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Design of controlled release delivery systems using a modified pharmacokinetic approach: a case study for drugs having a short elimination half-life and a narrow therapeutic index

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This paper is dedicated to a good friend, guide and philosopher Professor A.T. Florence, School of Pharmacy, London University

Abstract

The objectives of *peroral* controlled release drug delivery systems (CRDDS) are to maintain therapeutically effective plasma drug concentration levels for a longer duration thereby reducing the dosing frequency and to minimise the plasma drug concentration fluctuations at steady state by delivering drug in a controlled and a reproducible manner. Drug delivery rate, duration of delivery and the dosing interval are the target features for any temporal CRDDS. The classical pharmacokinetic model for designing CRDDS [Drug Dev. Ind. Pharm. 15 (1989) 1073] assumes the time of drug delivery (t_{del}) to be less than the dosing interval. However, termination of drug release from such a CRDDS at t_{del} and/or a declining drug input function towards the terminal phase of t_{del} from a first order kinetic CRDDS can have severe implications on plasma drug concentration and steady state fluctuations for a drug with very short half-life. A case study is presented in this paper, wherein by means of theoretical calculations using a classical pharmacokinetic approach, it is shown that a first order kinetic CRDDS for hypothetical drugs with short elimination half-life and different pharmacokinetic conditions would result in sub-therapeutic plasma concentrations at least for some time during the dosing interval at steady state. In order to avoid sub-therapeutic plasma drug concentrations a modification in classical pharmacokinetic model is proposed and discussed through theoretical calculations for different hypothetical pharmacokinetic situations and a practical single dose pharmacokinetic study with a first order kinetic CRDDS for nifedipine (a short half-life drug; about 2 h). It is shown that improved therapeutic efficacy could be expected from a CRDDS developed based on proposed modification in the classical pharmacokinetic model.

Keywords: Controlled release; Pharmacokinetic model; Nifedipine; Diltiazem

1. Pharmacokinetic basis of controlled drug delivery

Drug delivery in conventional dosage forms often suffers from the drawbacks of repeated drug administration and large fluctuations in drug blood levels. The frequency with which a rapidly absorbed and distributed drug must be given in a conventional dosage

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form is dependent upon two intrinsic properties of the drug, viz. elimination half-life ($t_{1/2}$) and therapeutic index (TI) (Eq. (1.1)) (Theeuwes and Bayne, 1977; Li and Lee, 1987). In turn, the dosing interval (τ) influences the ratio of maximum (C_{max}) to minimum (C_{min}) blood drug concentration levels attained from administration of a fixed dose of the drug (Eq. (1.2)).

$$\tau < t_{1/2}\left(\frac{\ln(\mathrm{TI})}{\ln(2)}\right) \tag{1.1}$$

$$\frac{C_{max}}{C_{min}} = e^{k_{el}t} \tag{1.2}$$

Hence, drugs with shorter half-lives require frequent administration to maintain blood concentration levels within therapeutically effective concentration range. As is well known, convenience of dosing frequency can be improved via controlled delivery where drug release is controlled from the system during a given time period so as to make up for the amount of drug metabolized and/or excreted from the body (Grass and Robinson, 1990). The goal is to give a drug at a sufficient rate, frequency and dose so that the ratio C_{max}/C_{min} in plasma at steady state is less than the TI and drug levels are always maintained at effective concentrations during the course of therapy. Thus, the predetermined drug delivery rates of controlled release drug delivery systems (CRDDS) allows the dosing interval τ to be a convenient time period that is much less dependent on $t_{1/2}$ and TI. The rate of drug delivery assumes even greater importance in the instances where pharmacodynamic effects (especially adverse effects) can be correlated to drug delivery rate. For example, Kleinbloesem et al. (1984, 1987) reported nifedipine to show pharmacodynamic differences at different delivery rates (the slower the delivery rate, the less the reflex tachycardia).

1.1. Design options for controlled release systems

In the case of controlled release systems, the rate of drug input into the body (the dosing rate) is governed by rate of drug release from delivery system. Although there are different kinetic models and equations that can be used to describe the drug release kinetics from a controlled release system, it is widely accepted that the ideal formulation for many drugs is one that gives zero order in vivo drug release. However, a controlled release product without such a release profile is not a faulty product; goals of controlled release therapy can be achieved with first order drug release also, which forms the basis for diffusion- and dissolution-controlled matrix-based drug release systems. Hence, one of the two release kinetic models (zero or first order) is presumed as a design option to calculate the desired drug release rates for a controlled drug release system (Ritschel, 1989). Accordingly on the basis of presumed release kinetics, a CRDDS is formulated and developed to achieve the desired drug release profile.

1.2. Design parameters for controlled release drug delivery systems

The dose, the delivery time and the dosing interval are the key features for any temporal controlled release system. The desired values are governed by multiplicity of factors such as therapeutically efficacious blood drug levels, the desired duration of efficacy and the pharmacokinetic characteristics of the drug. The three most important pharmacokinetic parameters are drug clearance (Cl_{tot}), volume of distribution (V_d) and elimination rate constant (k_{el}). The estimates of Cl_{tot}, effective drug concentration and extent of availability define the appropriate dosing rate (R^0, dose and dosing interval) of the drug by a particular route of administration (Eq. (1.3)) (Boxenbaum, 1982; Ritschel, 1988).

$$R^0 = \frac{F \times \mathrm{dose}}{\tau} = Cl_{tot} \times C_{ssav} \tag{1.3}$$

where F is bioavailable fraction of the dose that reaches the systemic circulation, and C_{ssav} is average blood drug concentration at steady state.

Ritschel (1989) described a simple approach to calculate design parameters (dose, delivery time and release rate) for a CRDDS that would achieve desired steady-state blood drug concentration levels on multiple dosing. A stepwise procedure, as described by Ritschel (1989), can be briefly described as follows:

(a) The time span of delivery (t_{del}) for a predetermined dosing interval is estimated using desired steady-state concentration levels and drug's elimination half-life.
(b) Pharmacokinetic data of the drug are used to predict the blood drug concentrations (from a test

dose, mostly the conventional dose) at different time points during the dosing interval.

If the drug release follows zero or pseudo-zero order kinetics then the plasma drug concentration at time 't', for a simple, one compartment heterogeneous system is determined by (Silber et al., 1987; Ritschel, 1989)

$$C_t = \frac{Fk_0(1 - e^{-k_{el}t})}{V_d k_{el}} \quad (1.4)$$

where k_0 is zero order release rate = dose/delivery time (t_{del}).

And blood drug concentration at steady state

$$C_{ss} = \frac{Fk_0}{V_d k_{el}} \quad (1.5)$$

which is same as Eq. (1.3). Hence, for drugs of short half-life (i.e. large k_{el}), the drug release rate has to be large to maintain effective drug blood concentrations at steady state.

If the drug is released at first order release rate k_1, then plasma drug concentration for a single one compartmental heterogeneous system is described by (Chien, 1982; Silber et al., 1987; Ritschel, 1989)

$$C_t = FDk_1\left(\frac{e^{-k_{el}t} - e^{-k_1 t}}{(k_1 - k_{el})V_d}\right) \quad (1.6)$$

$$C_t = \left(\frac{FDk_1k_a}{(k_a - k_{el})V_d}\right)(A + B + C) \quad (1.7)$$

where k_1 is first order release rate constant, k_a is absorption rate constant, $A = e^{-k_1 t}/(k_a - k_1)(k_{el} - k_1)$, $B = e^{-k_a t}/(k_1 - k_a)(k_{el} - k_a)$, $C = e^{-k_{el}t}/(k_a - k_{el})(k_1 - k_{el})$.

Blood drug concentration versus time data thus generated from the single dose of the drug are then applied to estimate accumulation to the steady state using the superposition method. Based on the predicted steady state levels, the test dose of the drug is modified so that the modified dose achieves the desired concentration levels at the steady state. The desired drug release rate is determined from the dose and t_{del} (Ritschel, 1989).

2. Drugs with short elimination half-life: a difficult category

One of the main assumptions of Ritschel's method is that drug release terminates at t_{del}, which is shorter than the dosing interval (Ritschel, 1989; Chaturvedi, 1999). Subsequent to the termination of drug release there is no drug input and the drug concentration levels attained in blood fall exponentially as a function of elimination half-life of the drug until dosing restarts after administration of the next dose. This can be an advantageous situation when the therapeutic need is for intermittent pulsatile drug concentrations rather than constant drug blood levels, e.g. nitroglycerine, gonadotropin releasing hormone and bactericidal drugs that act only on proliferating microbes. However, for drugs with a short elimination half-life and a low therapeutic index (TI, narrow therapeutically effective concentration range), the elimination phase during the dosing interval may have a significant influence on drug concentrations achieved at steady state. Termination of drug release at t_{del} followed by the elimination phase results in a sharp decline in the plasma concentration levels for short elimination half-life drugs and the trough concentrations may fall below therapeutically effective concentration level. As a result, it leads to sub-therapeutic drug concentrations for a certain time during the dosing interval and consequently a shorter than intended post-dose duration of action, D_a ($D_a < \tau$). The ratio of D_a to τ is defined as the forgiveness index (FI), which determines how much latitude the patient has in delaying the next dose (Urquhart, 1996) and reduction in D_a ensues "inferior forgiveness". Additionally, due to the lower accumulation effect into subsequent dosing interval, a drug that is multiple dosed, would show large fluctuations at steady state concentration levels. Further, in critical cases, sub-therapeutic drug concentrations combined with large fluctuations at the steady state may result in loss of intended therapeutic efficacy. The situation can be further worsened if the prescribed dose is taken at longer-than-prescribed intervals (Urquhart, 1996).

The implications of elimination phase and drug release kinetics (zero order or first order) on the performance of controlled release systems for two drugs nifedipine (DR1) and diltiazem hydrochloride (DR2) are discussed individually in the following sections. Theoretical calculations are used to predict the steady state levels for each drug under different hypothetical situations of half-life (2 or 4 h) and desired steady state concentration ranges (SN1, SN2, SN3 and SN4) defined as follows:

DR12: a drug with a pharmacokinetic profile identical to that of nifedipine but with a half-life of 2 h.
DR14: a drug with a pharmacokinetic profile identical to that of nifedipine but with a half-life of 4 h.
DR22: a drug with pharmacokinetic profile identical to that of diltiazem hydrochloride but with a half-life of 2 h.
DR24: a drug with pharmacokinetic profile identical to that of diltiazem hydrochloride but with a half-life of 4 h.
SN1: a situation where the therapeutically effective concentration range is very narrow with desired steady state concentration levels of 15–30 ng/ml.
SN2: a situation where the therapeutically effective concentration range is narrow with desired steady state concentration levels of 15–75 ng/ml.
SN3: a situation where the therapeutically effective concentration range is wider with desired steady state concentration levels of 15–150 ng/ml.
SN4: a situation where the therapeutically effective concentration range is very wide with desired steady state concentration levels of 15–300 ng/ml.

Hence, a combination of DR12 with SN1 would represent the category of drug with short elimination half-life and narrow effective concentration range. The pharmacokinetic properties of nifedipine and diltiazem hydrochloride that are used for calculations are taken from literature (Benet et al., 1996; Ritschel and Kearns, 1999).

2.1. Case 1: DR1 drugs

A twice a day formulation for DR12-SN1 drug with first order release kinetics (t_{del}: 10.64 h, k_r: 0.2164 h^{-1}) would require a dose of 42 mg to give C_{ssmax} (maximum blood drug concentration at steady state) of 30 ng/ml, however, C_{ssmin} (minimum blood drug concentration at steady state) would remain below the minimum effective concentration level (15 ng/ml) for about 4.5 h of the dosing interval (Table 1). Similarly, for DR12-SN2, DR12-SN3 drugs the steady state plasma concentrations are predicted to fall below effective levels towards the end of the dosing interval (Table 1). The drug blood levels from a first order kinetic controlled release system depend upon the release rate constant, k_1 and the amount of drug remaining in the delivery system, D (Eq. (1.7)). In the initial phase after dose administration, the drug input function predominates over the output function and the systemic drug levels increase as a function of first order input rate. As D becomes smaller during the drug release process, the amount of drug released per unit time also decreases exponentially (Costa and Lobo, 2001). A continuously decreasing rate of drug input (in terms of amount per unit time) into the systemic circulation causes plasma drug concentration levels to plateau (C_{max}) much before t_{del}. Subsequent to the t_{max} drug elimination function takes over the input function and the concentration levels start declining at a rate controlled by a combination of declining input function (amount per unit time) and inherent elimination kinetics. Elimination at this net resultant rate continues till t_{del}, after which concentration declines rapidly as a function of drug's elimination half-life. Hence, when the therapeutically effective concentration range is narrow (SN1, SN2, SN3), C_{ssmax} attained from a controlled drug release system tends to fall below the desired minimum blood drug concentration at steady state at the end of dosing interval, $C_{ssmindes}$. It is important to note that as the therapeutically effective concentration range becomes wider, the design of a controlled release system with first order release kinetics according to Ritchel's method requires faster release for a shorter duration t_{del} resulting in higher C_{max}. Hence, in the case of DR12 under SN4 condition a wide therapeutically effective concentration range and higher C_{ssmax} ensure that the concentrations do not fall below desired levels during dosing interval in spite of longer elimination period. However, at the same time design of a controlled drug release system for a wider range of desired steady state concentrations is expected to result in higher fluctuations in steady state drug concentration levels, which is undesirable even though the concentrations remain within the desired levels (Table 1).

Although first order release kinetic design of a twice a day controlled release system by Ritchel's method for DR12 and DR14 is predicted to result

Table 1
First order release system: predicted steady state levels for DR12, DR14, DR22 and DR24 under different situations of therapeutically effective concentration range

Drug-situation	$C_{ssmindes}$ – $C_{ssmaxdes}$ (ng/ml)	t_{del} (h)	k_r (h^{-1})	Dose (mg)	$C_{sminpred}$ – $C_{ssmaxpred}$ (ng/ml)	DI (% fluctuation)	FI
DR12							
SN1	15–30	10.64	0.2164	42	8.12–30.07	3.703 (114.95)	0.692
SN2	15–75	8.00	0.2879	92	10.49–75.07	7.156 (150.96)	0.872
SN3	15–150	6.00	0.3839	161	12.91–150.15	11.631 (168.33)	0.948
SN4	15–300	4.00	0.5760	276	16.13–299.86	18.590 (179.66)	1.018
DR14							
SN1	15–30	9.29	0.2480	25	13.65–30.69	2.248 (76.86)	0.933
SN2	15–75	4.00	0.5760	48	17.91–74.84	4.179 (122.76)	1.085
DR22							
SN1	15–30	10.64	0.2164	29	10.02–29.98	2.992 (99.8)	0.808
SN2	15–75	8.00	0.2879	64	13.06–74.98	5.741 (140.66)	0.967
SN3	15–150	6.00	0.3839	114	15.92–150.59	9.459 (161.76)	1.014
SN4	15–300	4.00	0.5760	201	18.75–300.70	16.037 (176.52)	1.053
DR24							
SN1	15–30	9.29	0.2480	21	15.15–29.98	1.979 (65.72)	1.005
SN2	15–75	4.00	0.5760	40	25.83–74.97	2.902 (97.50)	1.262

Predicted levels are from a twice a day ($\tau = 12$ h) first order drug release kinetic controlled release system design based on Ritschel's method and superposition method (Ritschel, 1989). DR14 and DR24 under SN3 and SN4 situations could achieve therapeutic concentration levels at steady state throughout the dosing interval and hence are not shown here. DI: dosage form index (Theeuwes and Bayne, 1977). FI: forgiveness index (Urquhart, 1996). Calculated from steady state blood drug concentration–time profile with an assumption that duration of action is correlated to blood drug concentration and is the period of dosing interval during which concentration remains above $C_{ssmindes}$; % fluctuation—(Skelly and Barr, 1987).

in sub-therapeutic C_{ssmin} values, a twice a day controlled release system with zero order release kinetics can be designed to give therapeutically effective concentrations under all four situations (Table 2). In the case of zero order drug release controlled absorption, the drug concentrations increase till t_{del} to give a C_{max} that declines subsequently as a function of the drug half-life during the elimination phase. However, declining concentrations do not fall below the minimum effective concentration during the elimination phase as the controlled release system design ensures t_{del} to be long enough and C_{max} to be high enough so that the elimination period is insufficient to cause sub-therapeutic concentrations after the termination of drug release (Table 2). Additionally, selecting a narrower desired steady state concentration range within the therapeutically effective concentration range can ensure reduced fluctuations, but at the same time it would demand a higher drug dose with precise delivery for longer durations. Thus, presuming a zero order kinetic controlled release system does not present any problems, so attention is focused more on first order controlled release systems (with the potential of large fluctuations and sub-therapeutic levels for drugs with short a half-life and narrow therapeutically effective concentration range).

2.2. Case 2: DR2 drugs

Similar to DR12, a first order kinetic controlled release system for DR22 is also predicted to result in sub-therapeutic concentrations towards t_{del} under SN1 and SN2 condition (Table 1). A first order controlled release system under SN3 and SN4 conditions as well as a zero order controlled release system under all four situations for DR22 can be designed to give concentrations within a desired range throughout the dosing interval (Tables 1 and 2). Similarly, first order as well as zero order controlled release systems for DR24 under all four situations result in therapeutic concentrations throughout the dosing interval as a result of relatively slower elimination kinetics (Tables 1 and 2).

Table 2
Zero order release systems: predicted steady state levels for DR12, DR14, DR22 and DR24 under different situations of therapeutically effective concentration range

Drug-situation	$C_{ssmindes}$ – $C_{ssmaxdes}$ (ng/ml)	t_{del} (h)	k_0 (h^{-1})	Dose (mg)	$C_{sminpred}$ – $C_{ssmaxpred}$ (ng/ml)
DR12					
SN1	15–30	10.00	1.17	11.73	15–30
SN2	15–75	7.36	3.08	22.68	15–75
SN3	15–150	5.35	6.74	36.09	15–150
SN4	15–300	3.35	16.54	55.49	15–300
DR14					
SN1	15–30	8.00	0.68	5.40	15–30
SN2	15–75	2.71	3.38	9.16	15–75
DR22					
SN1	15–30	10.00	5.45	54.47	15.0–29.9
SN2	15–75	7.36	14.32	105.35	15.0–74.9
SN3	15–150	5.35	31.31	167.66	15.0–149.9
SN4	15–300	3.35	76.99	258.26	15.0–300.0
DR24					
SN1	15–30	8.00	3.14	25.00	15.0–30.0
SN2	15–75	2.71	15.71	42.48	15.0–75.0

Predicted levels are from a twice a day ($\tau = 12$ h) zero order drug release kinetic controlled release system design based on Ritschel's method and superposition method (Ritschel, 1989). Desired steady state concentration levels for dosing interval can be achieved with zero order controlled release system in all four drugs under all the situations. Hence, DI and FI are not shown and also DR14 and DR24 under SN2 and SN3 situations are not shown in parallel to Table 1.

3. Avoiding sub-therapeutic concentration levels from first order CRDDS: increased dose or slower delivery approach?

From the above discussion it is clear that controlled release system design can be either a first order kinetic system (if the steady state concentration range is wide enough not to cause sub-therapeutic drug concentrations) or a zero order system. A first order release system with higher drug doses can be prepared for short elimination half-life drugs with narrow therapeutically effective concentration range in order to avoid sub-therapeutic concentrations and extend the duration of action within a dosing interval. However, this approach may be hazardous as use of the higher doses would result in the drug concentrations rising above the upper limit of concentration range considered to be safe (Table 3). Instead a drug delivery approach can be taken wherein the drug release rate is reduced to increase the t_{del} from the delivery system. As t_{del} is increased close to the dosing interval, it results in a lower C_{ssmax} (due to slower drug absorption for a longer period) and the higher C_{ssmin} values (due to reduced elimination phase during which drug concentration declines rapidly). This not only reduces the fluctuations at steady state levels (reduced DI and % fluctuations) but also provides a chance to increase the dose to achieve higher concentration levels within the desired concentration range so that the C_{ssmax} attained is equal to the $C_{ssmaxdes}$ (Table 4).

The advantage of achieving higher concentration levels within the desired range is that it provides the patient greater latitude in delaying the next dose, in other words greater FI values. This means a slight delay in taking a dose at the prescribed time would not result in sub-therapeutic concentration levels and consequent loss in therapeutic efficacy, though the maximum tolerable delay would depend on the value of FI (higher FI values provide greater latitude). Alternatively, if it is acceptable to achieve the entire steady state blood level–time curve above $C_{ssmindes}$ so that C_{ssmin} attained at the end of τ is equal to $C_{ssmindes}$ (e.g. with bacteriostatic antibiotics), a lower dose is required as compared to the requirement when steady state blood level–time curve is maintained within the effective concentration range with C_{ssmax} attained

Table 3
First order release systems: effect of increasing the dose on predicted steady state for different drugs under specified situations (SN1, SN2 or SN3; see text for details)

Drug-situation	$C_{ssmindes}$ – $C_{ssmaxdes}$ (ng/ml)	t_{del} (h)	k_r (h^{-1})	Dose (mg)	$C_{ssminpred}$ – $C_{ssmaxpred}$ (ng/ml)
DR12-SN1	15–30	10.64	0.2164	42	8.12–30.07
				78	15.03–55.83
DR12-SN2	15–75	8.00	0.2879	92	10.49–75.07
				132	15.06–107.71
DR12-SN3	15–150	6.00	0.3839	161	12.91–150.15
				187	15.00–174.40
DR14-SN1	15–30	9.29	0.2480	25	13.65–30.69
				28	15.29–34.37
DR22-SN1	15–30	10.64	0.2164	22	10.02–29.98
				43	14.84–44.45
DR22-SN2	15–75	8.00	0.2879	64	13.06–74.98
				74	15.09–86.69

The predicted levels are from a twice a day ($\tau = 12$ h) first order drug release kinetic controlled release system design-based Ritschel's method and superposition method (Ritschel, 1989). Only those cases, where $C_{ssminpred} < C_{ssmindes}$ and dose was required to be increased to see the effect on steady state levels, are presented. DI and FI are not shown, as there would not be any change in the values due to change in dose for any of the drug-situation combination. Change in dose with same delivery profile (rate and duration) results in proportional increase or decrease in min as well as max concentration levels and thus do not affect DI or % fluctuation values.

during τ equals $C_{ssmaxdes}$ (Table 4). As can be seen from Table 4, DI, % fluctuations and FI values are predicted to improve with increase in t_{del}. However, slight dose adjustment is required to maintain drug release for a longer period of time. Further, calculations indicate that dose requirements are lowered in order to achieve $C_{ssmindes}$ at end of dosing interval.

As stated earlier, one of the assumptions of Ritschel's method is that t_{del} is shorter than τ. In some cases, as for DR12-SN1 and DR22-SN1, even increasing t_{del} to the value of τ is not sufficient to ensure therapeutic levels throughout the dosing interval (Table 4). This is expected to happen when the net result of elimination and declining absorption (amount per unit time), subsequent to t_{max} is large enough to bring the concentration down to sub-therapeutic levels towards the end of dosing interval.

4. If t_{del} is greater than the dosing interval this ensures therapeutic levels throughout the dosing interval

Increasing t_{del} above the dosing interval results in drug release throughout the dosing interval with a predetermined fraction of dose remaining to be released in the next dosing interval. Continuous slow release of the drug during the dosing interval avoids the elimination phase, consequently avoiding sub-therapeutic drug concentration levels. At the same time, fraction of dose remaining at the end of first dosing interval would lead to accumulation in the second dosing interval, providing a higher accumulation effect and reduced concentration fluctuations at steady state (Table 5). Similar results can be obtained by using the same approach for other drugs DR22, DR14 and DR24 under situations described earlier.

In order to further demonstrate general applicability of the proposed concept, two drugs, viz. glipizide and zidovudine were taken as examples of short elimination half-life drugs ($t_{1/2}$: 2.4 and 1.1 h, respectively) (Benet et al., 1996; Ritschel and Kearns, 1999). Glipizide has a narrow effective concentration range (110–330 ng/ml), low volume of distribution (0.17 l/kg) and requires multiple dose chronic regimens. Zidovudine is a large dose drug (high volume of distribution, 1.4 l/kg and relatively wider effective concentration range with higher $C_{ssmaxdes}$, 100–600 ng/ml) used for chronic administration. As shown for two hypothetical drugs, ensuing that $t_{del} >$

Table 4
First order release systems: effect of increasing t_{del} equal to τ on predicted steady state concentration levels for different drugs under specified situations (SN1, SN2 or SN3; see text for details)

Drug-situation	$C_{ssmindes}$ – $C_{ssmaxdes}$ (ng/ml)	t_{del} (h)	k_r (h^{-1})	Dose (mg)	$C_{ssminpred}$ – $C_{ssmaxpred}$ (ng/ml)	DI (% fluctuation)	FI
DR12-SN1	15–30	10.64	0.2164	42	8.12–30.07	3.703 (114.95)	0.692
		12.00	0.1919	43.64	11.28–30.00	2.660 (90.70)	0.833
DR12-SN2	15–75	8.00	0.2879	92	10.49–75.07	7.156 (150.96)	0.872
		10.00	0.2302	102	17.22–74.89	4.349 (125.22)	1.033
		12.00	0.1919	109	28.18–74.92	2.659 (90.67)	1.152
		12.00	0.1919	58	14.99–39.88	2.660 (91.12)	1.000
DR12-SN3	15–150	6.00	0.3839	161	12.91–150.12	11.628 (168.32)	0.948
		8.00	0.2879	183	20.88–149.32	7.151 (150.93)	1.079
		12.00	0.1919	218	56.36–149.86	2.659 (90.68)	1.318
		12.00	0.1919	58	14.99–39.88	2.660 (91.12)	1.000
DR14-SN1	15–30	9.29	0.2480	24.4	13.36–29.97	2.243 (76.67)	0.933
		12.00	0.1919	26	17.58–30.01	1.707 (52.24)	1.077
		12.00	0.1919	22	14.94–25.50	1.707 (52.23)	1.000
DR22-SN1	15–30	10.64	0.2164	29	10.02–29.98	2.992 (99.80)	0.808
		12.00	0.1919	30	13.82–29.73	2.151 (73.07)	0.858
DR22-SN2	15–75	8.00	0.2879	64	13.06–74.98	5.741 (140.66)	0.967
		10.00	0.2303	70.7	21.39–74.99	3.506 (111.23)	1.085
		12.00	0.1919	75.7	34.88–75.02	2.151 (73.05)	1.203
		12.00	0.1919	32.55	15.00–32.27	2.151 (73.07)	1.000

The predicted levels are from a twice a day ($\tau = 12$ h) first order drug release kinetic controlled release system designed using superposition method (Ritschel, 1989). Only those cases, where $C_{ssminpred} < C_{ssmindes}$, are presented. DI: dosage form index (Theeuwes and Bayne, 1977). FI: forgiveness index (Urquhart, 1996). Calculated from steady state blood drug concentration–time profile with an assumption that duration of action is correlated to blood drug concentration and is the period of dosing interval during which concentration remains above $C_{ssmindes}$; % fluctuation—(Skelly and Barr, 1987).

Table 5
First order release systems: effect of increasing t_{del} longer than τ on predicted steady state concentration levels for DR12-SN1and DR22-SN2

Drug-situation	$C_{ssmindes}$ – $C_{ssmaxdes}$ (ng/ml)	t_{del} (h)	k_r (h^{-1})	Dose (mg)	$C_{ssminpred}$ – $C_{ssmaxpred}$ (ng/ml)	DI (% fluctuation)	FI
DR12-SN1	15–30	12.00	0.1919	43.6	11.28–30.00	2.660 (90.70)	0.833
		15.00	0.1535	43.5	12.29–29.97	2.439 (83.67)	0.850
		18.00	0.1279	45.7	13.64–29.99	2.199 (74.95)	0.869
		20.00	0.1152	48.0	14.77–30.02	2.033 (68.10)	0.889
		22.00	0.1047	49.0	16.25–30.01	1.847 (59.49)	1.019
DR22-SN1	15–30	12.00	0.1919	30.0	13.82–29.73	2.151 (73.06)	0.912
		14.00	0.1645	31	14.93–29.99	2.009 (67.05)	0.929
		16.00	0.1439	30	14.75–29.99	2.033 (67.85)	0.923
		18.00	0.1279	31	15.71–29.92	1.905 (62.28)	1.011

These drug-situation combinations were selected as even on increasing t_{del} to as long as τ could not avoid sub-therapeutic concentration levels. The predicted levels are from a twice a day ($\tau = 12$ h) first order kinetic controlled release system designed using superposition method. Only those cases, where $C_{ssminpred} < C_{ssmindes}$, are presented. DI: dosage form index (Theeuwes and Bayne, 1977). FI: forgiveness index (Urquhart, 1996). Calculated from steady state blood drug concentration–time profile with an assumption that duration of action is correlated to blood drug concentration and is the period of dosing interval during which concentration remains above $C_{ssmindes}$; % fluctuation—(Skelly and Barr, 1987).

Table 6
Predicted blood drug levels of glipizide (C_{ssdes} is 110–330 ng/ml) and zidovudine (C_{ssdes} is 100–600 ng/ml) at steady state from a twice a day ($\tau = 12$ h) first order kinetic controlled release system with different delivery profiles

Drug	t_{del} (h)	k_r (h^{-1})	Dose (mg)	$C_{ssminpred} - C_{ssmaxpred}$ (ng/ml)	DI (% fluctuation)	FI
Glipizide	8.97	0.2568	25	80.1–328.9	4.106 (121.66)	0.908
	12.00	0.1919	27.7	143.8–329.9	2.294 (78.57)	1.078
	14.00	0.1645	28.4	155.1–330.1	2.128 (72.13)	1.099
	16.00	0.1439	27.8	157.2–330.0	2.099 (70.94)	1.103
	18.00	0.1279	28.93	168.5–329.6	1.956 (64.49)	1.123
	18.00	0.1279	18.9	110.2–215.6	1.956 (64.47)	1.000
Zidovudine	9.51	0.2422	968	38.6–597.7	15.484 (175.73)	0.875
	12.00	0.1919	1100	149.4–600.0	4.016 (120.25)	1.053
	12.00	0.1919	736	99.9–401.3	4.017 (120.27)	1.000
	14.00	0.1645	1136	171.7–600.0	3.494 (111.00)	1.072
	14.00	0.1645	662	100.1–349.6	3.493 (110.96)	1.000
	16.00	0.1439	1132	182.8–600.1	3.282 (106.60)	1.080
	16.00	0.1479	619	100.0–328.1	3.281 (106.47)	1.000
	18.00	0.1279	1194	201.5–599.7	2.976 (99.40)	1.093
	18.00	0.1279	593	100.1–297.9	2.976 (99.39)	1.000

For zidovudine, calculations are done at each level of t_{del} for achieving $C_{ssmindes}$ as well as for $C_{ssmaxdes}$ to see the possibility of reducing the dose requirement for a CRDDS. Note that a controlled release system with lower dose (so that C_{ssmin} is $C_{ssmindes}$) would have low forgiveness index. Also changed dose at same delivery profile (delivery rate and duration) does not produce any change in DI or % fluctuations. DI: dosage form index (Theeuwes and Bayne, 1977). FI: forgiveness index (Urquhart, 1996). Calculated from steady state blood drug concentration–time profile with an assumption that duration of action is correlated to blood drug concentration and is the period of dosing interval during which concentration remains above $C_{ssmindes}$; % fluctuation—(Skelly and Barr, 1987).

τ results in therapeutically effective steady state concentrations throughout τ with reduced fluctuations for both the drugs (Table 6). It can be seen from Table 6 that zidovudine (a high dose and short half-life drug, which needs to be administered frequently, i.e. 250 mg every 4 h) is difficult to formulate as a controlled release system due to high dose. However, dose requirements for twice a day controlled release systems can be reduced by developing a delivery system to release the drug for 16–18 h at first order kinetics.

5. Practical experience with nifedipine

Nifedipine is a short half-life drug with good absorbability throughout the intestine (Martindale, 1996; Sorkin et al., 1985). Desired steady state concentration levels was taken to be 15–30 ng/ml for theoretical calculations of t_{del}, first order release rate and dose. The delivery profile thus calculated (drug release rate constant, k_{rdes}: 0.2164 h^{-1}, dose: 40 mg, time duration of drug delivery, t_{del}: 10.64 h) was predicted to result in sub-therapeutic steady state concentration levels in the later phase of the dosing interval (12 h) with large concentration fluctuations. However, reducing drug release from 0.2164 to 0.1047 h^{-1} would predictably reduce the fluctuations in steady state concentration levels from 7.67–28.62 to 14.56–24.84 ng/ml, while at the same time, periods of sub-therapeutic drug concentration (<15 ng/ml) would also be avoided (Table 7, Fig. 1b). At a delivery rate of 0.1047 h^{-1}, 70% of the dose would be released in the dosing

Table 7
Predicted blood drug concentration levels for nifedipine (C_{ssdes} is taken as 15–30 ng/ml) at steady state from a twice a day ($\tau = 12$ h) first order drug release kinetic controlled release system with different t_{del} and release rate constants at same dose level (40 mg)

t_{del} (h)	k_r (h^{-1})	% drug delivery in τ[a]	C_{sspred} (ng/ml)
10.64	0.2164	92.52	7.67–28.62
12.00	0.1919	90.00	10.34–27.50
14.00	0.1645	86.11	11.04–27.08
16.00	0.1439	82.21	11.53–27.37
18.00	0.1279	78.45	11.94–26.25
20.00	0.1152	74.90	12.75–25.36
22.00	0.1047	71.53	14.56–24.84

[a] Remaining drug is released in next dosing interval and gives accumulation effect to reach steady state levels.

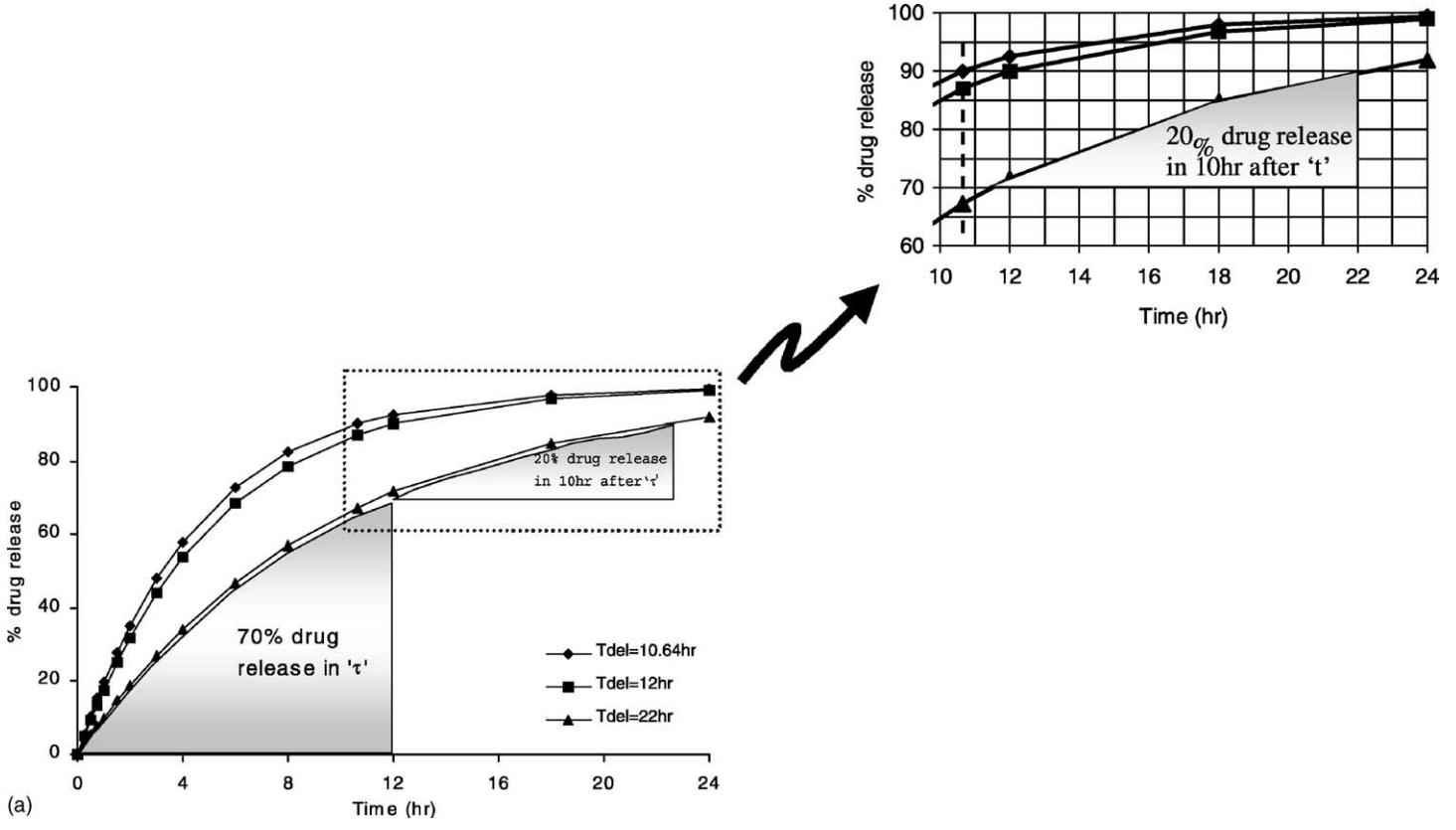

Fig. 1. (a) Desired drug delivery profiles (first order kinetics) from twice a day nifedipine formulations (40 mg nifedipine strength) with different time of delivery (t_{del}) values. t_{del} values of 10.64, 12 and 22 h give first order release rates of 0.2164, 0.1919 and 0.1047 h^{-1}, respectively so as to achieve 90% drug release in t_{del}. (b) Predicted steady state blood drug concentration–time profiles for twice a day nifedipine formulations with different t_{del}. Predictions are done based on drug pharmacokinetics and superposition method with 15–30 ng/ml as desired steady state concentrations.

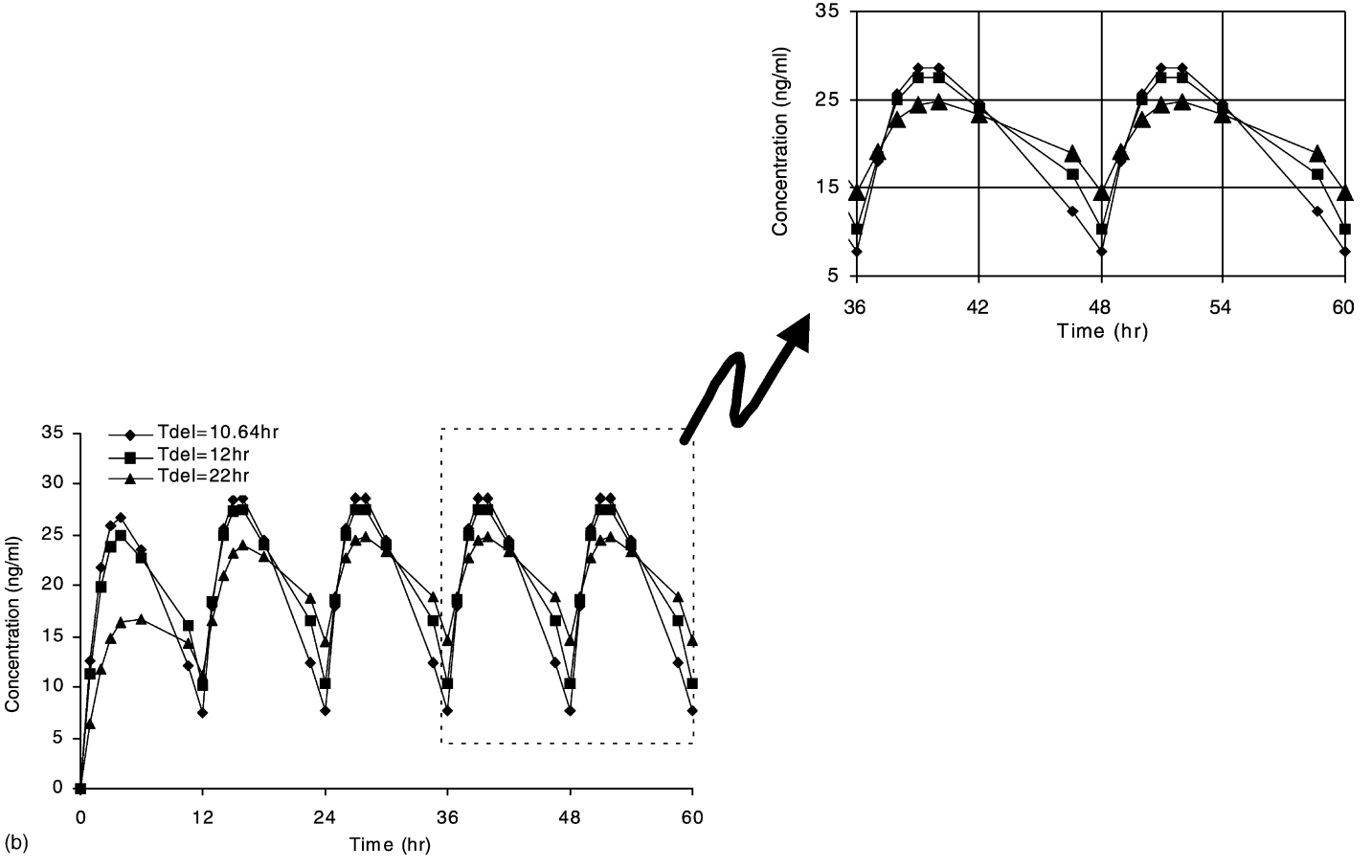

Fig. 1. (*Continued*).

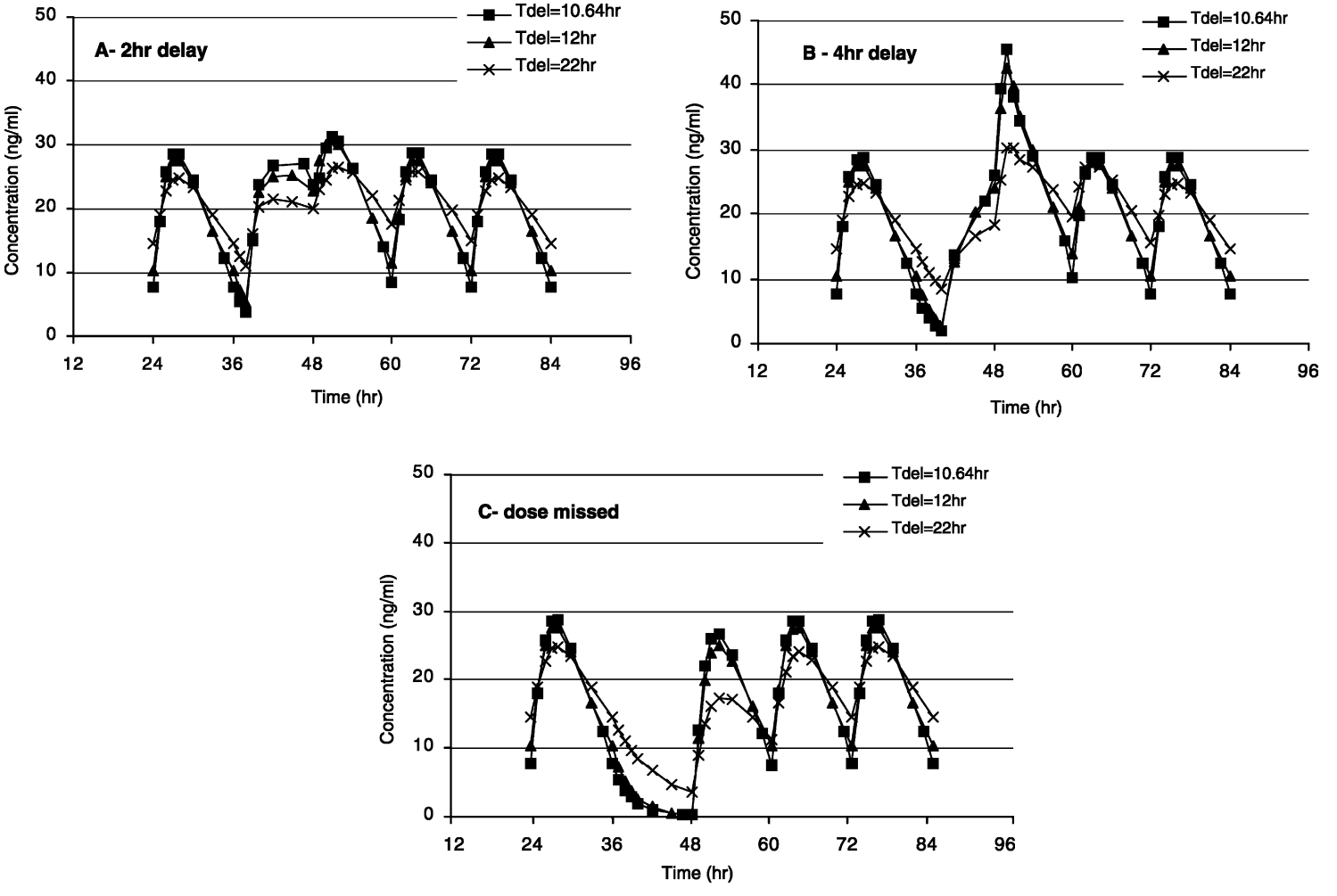

Fig. 2. Predicted steady state blood drug concentration–time profiles for twice a day nifedipine formulations (first order kinetic controlled release systems with different delivery profiles) after 36th hour dose is delayed by 2 h (frame A), 4 h (frame B) or missed (frame C). Dose (D), first order release rate (k_r) and delivery time (t_{del}) are calculated based on drug pharmacokinetics and superposition method with 15–30 ng/ml as desired steady state concentrations.

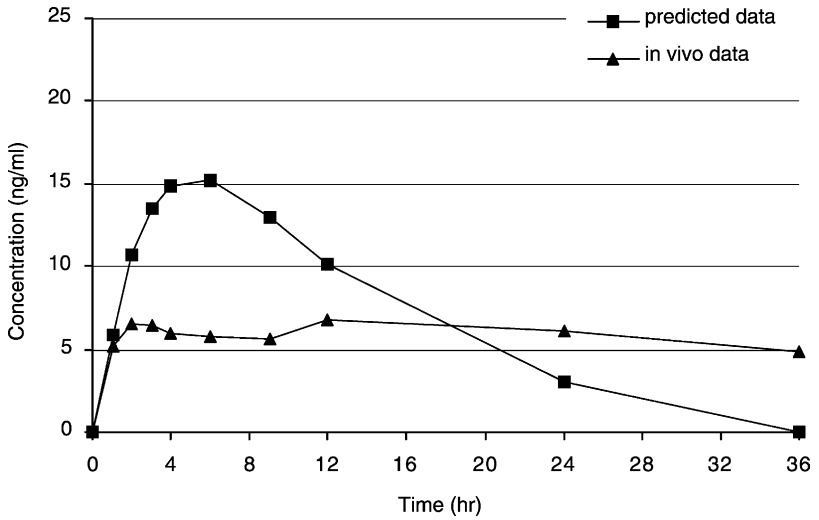

Fig. 3. Mean blood drug concentration–time profile for nifedipine (40 mg) from MUMPS (k_r: 0.1021 h^{-1}) administered *perorally* as single dose in 12 healthy human volunteers in comparison to predicted blood drug level–time profile from desired delivery profile (k_r: 0.1047 h^{-1}).

interval (12 h period) and the remaining 20% (assuming that 90% of the drug is released from the dosage form) would be carried forward and released into next dosing interval (Fig. 1a). The effect of delaying the dose by 2 or 4 h or missing a dose at the steady state concentration levels is also predicted for three selected delivery profiles, viz. k_r of 0.2164, 0.1919 and 0.1047 h^{-1} (Fig. 2). It is clear that the steady state concentration levels resulting from a delivery rate of 0.1047 h^{-1} are more tolerant to delayed dosing compared to higher delivery rates, which are predicted to result in lower trough and higher peak levels due to delayed dose before regaining the steady state levels.

In order to test the hypothesis presented here a multiple unit matrix-based particulate system (MUMPS) was developed for nifedipine (formulation related details not provided here) with a first order drug release rate of 0.1021 h^{-1}. The product (40 mg dose) was

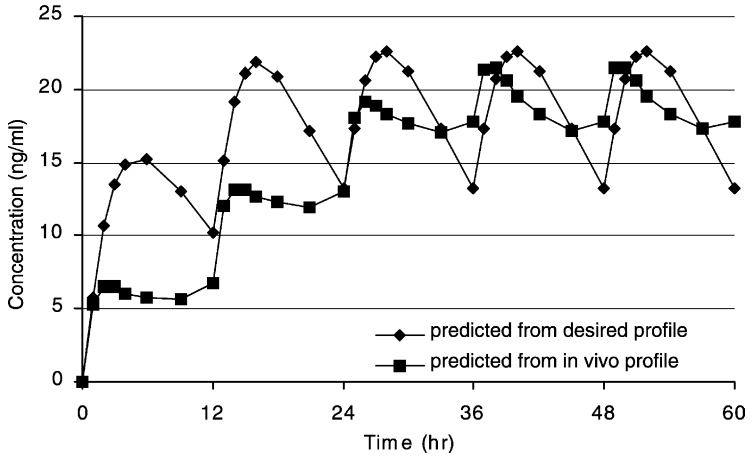

Fig. 4. Mean blood drug concentration–time profile for nifedipine from: in vivo blood drug concentration–time profile obtained after single dose oral administration of nifedipine-MUMPS (=40 mg nifedipine) in 12 healthy human volunteers; and desired drug delivery profile (t_{del}: 10.64 h, k_r: 0.1047 h^{-1}, D: 40 mg, τ: 12 h).

studied in vivo in a single dose pharmacokinetic study performed on 12 healthy human volunteers. The clinical study (details not given here) was approved by the Drug Controller General of India and the Institute's Ethical Committee.

The blood drug concentration–time profile obtained from single 40 mg dose of nifedipine from the MUMPS is shown in Fig. 3 along with the predicted values (Ritschel, 1989) obtained from the desired drug delivery profile. It is evident that the drug formulation resulted in slower drug delivery (lower C_{max}) for a longer period of time (drug concentrations maintained until 36 h post-dose). The difference in two profiles could be because of either a deviation in the delivery rate from the desired rate or may be a consequence of a difference in the actual in vivo pharmacokinetic parameters (absorption kinetics, distribution volume and elimination kinetics) and values taken from literature.

Single dose blood drug concentration–time profile, pharmacokinetic data and the superposition method were used to predict the steady state concentration–time profile and this then compared to the predicted steady state concentration–time profiles from desired drug delivery profile (Figs. 4 and 5). It can be seen that steady state concentrations from observed in vivo data are predicted to result in even lesser fluctuations than expected from the desired 0.1047 h^{-1}delivery profile. However, it would require longer duration to reach steady state concentration levels (about 36 h, i.e. three dosing intervals) as compared to 0.1047 h^{-1} delivery profile. Hence, the observed in vivo profile would be more tolerant to delayed doses but less tolerant to missed doses.

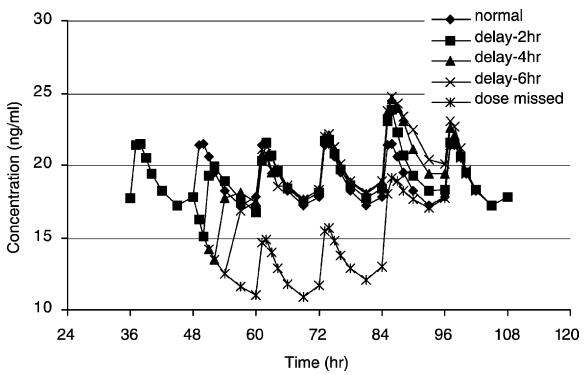

Fig. 5. Effect of delay in dose administration (2, 4 or 6 h) or a missed dose on predicted steady state blood drug concentration–time profiles for nifedipine from twice a day nifedipine-MUMPS (=40 mg NFD, k_r: 0.1021 h^{-1}, t_{del}: 22 h) after oral administration at a dosing interval of 12 h.

6. Conclusions

In the present discussion, a modification in Ritschel's method of design and development for controlled release systems is proposed with the objectives of avoiding sub-therapeutic drug concentrations and reducing the fluctuations in concentration levels at steady state for the drugs with short half-life. Mathematical calculations for two drugs under different hypothetical pharmacokinetic situations show that on increasing drug delivery time from a controlled release system higher than dosing interval, better therapeutic efficacy could be achieved for short half-life drugs. It is also shown with theoretical calculations that by continuous slow drug release over time (longer than the dosing interval), drug delivery systems can be made more tolerant to delay in dose administration providing a higher FI. However, caution is indicated in case of a missed dose where a slower delivery profile would require longer time to regain steady state concentration levels due to the much higher contribution of accumulation effect in achieving steady state levels.

The approach is shown to be effective in obtaining its proposed objectives by applying it to two drugs (glipizide and zidovudine) with data taken from literature. From the results of single dose in vivo pharmacokinetic study with a first order kinetic twice a day nifedipine multi-particulate formulation it is observed that predicted therapeutic efficacy at steady state can be achieved. However, it is important to mention here that although the steady state concentration profile predicted from the single dose in vivo study match values predicted from desired delivery profile calculated theoretically, a multiple dose study is required to confirm and prove conclusively the applicability of proposed modified method.

Hence, the presented approach can be seen as an opportunity to formulate different drugs as controlled release systems in order to improve their therapeutic effectiveness by means of reducing fluctuations, and avoiding sub-therapeutic concentration levels at steady state. The dose requirements for controlled release

systems for short half-life large dose drugs can be reduced that are otherwise considered poor candidates for controlled drug delivery with low possibility of achieving an effective controlled release system using conventional formulation development approaches.

A very important point to note here is that all the assumptions of Ritschel's method, other than $t_{del} < \tau$, are obeyed, i.e. drug release rate is very small compared to intrinsic absorption and distribution rate constant, and the drug does not exhibit dose dependency or saturation kinetics.

It is important that the drug should exhibit good absorption throughout gastrointestinal tract including terminal segments, so that drug absorption during t_{del} (especially when it is as high as 18–20 h) is not limited by total intestinal transit and residence time. However, if the drug exhibits reduced or no absorption in the colon then a mucoadhesive or gastroretentive dosage form would be required to ensure drug delivery for complete duration of t_{del} with in drug absorbable intestinal regions.

References

Benet, L.Z., Oie, S., Schwartz, J.B., 1996. Design and optimization of dosage regimens: pharmacokinetic data. In: Hardman, J.G., Limbird, L.E. (Eds.), Goodman and Gilman's Pharmacological Basis of Therapeutics. McGraw-Hill, New York, pp. 1707–1792.

Boxenbaum, H.G., 1982. Physiological and pharmacokinetic factors affecting performance of sustained release dosage forms. Drug Dev. Ind. Pharm. 8, 1–25.

Chaturvedi, P.R., 1999. Pharmacokinetics. In: Methiowitz, E. (Ed.), Encyclopedia of Controlled Drug Delivery. Wiley, New York, pp. 833–851.

Chien, Y.W., 1982. Controlled release drug administration: logic. In: Novel Drug Delivery Systems: Fundamentals, Developmental Concepts, Biomedical Assessments. Marcel Dekker, New York, pp. 1–11.

Costa, P., Lobo, J.M.S., 2001. Modeling and comparison of dissolution profiles. Eur. J. Pharm. Sci. 13, 123–133.

Grass, IV, G.M., Robinson, J.R., 1990. Sustained- and controlled-release drug delivery systems. In: Banker, G.S., Rhodes, C.T. (Eds.), Modern Pharmaceutics. Marcel Dekker, New York, pp. 635–671.

Kleinbloesem, C.H., van Brummelen, P., van de Linde, J.A., Voogd, P.J., Breimer, D.D., 1984. Nifedipine: kinetics and dynamics in healthy subjects. Clin. Pharmacol. Therap. 35, 742–749.

Kleinbloesem, C.H., van Brummelen, P., Danhof, M., Faber, H., Urquhart, J., Breimer, D.D., 1987. Rate of increase in plasma concentration of nifedipine as a major determinant of its haemodynamic effects in man. Clin. Pharmacol. Therap. 41, 407–412.

Li, V.H.K., Lee, V.H.L., 1987. Influence of drug properties and routes of drug administration on the design of sustained and controlled release systems. In: Robinson, J.R., Lee, V.H.L. (Eds.), Controlled Drug Delivery: Fundamentals and Applications. Marcel Dekker, New York, pp. 3–94.

Martindale: The Extra Pharmacopoeia, 1996. In: Reynolds, J.E.F. (Ed.), Royal Pharmaceutical Society, London, pp. 916–921.

Ritschel, W.A., 1988. Pharmacokinetic and biopharmaceutical aspects in drug delivery. In: Tyle, P. (Ed.), Drug Delivery Devices: Fundamentals and Applications. Marcel Dekker, New York, pp. 19–79.

Ritschel, W.A., 1989. Biopharmaceutic and pharmacokinetic aspects in the design of controlled release peroral drug delivery systems. Drug Dev. Ind. Pharm. 15, 1073–1103.

Ritschel, W.A., Kearns, G.L., 1999. Pharmacokinetic parameters of important drugs. In: Handbook of Basic Pharmacokinetics. American Pharmaceutical Association, Washington, DC, pp. 479–503.

Silber, B.M., Bialer, M., Yacobi, A., 1987. Pharmacokinetic/pharmacodynamic basis of controlled drug delivery. In: Robinson, J.R., Lee, V.H.L. (Eds.), Controlled Drug Delivery: Fundamentals and Applications. Marcel Dekker, New York, pp. 213–251.

Skelly, J.P., Barr, W.H., 1987. Regulatory assessment. In: Robinson, J.R., Lee, V.H.L. (Eds.), Contuhart, J., 1994. Role of patient compliance in clinical pharmacokinetics: review of recent research. Clin. Pharmacokinet. 27, 202–215.

Sorkin, E.M., Clissold, S.P., Brogden, R.N., 1985. Nifedipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in ishaemic heart disease, hypertension and related cardiovascular disorders. Drugs 30, 182–274.

Theeuwes, F., Bayne, W., 1977. Dosage from index: an objective criterion for evaluation of controlled-release drug delivery systems. J. Pharm. Sci. 66, 1388–1392.

Urquhart, J., 1996. How much compliance is enough? Pharm. Res. 13, 10–11.