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Drug release evaluation of diltiazem CR preparations[1]

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Abstract

The objectives of this study were (a) to evaluate the effects of dissolution medium pH and dosage form structural integrity on the release mechanisms and kinetics of Diltiazem HCl (DLTZ) from peroral CR/SR preparations, and (b) to evaluate the CR/SR products comparatively for their drug release parameters. Four marketed CR/SR products of DLTZ were used in the study. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Criteria for selecting the most appropriate model was based on best goodness of fit, smallest sum of squared residuals and F-statistics. Marked differences in dissolution characteristics of three preparations were observed in different dissolution media of pH between 1.2 and 8.0. Based on the best fit of release data to different mathematical models an attempt was made to elucidate the mechanism of drug release. Drug release parameters (duration of drug release, release rate), expected steady state plasma drug concentrations and dosage form index were calculated and compared with theoretical controlled release parameters developed based on the pharmacokinetic characteristics of the drug. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Diltiazem hydrochloride; Evaluation; In vitro drug release; Kinetic models; Release mechanisms

1. Introduction

In the last few decades, many different types of peroral controlled release (CR) formulations have been developed to improve clinical efficacy of the drug and patient compliance. These formulations are designed to deliver the drugs at a controlled and predetermined rate, thus maintaining their therapeutically effective concentrations in systemic circulation for prolonged periods of time. In-vivo performance of these dosage forms depends greatly on their physical and structural properties, and consequently on their drug release

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mechanisms and its kinetics. However, a particular formulation may exhibit different drug release profiles under different chemical environments and in different physical states owing to the nature of excepients and the method of manufacturing. CR formulations with drug release patterns independent of these variable factors, encountered most commonly when administered through per-oral route, are always desirable in order to ensure a reliable in-vivo performance (Gupta and Robinson, 1992).

Though dividing a solid dosage form offers the advantage of ease of administration to the elderly, children or patients who have difficulty in swallowing (Mandal, 1996), it may pose a serious risk in CR formulations where structural integrity plays an important role in controlling their drug release pattern (Simons et al., 1982; Shah et al., 1987) and may result in faster drug release and lower blood levels (Costa et al., 1997). In order to be divisible, a CR/SR dosage form must not loose its controlled release characteristics upon division to avoid dose dumping.

Diltiazem HCl (DLTZ) is a calcium channel blocker widely used for the treatment of angina pectoris, arrhythmias and hypertension (Chaffman and Brogden, 1985). Its short biological half life and thus frequent administration (usually three to four times a day) makes it a potential candidate for CR/SR preparations.

The objective of the present study was to investigate the robustness of drug release from commercially available DLTZ CR/SR preparations for structural integrity and different pH environments in order to evaluate the changes in their drug release properties due to splitting of dosage form and variable pH of GIT. The drug release kinetics and mechanisms, and the effects of pH and dosage form structural integrity exerted thereon were studied. The applicability of different models, used to describe the drug release kinetics, to the selected products was checked in this work. Finally, drug release parameters were calculated and in vivo performance of the products was predicted and then compared to desired values calculated for a theoretically developed controlled release profile for DLTZ.

Table 1
Average saturation solubility of DLTZ in different pH buffers at 37.5°C ($n = 3$)

Buffer (pH)	Solubility (mg/ml) $\pm$ % RSD
HCl buffer (1.2)	658.83 $\pm$ 4.40
Phosphate buffer (5.0)	597.51 $\pm$ 1.54
Phosphate buffer (7.4)	593.20 $\pm$ 3.67
Phosphate buffer (8.0)	511.06 $\pm$ 3.94

% RSD = percentage relative standard deviation

2. Materials and methods

2.1. Materials

DLTZ was obtained as a gift sample from Cheminor Drugs, India. Four DLTZ (90 mg) CR/SR preparations; Dilzem™ SR, Dilcontin™ 90, Diltime™ SR and Dilter™ CD (coded as A, B, C and D, respectively), were purchased from local retail outlets. Three of the products; 'A', 'B', and 'C', are uncoated matrix based tablets, whereas 'D' is a transparent hard gelatin capsule filled with different coloured pellets. All the products were found to contain the labeled amounts of the drug when analyzed by the method described in Indian Pharmacopoeia (Indian Pharmacopoeia, 1996).

2.2. Methods

2.2.1. DLTZ calibration curves

Calibration curves of DLTZ were prepared in different pH buffers (HCl buffer pH 1.2, phos-

Table 2
Analysis of diffusional drug release

Diffusion exponent (n)	Drug release mechanism	Time dependence of release rate
0.5	Fickian diffusion	$t^{-0.5}$
$0.5 < n < 1.0$	Non-Fickian diffusion	t^{n-1}
1.0	Case II transport	t^0 (zero order release)
$n > 1.0$	Super case II transport	t^{n-1}

Table 3
Regression analysis and correlation coefficient values for dissolution data of different products according to various kinetic models

Product	pH	Zero order (Eq. 1)			First order (Eq. 2)			Higuchi model (Eq. 3)			Hixon–Crowell model (Eq. 4)			Baker and Lonsdale model (Eq. 5)		
		r	SSQ	k_0	r	SSQ	k_1	r	SSQ	k_H	r	SSQ	k_{HC}	r	SSQ	k_{BC}
A	1.2	0.8497	4810.7	3.78	−0.9208	0.34	0.002	0.9531	1584.5	2.742	0.8986	2.65	0.002	0.9236	0.0278	0.0002
A	5.0	0.8976	3887.1	4.19	−0.9969	0.02	0.003	0.9791	825.7	3.028	0.9912	0.57	0.004	0.9953	0.0008	0.0003
A	7.4	0.9315	1149.0	2.95	−0.9723	0.02	0.001	0.9909	157.0	2.019	0.9601	0.31	0.001	0.9940	0.0003	0.0001
A	8.0	0.9431	407.0	2.03	−0.9680	0.01	0.001	0.9953	34.7	1.331	0.9605	0.10	0.001	0.9965	0.0001	0.00003
A (H)	7.4	0.9002	3611.7	4.14	−0.9896	0.16	0.002	0.9773	804.3	2.864	0.9783	0.82	0.002	0.9936	0.0035	0.0003
B	1.2	0.8385	5614.8	3.93	−0.9316	0.40	0.002	0.9482	1907.0	2.815	0.9019	3.13	0.002	0.9910	0.0343	0.0003
B	5.0	0.7376	8719.5	4.01	−0.8494	1.19	0.002	0.8816	4260.4	2.666	0.8098	7.07	0.002	0.9101	0.1020	0.0003
B	7.4	0.8044	6658.2	3.97	−0.9324	0.38	0.002	0.9275	2637.5	2.786	0.8890	3.40	0.002	0.9647	0.3221	0.0003
B	8.0	0.8071	3347.2	2.85	−0.8578	0.13	0.001	0.9282	1330.1	1.989	0.8408	1.26	0.001	0.9497	0.0050	0.0001
B (H)	7.4	0.7353	8930.8	3.89	−0.8191	1.05	0.002	0.8715	4545.7	2.620	0.7851	6.84	0.002	0.8114	0.0938	0.0002
C	1.2	0.8289	5848.8	4.00	−0.9255	0.54	0.002	0.9421	2101.0	2.816	0.8940	3.76	0.002	0.9163	0.0479	0.0003
C	5.0	0.8288	6048.4	4.09	−0.9562	0.48	0.003	0.9427	2149.4	2.865	0.9150	3.74	0.003	0.9386	0.0495	0.0003
C	7.4	0.9231	1254.4	3.02	−0.9686	0.03	0.001	0.9898	172.2	1.993	0.9551	0.36	0.001	0.9909	0.0005	0.0001
C	8.0	0.9435	539.9	2.37	−0.9722	0.01	0.001	0.9954	45.1	1.527	0.9639	0.13	0.001	0.9940	0.0000	0.0001
C (H)	7.4	0.9080	2286.2	3.69	−0.9772	0.05	0.001	0.9801	480.7	2.368	0.9590	0.62	0.002	0.9919	0.0014	0.0002
D	1.2	0.7079	11869.6	4.14	−0.9271	0.79	0.003	0.8523	6510.2	2.874	0.8548	7.16	0.003	0.8874	0.0854	0.0003
D	5.0	0.7422	10512.7	4.17	−0.9558	0.25	0.005	0.8786	5338.8	2.939	0.9429	3.58	0.004	0.9479	0.0185	0.0006
D	7.4	0.7254	10759.5	3.90	−0.8287	1.14	0.002	0.8708	5487.8	2.870	0.7951	7.30	0.002	0.8296	0.0883	0.0003
D	8.0	0.7330	11232.6	4.20	−0.9048	0.89	0.003	0.8748	5696.8	2.980	0.8918	6.70	0.003	0.9011	0.0785	0.0004

r, is the correlation coefficient; SSQ is the sum of squared residuals; k is the release rate constant for respective models; and (H) represents halved tablets.
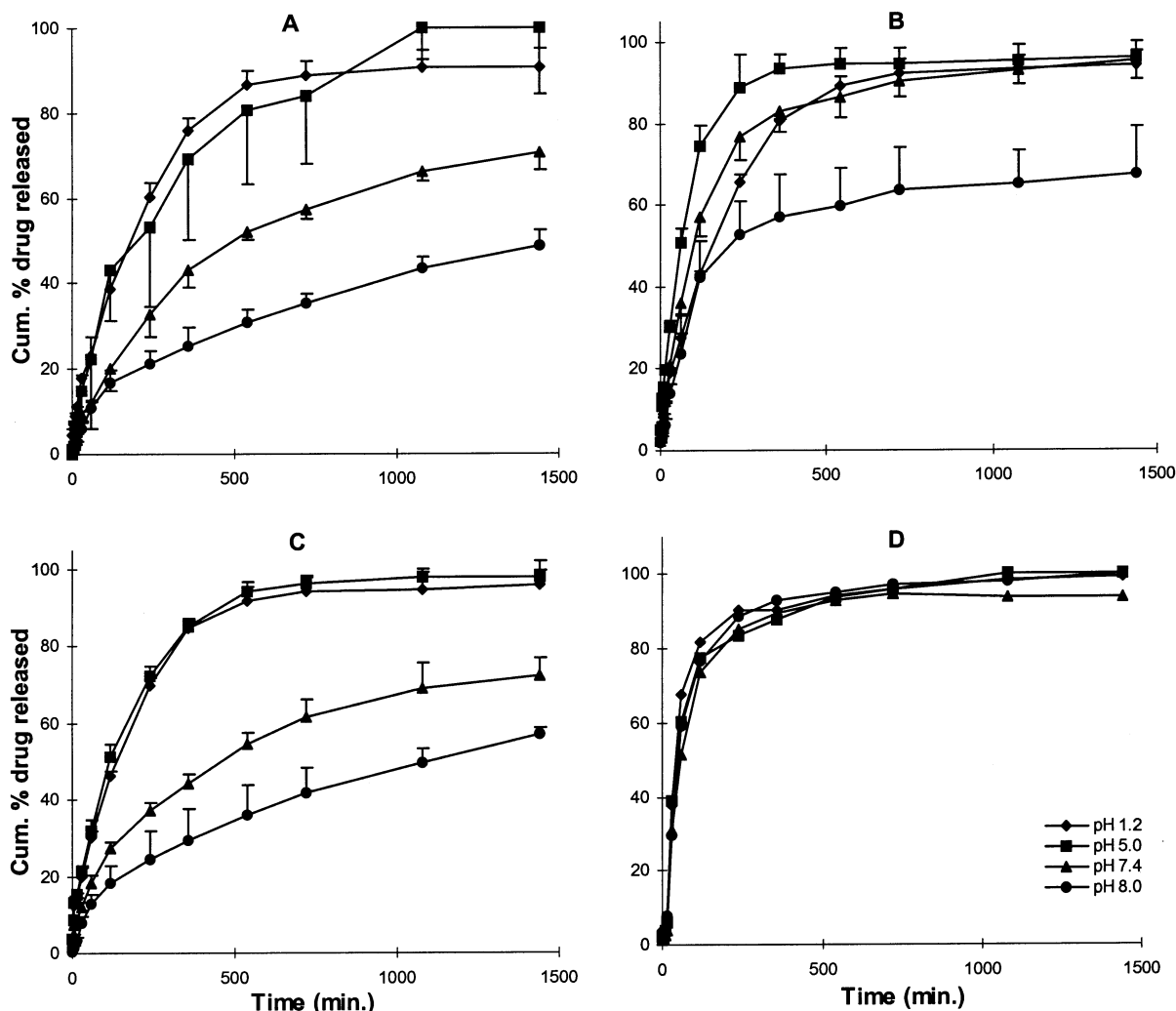
Fig. 1. Drug release profile of CR formulations of DLTZ (A, B, C and D) in different buffers.

phate buffer pH 5.0, phosphate buffer pH 7.4 and phosphate buffer pH 8.0) in the concentration range of 0.5–20 μg/ml. The drug was analyzed spectrophotometrically (Beckman DU 640) at 237 nm (correlation coefficient, $r > 0.9998$ in all four buffers).

2.2.2. DLTZ solubility studies

Solubility of DLTZ was checked in different pH buffers (pH 1.2, 5.0, 7.4 and 8.0). Excess amounts of DLTZ (1.3 g) were taken in teflon lined screw capped glass tubes and 1 ml of buffer was added to each tube ($n = 3$ at each pH level).

The tubes were shaken for 72 h in a shaking water bath (Julabo SW 21, Germany) at 175 rpm and 37.5°C. Saturated drug solutions were centrifuged at 3000 rpm for 5 min and three different volume (4, 6 and 8 μl) samples were withdrawn from each tube. The samples were suitably diluted and concentrations determined by analyzing spectrophotometrically at 237 nm. The results obtained are shown in Table 1. The stability of the drug under the test conditions was established by FT-IR spectroscopy (410 Impact, Nicolet, USA with Omnic 2.1 software) and GC-MS (QP 5000, Shimadzu, Japan with Class 5000 software). The drug did
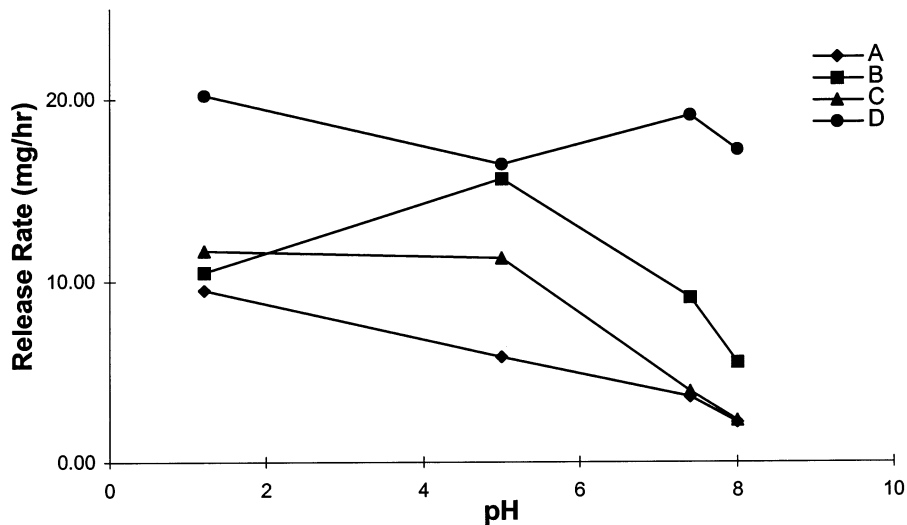
Fig. 2. Drug release rate from different formulations as a function of pH.

not degrade to its des-acetyl derivative during the solubility studies at any of the tested pH levels (data not shown here).

2.2.3. In vitro dissolution studies

Dissolution studies with all the products were performed at four different pH levels (dissolution media volume—1000 ml; $n = 4$ at each pH) using rotating basket method at 100 rpm and $37 \pm 0.5°C$ temperature (Electrolab, TDT-0P, India). The samples (5.0 ml) were withdrawn at different time intervals and analyzed or preserved in refrigerator till analyzed (within 24 h). The amounts of DLTZ released in media at different time points were determined by measuring their absorbance at 237 nm. The detection method was found to be free from excipient interference by comparing the UV scans (200–400 nm) of different products with that of pure drug. In the studies with halved tablets, the tablets were weighed (Mettler Toledo, AG245) and then carefully cut at the middle using a sharp surgical blade. Their weights were checked prior to use. All products were observed for any physical changes occurring during the dissolution study. Final condition of the products, remaining after 24 h of experiment, was examined using a magnifying glass and under a microscope (Leitz Laborlux S, Leica, Germany).

2.2.4. Release models

In order to describe the kinetics of the drug release from the CR formulations various mathematical equations are used. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Najib and Suleiman, 1985). The first order Eq. (2) describes the release from systems where release rate is concentration dependent (Desai et al., 1966; Singh et al., 1967). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion (Eq. (3)). The Hixson–Crowell cube root law (Eq. (4)) describes the release from systems where there is a change in surface area and diameter of the particles or tablets (Hixson and Crowell, 1931; Abdou, 1989).

$$Q_t = k_0 t \tag{1}$$

$$\ln Q_t = \ln Q_0 - k_1 \cdot t \tag{2}$$

$$Q_t = K \cdot S \sqrt{t} = k_H \cdot \sqrt{t} \tag{3}$$

$$\sqrt[3]{Q_0} - \sqrt[3]{Q_t} = k_{HC} \cdot t \tag{4}$$

where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet, S is the surface area of the tablet and k_0, k_1, k_H and k_{HC} are release rate constants for zero order, first order, Higuchi and Hixson–Crowell rate equa-
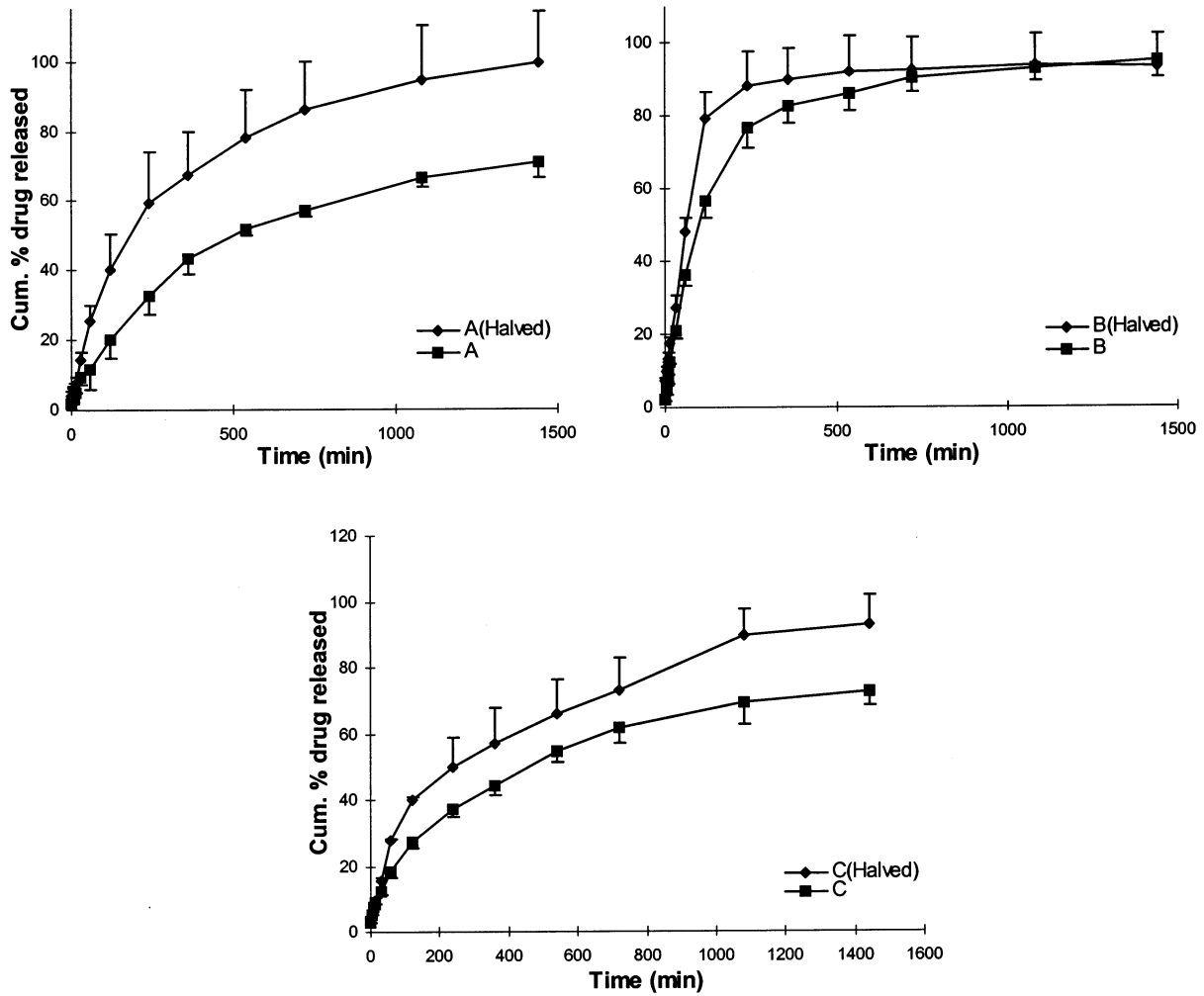
Fig. 3. Effect of structural integrity on the drug release profile of different formulations A, B and C.

tions, respectively. In addition to these basic release models, there are several other models and equations described in the literature to characterize the drug release kinetics and mechanisms from different types of systems (Langenbucher, 1972; Korsenmeyer et al., 1983; Peppas, 1985; Karajgi et al., 1993). Baker and Lonsdale described the release rate of a drug from a spherical matrix as follows (Baker and Lonsdale, 1987; Karajgi et al., 1993):

$$\frac{3}{2}[1 - (1 - F)^{2/3}] - F = k_{\mathrm{BC}} t \tag{5}$$

where, F is the fraction of drug released at time t and k_{BC} is the release rate constant.

In order to define a model which will represent a better fit for the formulations, dissolution data can be further analyzed using Peppas and Korsenmeyer equation (power law) (Korsenmeyer et al., 1983; Ritger and Peppas, 1987a,b):

$$M_t / M_\infty = k \cdot t^n \tag{6}$$

where, M_t is the amount of drug released at time t and M_∞ is the amount released at time $t = \infty$ (usually taken as 24 h for peroral CR drug delivery systems), thus M_t / M_α is the fraction of drug
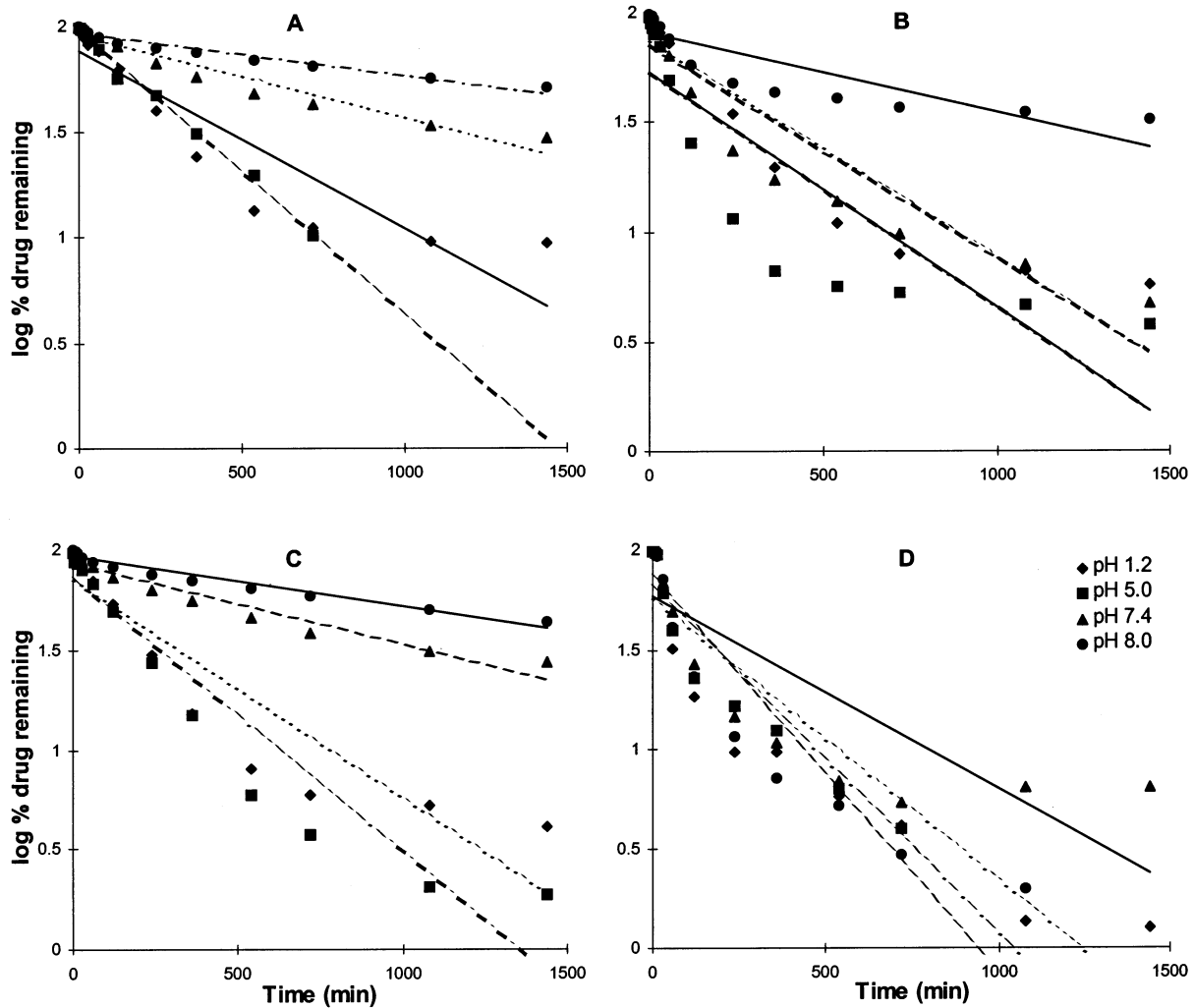
Fig. 4. First order plots for different formulations A, B, C and D.

released at time t, k is kinetic constant, and n is the diffusional exponent. The value of exponent n can be used to characterize the mechanism for both solvent penetration and drug release as abstracted in Table 2 (Peppas, 1985; Schwartz et al., 1968).

Drug release data obtained was subjected to different drug release models in order to establish the drug release mechanisms and kinetics. Criteria for selecting the most appropriate model was based on best goodness of fit and smallest sum of squared residuals (Parab et al., 1986). F-statistic was used to check whether the correlations occurred by chance.

2.2.5. Theoretical performance prediction

A theoretical controlled drug release profile for DLTZ was developed based on desirable target blood concentration and pharmacokinetic characteristics of the drug using the method described by Ritschel (1989). Zero order drug release kinetics (R^0) was chosen for the calculations which would release the drug for a period of time (t_{DEL}) shorter than the selected dosing interval (τ). In order to
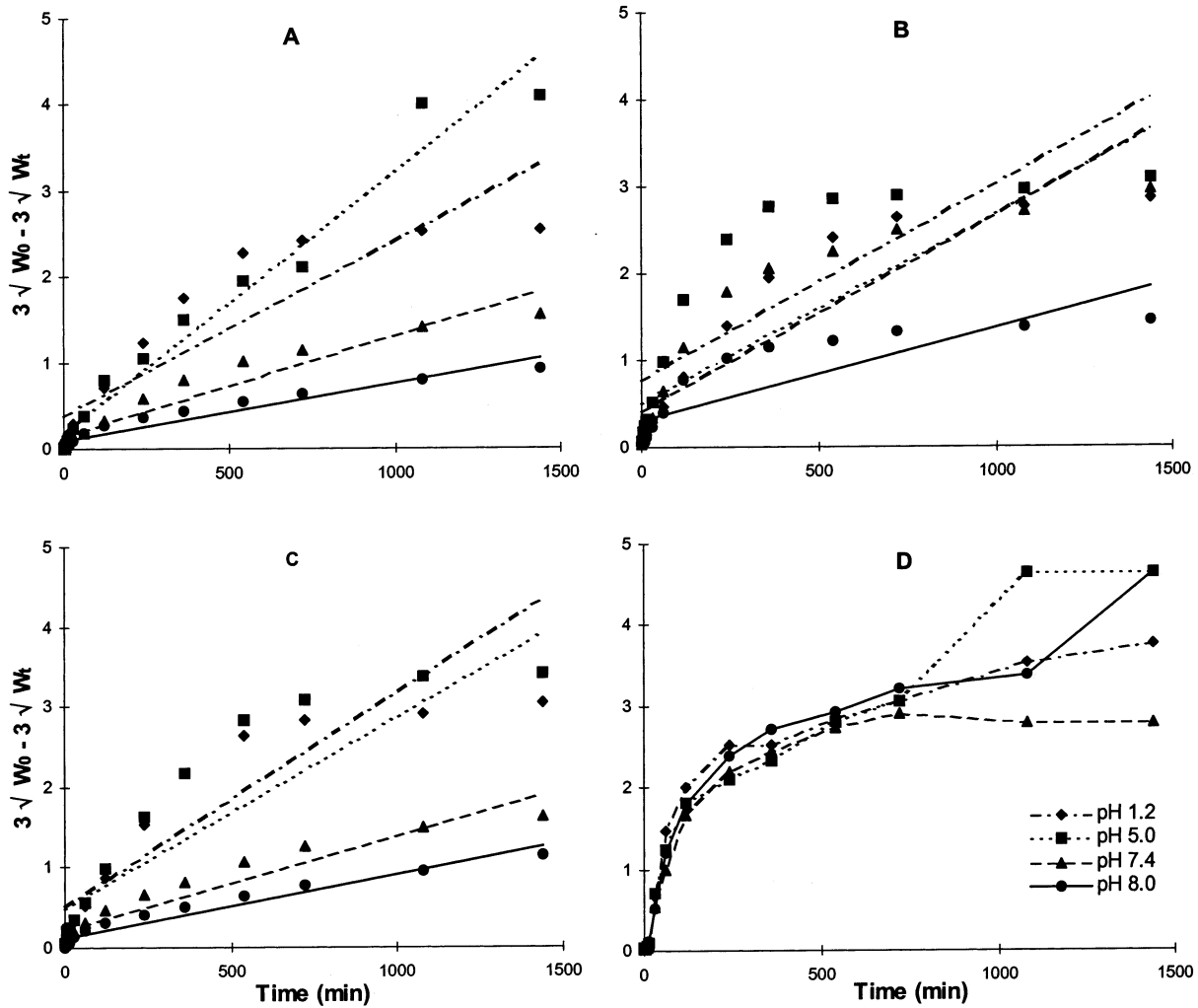
Fig. 5. Hixson–Crowell cube root plots of different formulations A, B, C and D. W_0 = initial drug load at time zero; taken as 100%. W_t = percentage drug undissolved at time t.

predict the steady state drug concentration in blood, the superposition method was used (Ritschel, 1989). The goodness of CR formulation can be evaluated by dosage form index, DI (Gibaldi and Perrier, 1982):

$$DI = C_{SS\,MAX}/C_{SS\,MIN} \qquad (7)$$

The closer the ratio to unity, the less the blood drug concentration fluctuations and the higher the therapeutic efficacy of dosage form.

The drug release parameters (R^0 and t_{DEL}) were calculated for different products from their respective drug release data, and steady state blood drug concentrations were predicted. The values thus obtained were compared to the desired values obtained for theoretically developed controlled drug release profile.

3. Results and discussion

3.1. Effect of pH

The cumulative amounts of DLTZ released versus time plots for all four products are shown in Fig. 1. Although the drug release was sustained
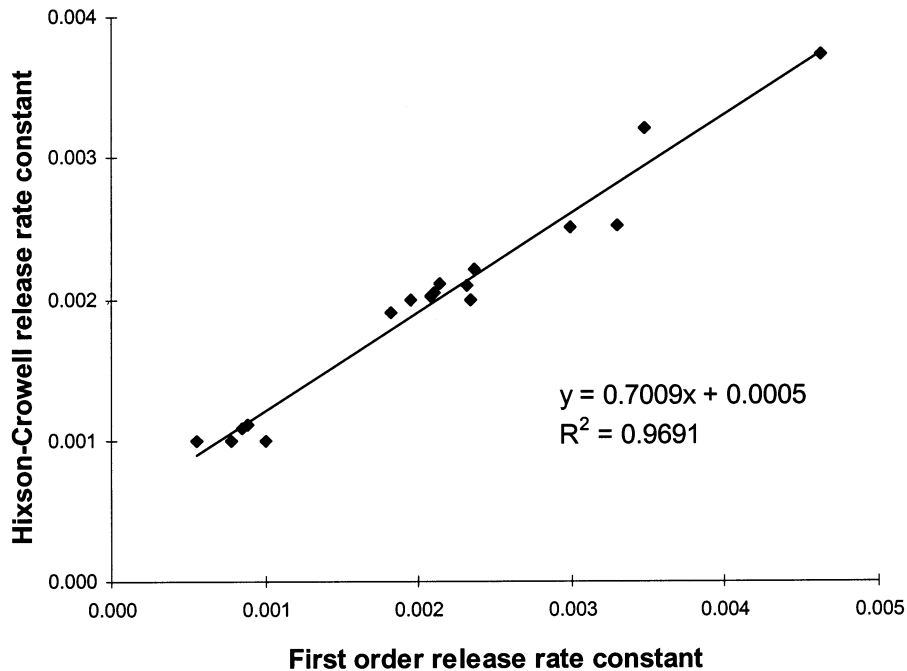
Fig. 6. A plot of first order release rate constant vs Hixson–Crowell cube root release rate constant for all data points.

for all the products in different pH dissolution media (without delaying the release; lag time ≈ 0), a distinct pH-dependency of drug release was observed in case of products 'A', 'B', and 'C'. The drug release was most sustained in pH 8.0 for 'A', 'B', and 'C', whereas 'D' did not show any significant differences in release patterns as a function of pH. Drug release rate (90% of the drug released in mg/time taken for drug release in h), a parameter characterizing the release curves, for different products as a function of pH is shown in Fig. 2. From the solubility studies performed, the solubility of DLTZ was found to be fairly independent of the pH of the media (Table 1). Additionally, the concentration levels expected to be achieved in dissolution media after 100% drug release (≈ 90 μg/ml, i.e. 0.01–0.02% of saturation solubility) are so low that very small saturation solubility differences of the drug at different pH levels can be excluded as the reason for pH dependent drug release from these products. However, depending on the formulation excepients used, a changed mechanism of drug release in different pH buffers may be a reason

for pH-dependent behaviour of the products. This was supported by the observation that at pH levels 1.2 and 5.0, tablets ('A', 'B', and 'C') eroded/dissolved either completely or near to completion forming a very loose porous mass sticking to the basket mesh at the end of dissolution experiment. Whereas, at pH 7.4 and 8.0, tablets retained their shape and formed a loose and seemingly exhausted matrix at the end of dissolution study. These observations, coupled with the observation that relatively lower amounts of drug were released from 'A', 'B', and 'C' at pH 7.4 and 8.0 (Fig. 1), suggest that the tablets may be erodible matrix type of systems with relatively slower erosion rates at higher pH levels. In the case of 'D', pellets did not disintegrate, dissolve or swell in any of the pH media and remained consistently spherical through out the dissolution study. However, almost all the pellets remaining at the end, showed a crack on the surface which pierced into the structure of pellets (not shown). All these observations suggest a pH-independent membrane controlled diffusion for drug release from 'D'.

3.2. Effect of dosage form structural integrity

The dissolution data obtained from halved tablets (Products 'A', 'B', and 'C') in pH 7.4 was compared to that obtained from intact tablets in the same pH. The average dissolution data indicated that for 'A' and 'C', in-vitro release of DLTZ was consistent with the intended sustained release tablets only when the tablets were intact. The split tablets showed a consistently higher release profile over time (Fig. 3) due to broken matrix structure of the tablets and increased surface area exposed to the dissolution media. Product 'B', did not show any significant effect of integrity on total amount of drug released, however, the rate of release was found to be significantly higher for the halved tablet. For all three products, standard deviation associated with the dissolution data of the split tablets was also higher than that of the intact tablets (Fig. 3), which shows that the split tablets had higher variability as compared to the intact tablets.

Table 4
Curve fitting of dissolution data to Korsenmeyer and Peppas Power model (Eq. 6)

Product	pH	n	r	k
A	1.2	0.5181	0.9901	2.911
A	5.0	0.7809	0.9741	0.598
A	7.4	0.5995	0.9959	1.102
A	8.0	0.7312	0.9812	0.337
A (H)	7.4	0.5669	0.9883	2.053
B	1.2	0.5706	0.9844	2.296
B	5.0	0.4515	0.9623	5.630
B	7.4	0.5680	0.9727	2.487
B	8.0	0.5991	0.9733	1.410
B (H)	7.4	0.4401	0.9898	2.521
C	1.2	0.4940	0.9807	3.802
C	5.0	0.4872	0.9793	4.102
C	7.4	0.4931	0.9957	2.373
C	8.0	0.6963	0.9933	0.493
C (H)	7.4	0.5148	0.9644	5.659
D	1.2	0.6529	0.9637	1.679
D	5.0	0.7063	0.9738	1.211
D	7.4	0.7592	0.9604	0.837
D	8.0	0.7336	0.9525	1.049

(H) indicates halved tablets.
n is the diffusion exponent; r the correlation coefficient; and k the kinetic constant.

Table 5
Comparative evaluation of drug release from selected products in pH 7.4 with a theoretically developed controlled drug release profile

Product[a]	CR parameters[b]			
	t_{DEL}^{c} (h)	R^{0} (mg/h)	C_{SS} (μg/ml)	DI
A	16.00	3.58	0.047-0.063	1.34
A (H)	14.85	5.45	0.067-0.089	1.33
B	8.55	9.02	0.046-0.084	1.83
B (H)	3.05	24.80	0.027-0.128	4.74
C	14.91	3.94	0.048-0.064	1.33
C (H)	18.00	4.96	0.070-0.096	1.37
D	4.00	19.17	0.031-0.098	3.16
T[d]	6.71	14.00	0.03- 0.20	2.5

DI is the dosage form index; and (H) represents halved tablet.
[a] Products with 90 mg DLTZ per unit and recommended dosage regimen of twice a day.
[b] Parameters calculated from the drug release profile of different products.
[c] t_{DEL} is the time taken for release of 90% of the total drug released in 24 h.
[d] Theoretical CR profile (T), Parameters calculated based on pharmacokinetic characteristics of the drug at a target concentration of 0.05–0.125 μg/ml which gives a dose of 95.66 mg DLTZ at a dosing interval of 12 h.

3.3. Drug release kinetics

The curvilinear nature of the cumulative % drug released versus time plots (Fig. 1) suggest that none of the products follow zero order drug release kinetics which is confirmed by poor correlation coefficients and a very high sum of squared residuals (SSQ) in all the cases (Table 3). Similarly, non-linearity of the Higuchian plots, poor correlations of the data and high value of SSQ for all the products except 'A', suggest non-applicability of Higuchi model (Table 3).

The dissolution data from all the products was plotted in accordance with the first order equation (Fig. 4). As seen in the figure, a linear relationship was obtained for 'A', 'B', and 'C' indicating that the drug release was matrix drug load dependent. All these three products showed higher correlations and better fit at pH 7.4 and 8.0 as compared to those at pH 1.2 and 5.0 (Table 3) indicating different release kinetics predominating at different pH levels. Dissolution data from 'D' did not

fit to the first order equation which suggests a drug load independent release kinetics. However, this observation could also be due to the presence of a heterogeneous multiparticulate type of system (different coloured pellets releasing the drug at different rates) where more than one type of release mechanisms may be operational from different coloured pellets.

The dissolution data was also plotted in accordance with Hixson–Crowell cube root law (Fig. 5). Applicability of 'A' and 'C' to the equation indicated a change in surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time. The dissolution rate constants obtained from the first order plots (k_1) were similar to those obtained from Hixson–Crowell plots (k_{HC}) for 'A', 'B', and 'C'. A linear relationship was obtained between 'k_1' and 'k_{HC}' with high correlation coefficient value (Fig. 6), indicating that the change in diffusional path length alongwith the change in diameter and surface of the tablets during dissolution process follows cube root law.

When the Baker and Lonsdale model (Eq. (5)) was applied to the dissolution data, linear plots were obtained for 'A', 'B', and 'C'. Thus it can be assumed that the drug release from these three products took place by dissolution and diffusion through water filled channels. However, once again the correlation coefficients were higher in pH 7.4 and 8.0 than 1.2 and 5.0. The data from product 'D' exhibited poor correlations.

Dissolution data of halved tablets 'A', 'B', and 'C' in pH 7.4 buffer fit to different models almost in the same way as that of respective intact tablets (Table 3). The observation is attributable to the fact that the formulation materials remain same in both intact and halved tablets of any particular formulation.

F-observed value, obtained from F-statistics, was found to be greater than F-critical values (assuming a single tailed test at $\propto = 0.05$ and $v_1 = 1$ and $v_2 = n - (k + 1)$; n is the number of data points and k is the number of variables) for all the cases.

3.4. Curve fitting

Based on Eq. (6), drug release data from different products was analyzed and the results confirmed that products 'B', and 'C' followed Fickian kinetics at all tested pH levels with $n = 0.5$–0.6 (Table 4). In case of product 'A', a shift in the diffusion kinetics from Fickian to non-Fickian transport at higher pH levels was observed, whereas, 'D' exhibited non-Fickian (anomalous) diffusion behaviour (n > 0.6) independent of dissolution media pH. No particular reason could be ascribed to the observed shift in the diffusion kinetics for 'A' since the formulation components of the product are not known. Split tablets showed similar diffusion kinetics as their respective intact forms, suggesting that the release mechanisms did not change due to splitting of the tablets though the release was faster with the split tablets.

3.5. Performance evaluation of the products

Drug release parameters obtained for different products, intact as well as halved, are presented in Table 5. As seen in the table, predicted steady state blood drug concentrations for all four products lie within the therapeutically effective concentration range even though t_{DEL} and R^0 values differed from the corresponding values calculated theoretically. DI ratios were always found to be lower than therapeutic index of the drug (i.e. 6.67) and desirably close to unity for 'A', 'B', and 'C' predicting lesser blood drug concentration fluctuations at steady state. For halved tablets, 'A' and 'C' showed higher release rates with relatively higher expected blood drug concentrations but DI was found to be in close resemblance to values for intact tablets. Further, the expected steady state concentrations were within desirable concentration window for both of these products indicating their safety even upon splitting. Therapeutic efficacy of halved 'B', was however doubtful due to very high drug release rate and large fluctuations in the blood drug concentrations at steady state as indicated by the high DI value.

4. Conclusions

From the results obtained, it can be inferred that in-vitro drug release process from three of the tested products is pH dependent and only one product showed pH independent release behaviour. The products showed large brand to brand variations in the release patterns. Splitting of the tablets not only gave faster drug release, unlike the intended slower release profiles, but also increased the variability thereby reducing the reproducibility. The kinetics of drug release from the selected products at different pH levels were established and drug release was found to be Fickian diffusion controlled from 'B', and 'C', whereas, it followed non-Fickian anomalous diffusion patterns from 'A' and 'D'. However, the value of diffusion exponent '*n*' changed with the change in pH of dissolution media. It was also shown that change in diffusional path length during the dissolution process is proportional to the change in surface area and diameter of the tablets and follows Hixson–Crowell cube root law. The data from split tablets showed almost similar goodness of fit to different models as compared to respective intact tablets. Predicted plasma drug concentrations in the case of all four products were found to match the desired characteristics of a theoretically designed controlled drug release profile. The values of DI calculated for the three products were less than the desired value calculated theoretically and approached unity suggesting their safety. The drug release parameters were not adversely affected due to splitting of the products except for the product 'B'.

It is concluded from the study that pH of the dissolution media as well as structural integrity of dosage form play a significant role in describing the in-vitro drug release and predicted in-vivo performance of the CR dosage formulations.

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