a very efficient SR performance because it provides drug and metabolite plasma levels that fluctuate the least over the longest period of time.

Moreover, it can be reliably assumed that immediate and complete ucb 11056 delivery from an IR capsule, with subsequent solubilization in the most acidic portion of the tract (i.e. the stomach) should theoretically result in the highest extent of bioavailability obtainable in the present study conditions. This means that the SR matrix and SR pellets batch 15 with similar exposure results to that of the IR capsule (not significantly different $AUC_{0\text{-}48\ hr}$ values) probably achieve an almost total release of their drug contents over the GI absorptive length available in the Beagle dog. On the contrary, the SR pellets batch 11 is the only one among the SR forms showing an $AUC_{0\text{-}48\ hr}$ value well inferior to, and statistically different from, that of the IR capsule ($p < 0.02$). Its AUC ratio is also one of the lowest observed: 26 ±

Table 1

ucb 11056 Plasma Pharmacokinetic Parameters (Mean ± SD Results)

Parameter	Units	Entire Study Population: IR Capsule (n = 12)	SR Matrix (n = 12)	SR Pellets b-11 (n = 12)	SR Pellets b-15 (n = 12)
C_{max}	ng/ml	2999 ± 1024[a]	1447 ± 440	313 ± 129	1295 ± 384
t_{max}	hr	1.1 ± 0.5	3.4 ± 1.1	2.8 ± 1.2	3.0 ± 1.6
k_a (r^2)[b]	ng/hr	1332 (0.898)	588 (0.959)	73 (0.985)	380 (0.938)
$C_{12\ hr}$	ng/ml	19 ± 31[a]	85 ± 71	22 ± 16	57 ± 58
$C_{12\ hr}/C_{max}$		0.006	0.059	0.071	0.044
HVD[c]	hr	2.0	6.3	4.8	4.6
$AUC_{0-48\ hr}$	ng · hr/ml	3900 ± 1216[a]	5167 ± 2415	1176 ± 554	4012 ± 2306
AUC ratio (90% CI)	%	-	138 (105–172)	31 (23–40)	107 (75–139)

Parameter	Units	Selected Study Population (Dogs with Emesis Excluded): IR Capsule (n = 5)	SR Matrix (n = 7)	SR Pellets b-11 (n = 12)	SR Pellets b-15 (n = 8)
C_{max}	ng/ml	3202 ± 1131[a]	1347 ± 195	313 ± 129	1245 ± 215
t_{max}	hr	1.5 ± 0.5	3.6 ± 1.3	2.8 ± 1.2	2.4 ± 1.0
k_a (r^2)[b]	ng/hr	1247 (0.925)	541 (0.941)	73 (0.986)	466 (0.979)
$C_{12\ hr}$	ng/ml	11 ± 11[a]	88 ± 44	22 ± 16	72 ± 70
$C_{12\ hr}/C_{max}$		0.003	0.066	0.071	0.058
HVD[c]	hr	2.2	6.3	4.8	3.8
$AUC_{0-48\ hr}$	ng · hr/ml	4710 ± 1175[a]	5001 ± 986	1176 ± 554	3567 ± 965
AUC ratio (90% CI)	%	- (93–124)	109 (19–32)	26 (62–93)	78

[a]Adjusted to a dose of 125 mg (normalized data).
[b]From linear least-squares regression analysis of mean plasma concentrations during the absorption phase (r^2: regression coefficient).
[c]Interpolated from the mean plasma concentration curves.
CI: confidence interval.

12% (90% CI: 19–32%). The initial dose content of the SR pellets batch 11 might therefore be far from exhausted when this slow-release dosage form reaches the end of the absorptive transit and a portion of unabsorbed drug load is likely eliminated as such from the body.

If one takes into account that some GI physiology differences exist between the human and dog species (6,12) and that these would tend to predict a lower extent of drug absorption for dogs in the present circumstances (e.g., consistently higher intestinal pH, shorter and about two-times faster small intestinal transit), it becomes clear that part of the SR pellets batch 11 performances might be presently observed in the Beagle dog, whereas a longer intestinal transit time in man could conceivably result in a more important fraction of drug absorbed.

Therefore, the low exposure results observed following SR pellets batch 11 administration should certainly not be considered at the present time as an exclusion criterion, and this dosage form obviously deserves further assessment in man. Note that, contrary to the matrix tablet dosage form, it is possible that the release rate characteristics of the newly developed film-coated pellets can be finely adjusted over a very wide range, and that the dose to be administered can be modified with no expected consequence on the release pattern.

Finally, it is important to note that the ratios of the plasma concentrations of ucb 26201 to those of ucb 11056 are much higher in the case of the SR pellets batch 11 than for the other dosage forms (ucb 26201/ucb 11056 ratios reported in Table 3 for C_{max} and $AUC_{0-48\ hr}$). This would suggest that higher release rates resulting in higher plasma levels can by-pass the first-pass metabolization to a certain extent. In other words, slowing the release rate of ucb 11056 SR dosage form is seen to offer an additional advantage in terms of a

Table 2

ucb 26201 Plasma Pharmacokinetic Parameters (Mean ± SD Results)

Parameter	Units	Entire Study Population: IR Capsule (n = 12)	SR Matrix (n = 12)	SR Pellets b-11 (n = 12)	SR Pellets b-15 (n = 12)
C_{max}	ng/ml	401 ± 169[a]	256 ± 87	149 ± 78	222 ± 108
t_{max}	hr	1.7 ± 0.6	3.8 ± 1.5	3.5 ± 1.9	3.3 ± 1.5
k_a (r^2)[b]	ng/hr	146 (0.911)	100 (0.983)	33 (0.993)	75 (0.938)
$C_{12\ hr}$	ng/ml	56 ± 57[a]	51 ± 31	37 ± 30	50 ± 43
$C_{12\ hr}/C_{max}$		0.139	0.199	0.245	0.225
HVD[c]	hr	3.5	6.9	7.2	7.7
$AUC_{0-48\ hr}$	ng · hr/ml	1308 ± 729[a]	1358 ± 512	941 ± 564	1140 ± 747
AUC ratio	%	-	119	82	100
(90% CI)			(95–142)	(57–108)	(66–133)

Parameter	Units	Selected Study Population (Dogs with Emesis Excluded): IR Capsule (n = 5)	SR Matrix (n = 7)	SR Pellets b-11 (n = 12)	SR Pellets b-15 (n = 8)
C_{max}	ng/ml	446 ± 78[a]	265 ± 98	149 ± 78	215 ± 78
t_{max}	hr	2.1 ± 0.5	3.6 ± 1.3	3.5 ± 1.9	2.9 ± 0.9
k_a (r^2)[b]	ng/hr	145 (0.971)	98 (0.977)	33 (0.993)	86 (0.971)
$C_{12\ hr}$	ng/ml	81 ± 68[a]	58 ± 26	37 ± 30	48 ± 32
$C_{12\ hr}/C_{max}$		0.182	0.220	0.245	0.222
HVD[c]	hr	3.8	6.6	7.2	6.2
$AUC_{0-48\ hr}$	ng · hr/ml	1619 ± 894[a]	1474 ± 275	941 ± 564	1034 ± 371
AUC ratio	%	-	103	60	72
(90% CI)			(89–117)	(41–80)	(53–91)

[a]Adjusted to a dose of 125 mg (normalized data).
[b]From linear least-squares regression analysis of mean plasma concentrations during the absorption phase (r^2: regression coefficient).
[c]Interpolated from the mean plasma concentration curves.
CI: confidence interval.

more efficient production of the active metabolite ucb 26201.

When considering the mean ucb 11056 C_{max} and $AUC_{0-48\ hr}$ values reported in Tables 1 and 2, it is obvious that the differences between the raw results and those recalculated with emesis excluded do not follow a similar trend for each study group of dosage form. This could be explained by the distinct patterns in on-

Table 3

Comparison in Terms of Ratio Between ucb 26201 (Major Metabolite) and ucb 11056 (Parent Drug) Values for Selected Plasma Pharmacokinetic Parameters

Ratio (%)	Selected Study Population (Dogs with Emesis Excluded): IR Capsule (n = 5)	SR Matrix (n = 7)	SR Pellets b-11 (n = 12)	SR Pellets b-15 (n = 8)
ucb 26201 C_{max}/ucb 11056 C_{max}	13.9[a]	19.7	47.6	17.3
ucb 26201 $AUC_{0-48\ hr}$/ucb 11056 $AUC_{0-48\ hr}$	34.4[a]	29.5	80.0	29.0

[a]Dose-adjusted (normalized data).

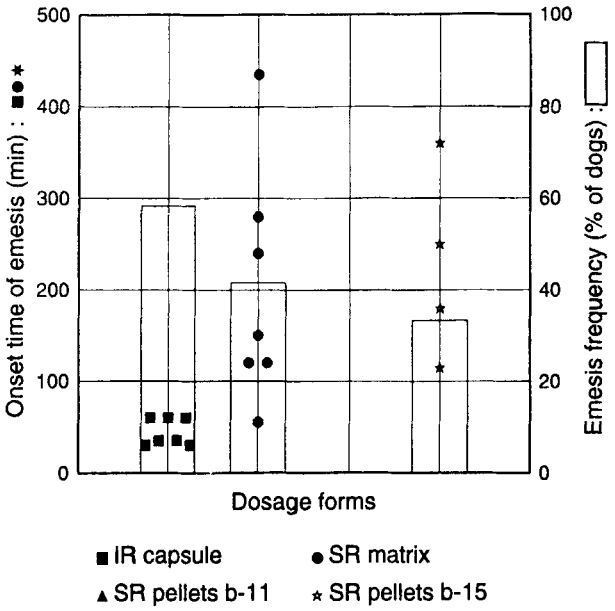

Figure 2. Onset time post-dosing (min) and frequency (percent of animals) of emesis in Beagle dogs represented for the ucb 11056 IR capsule (62.5 mg dose) and the three SR dosage forms (125 mg dose).

set time and frequency of emesis that are illustrated in Fig. 2.

The IR capsule-dosed animals are seen to vomit very soon after drug administration (44 ± 15 min). It is therefore more than likely that total gastric emptying of the dosage form content is not yet achieved at that time and that a substantial fraction of the given dose is regurgitated. So, by mostly excluding the less exposed animals, the recalculated mean C_{max} and $AUC_{0\text{-}48\ hr}$ values should indeed be higher than the raw results.

For the SR matrix and SR pellets batch 15, on the contrary, the animals having vomited are among the more exposed ones, which conforms to expectation because this side effect is known to be concentration dependent, as will be confirmed. Furthermore, vomiting is seen to occur much later (up to more than 7 hr post-dosing) and there is consequently less chance that a significant fraction of the dose would be regurgitated. As a result, the recalculated mean C_{max} and $AUC_{0\text{-}48\ hr}$ values are inferior to the raw results.

Finally, not a single animal of the SR pellets batch 11 study group was seen to vomit, and the raw and recalculated results are therefore the same.

It has also become apparent that the quite distinct patterns of emesis generally obey to the pharmacokinetic profiles of the different dosage forms.

The IR capsule study group showing the highest ucb 11056 peak plasma concentration is the most frequently affected by emesis (even if one considers the unnormalized results corresponding to a half-dose administration compared to the SR forms), whereas no emesis is observed following the SR pellets batch 11 dosing that produces a comparatively 10-times lower C_{max} value. The SR matrix and SR pellets batch 15, in addition to having a comparable pharmacokinetic profile, show a very similar pattern of vomiting symptoms with a frequency of occurrence reduced by about one-third compared to the IR capsule.

In addition, the shorter the plasma t_{max} value, the sooner the onset time of vomiting. The SR dosage forms therefore exhibit a delayed pattern of side effects in comparison with the IR formulation.

Figure 3 (top) further confirms that the importance of the side effect, as expressed by the number of dogs affected by emesis, is well correlated for each study dosage form with concentration-related pharmacokinetic parameters such as C_{mas} and k_a (SR pellets b-11 < SR pellets b-15 < SR matrix < IR capsule).

Emesis can thus be defined as a dose-dependent effect or, perhaps more rigorously speaking in the case of SR forms, as a concentration-dependent effect. There seems nevertheless to be no straightforward relationship between the occurrence of emesis in dogs and other pharmacokinetic parameter such as $AUC_{0\text{-}48\ hr}$ or HVD (Fig. 3, bottom), suggesting that the overall extent of exposure of the animals or the duration of exposure are not among the main causes of this side effect. The use of SR formulations as a means to overcome the major side effect of ucb 11056 appears therefore to be further justified in the present situation.

The pattern of behavioral symptoms other than emesis was also examined in order to disclose any additional correlation with the plasma drug levels.

First, if one considers a global effect such as a reduction of the spontaneous activity of the animals, there is no marked difference observed between the four study groups. The explanation of this might be either that low drug plasma levels already prove sufficient to induce a significant hypoactivity, or that hypoactivity is here the result of something other than drug activity, e.g., an external cause such as the overall stress related to the experimentation (Fig. 4).

Clear trends nevertheless appear for specific behavioral symptoms which could be more precisely assessed during clinical monitoring and be ranked according their degree of severity. This is illustrated in Fig. 5, where the increasing severity of the reported observation is

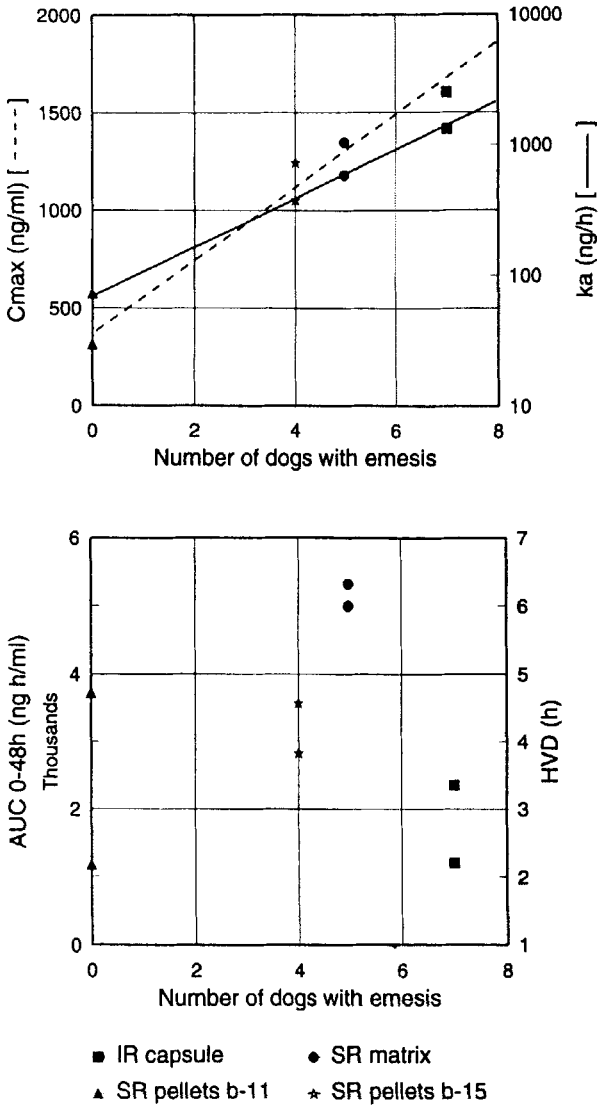

Figure 3. Correlation between the frequency of the major side effect observed in Beagle dogs (number of animals affected by at least one emesis) and different mean ucb 11056 pharmacokinetic parameters of the dosage forms (normalized data) separated as concentration-related parameters: C_{max}, k_a (top), or exposition-related parameters: $AUC_{0-48\ hr}$, HVD (bottom).

ranked as restlessness < discomfort < indisposition, and the number of dogs affected in each specific class of severity is plotted against the time post-administration.

Even for the class of minor severity (restlessness), the respective effects of the dosage forms can already be differentiated and correlated to their pharmacokinetic profiles. For example, the symptom manifestation ends

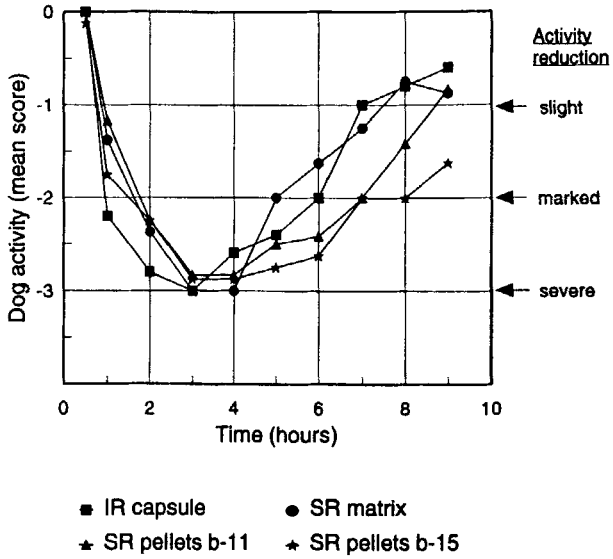

Figure 4. Monitoring of the spontaneous activity of animals (mean scores of activity reduction) after administration of an IR capsule (62.5 mg dose) or three different SR dosage forms (125 mg dose) (animals with emesis excluded from calculation).

sooner for the IR capsule, and fewer dogs are affected in the case of the SR pellets batch 11 compared to the other two SR dosage forms. The SR pellets batch 11 effects are no longer detectable in the class of middle severity (discomfort). Note also the peak of symptom frequency of the IR capsule that corresponds to its plasma t_{max} value, and the more leveled as well as delayed profiles of discomfort symptoms noticed with the two remaining SR dosage forms. Indisposition, ranked as the highest severity score, is finally observed (almost entirely) for the IR capsule.

These data bear evidence that ucb 11056 side effects other than emesis can be related to the plasma levels and that a reasoned adjustment of the drug delivery characteristics from an SR system would probably represent an effective means to improve the tolerance of the compound while concurrently prolonging the duration of activity.

CONCLUSIONS

For selected formulations evaluated in the Beagle dog, the SR approach was observed to be effective in prolonging the relatively short biological half-life of the compound and reducing the incidence of a number of concentration-related side effects. The flexibility of re-

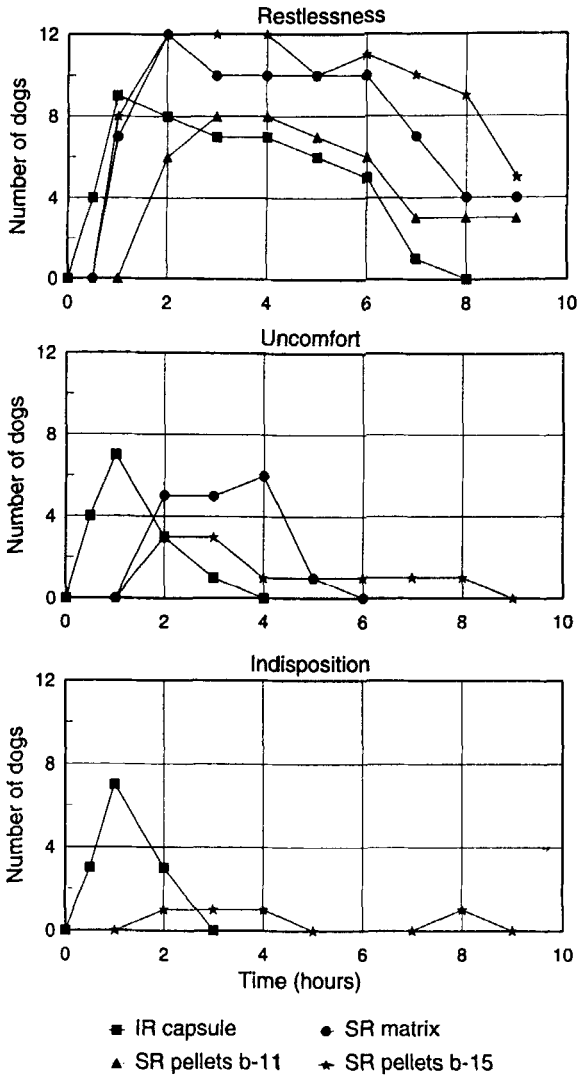

Figure 5. Monitoring of related behavioral symptoms (with severity graded as restlessness < discomfort < indisposition) observed in animals (expressed as number of dogs affected) after administration of an IR capsule (62.5 mg dose) or three different SR dosage forms (125 mg dose) (animals with emesis excluded from calculation).

lease rate adjustment and greater pH independence of release pattern obtainable from the film-coated pellets was seen to offer a number of advantages over a monolithic matrix delivery system.

Known differences of gastrointestinal physiology between the dog and human species incline us to believe that more promising results might be obtained in man. Thus, after having assessed the overall performance of the newly developed film-coated pellets dosage forms and having confirmed their reliability in vivo, a similar study may now be conducted in human volunteers in order to clarify the specific pharmacokinetic data and proceed to final selection of the more appropriate SR formulation.

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