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Drug release evaluation of Diltiazem HCl CR preparations

ANURAG SOOD AND RAMESH PANCHAGNULA

Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, Phase X, Mohali 160 062, India

The objectives of the 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 predict the steady state plasma drug levels of DLTZ based on the pharmacokinetic properties of the drug and perform a comparative evaluation of CR/SR formulations. Four marketed CR/SR formulations of DLTZ (coded as A, B, C and D) were used in the study. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. A theoretical CR formulation of DLTZ was developed and drug release parameters (release rate, R^0 and delivery time, t_{DEL}) were calculated based on desirable target blood concentration and pharmacokinetic characteristics of the drug (Ritschel, 1989). The goodness of CR formulation was evaluated by dosage form index, DI. Marked differences in dissolution characteristics of three preparations were observed in different dissolution medium of pH between 1.2 and 8.0. Structural integrity of the formulations proved to be an important requirement for two of the formulations with split tablets showing consistently higher release profiles. Based on the goodness of fit of release data to different mathematical models the drug release kinetics as well as mechanisms appeared to be affected by the pH of the dissolution media. Similar parameters were calculated for different formulations from their respective drug release data and then compared to the theoretically calculated values. The results show that even though the drug release parameters (R^0 and t_{DEL}) from different formulations varied significantly from desired values, dosage form index values for three formulations were well within the desirable limits (less than therapeutic index of the drug, i.e., 6.67) and close to unity predicting minimal plasma drug concentration fluctuations at steady state (Table 1). 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. The possibility of using *in-vitro* dissolution data to predict the *in-vivo* performance of the formulations has also been demonstrated.

Table 1: Comparative evaluation of drug release from selected formulations in pH 7.4 with a theoretically developed CR formulation.

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

a 90 mg DLTZ preparations and recommended dosage regimen is twice a day, i.e., τ = 12 hr.;
b Parameters calculated based on the drug release profile of different formulations;
c t_{DEL} = time taken for release of 90 % of the total drug released in 24 hr.;
d Theoretical formulation (T);
DI Dosage form index; and
(H) Halved tablet.

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