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Research Article

PREPARATION AND EVALUATION OF CONTROLLED RELEASE DILTIAZEM HCl TABLETS BY USING ETHYL CELLULOSE AND ETHYLENE-VINYL ACETATE POLYMERS AS RETARDANT

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ABSTRACT

The aim of this study was to prepare and evaluate controlled release tablets of Diltiazem by a wet granulation method using Ethyl cellulose and Ethylene vinyl acetate as a retardant and chloroform (solvent for the polymer) as granulating fluid. The polymers were used at 2, 5 and 10 % concentrations in the formulae. Diltiazem release from the matrix tablets was slow and spread over a period of 12 h depending on the type of the polymer and its concentration. Based on values of correlation coefficient the drug release was found to be by diffusion mechanism following zero order kinetics. From 'n' values, tablets prepared with Ethylene vinyl acetate and ethyl cellulose followed Fickian and non-fickian diffusion mechanisms respectively. Among all the formulations CRF4 exhibited better controlled release for 12 hours, when compared to marketed tablets.

Keywords: Controlled Release Tablets, Diltiazem Hydrochloride, Ethyl Cellulose and Ethyl Vinyl Acetate

INTRODUUCTION

In the last two decades, controlled release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Controlled release drug delivery systems are those formulations designed to release an active ingredient at rates, which differ significantly from their corresponding conventional dosage forms. The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of the drug to a tissue.

Drug release from these systems should be at a desired rate, predictable and reproducible. Among the various approaches/methods for preparation of controlled and sustained release drug delivery systems, preparation of the drug embedded matrix is one of the least complicated and industrially used approaches for oral controlled release (CR). Polymer used as release retarding and a rate controlling matrix former, placed a vital role in regulating drug delivery form the controlled release tablets.

A wide range of polymeric substances are available as release retarding matrix formers viz., CMC, HPMC, MC, alginates, ethyl cellulose, Ethylene vinyl acetate co-polymers, eudragits etc., have been used in the design of controlled release tablets of various drugs. In the present study a comparative evaluation of two polymers namely ethyl cellulose (EC) and ethylene-vinyl acetate (EVA) as a release retardant and rate controlling matrix formers in the design of controlled release tablets of diltiazem HCl.

Diltiazem HCl is a calcium channel blocker, which has been used in the treatment of various

cardiovascular disorders, particularly angina pectoris and systemic Hypertension[1]. It has a short biological half-life of about 3.5 h and it is rapidly eliminated. The oral bioavailability of diltiazem is 40% in humans[3]. Because of its low bioavailability and short biological half-life attempts have been made to develop sustained release products with extended clinical effects and a reduced dosing frequency[4]. As diltiazem HCl is a highly water soluble drug, its formulation into SR products is rather difficult. The objective of the present study reveals that comparative evaluation of ethyl cellulose (EC) and ethylene-vinyl acetate (EVA) as a release retardant and a rate controlling matrix formers in the design of controlled release tablets of diltiazem HCl, evaluation of drug release kinetics and mechanism of the controlled release matrix tablets.

MATERIALS AND METHODS

Materials

Diltiazem HCl donated by M/s. Micro Labs Ltd., Pondicherry. EVA, EC, Lactose, dicalcium phosphate, talc, and magnesium Stearate were purchased from S.D. Fine Chemicals (Mumbai, INDIA).

Preparation of the Tablets

Matrix tablets each containing 90 mg of Diltiazem HCl were prepared by employing EVA and the EC in different concentrations. The tablets were prepared as per the formulae given in Table 1. The required quantities of medicament and matrix materials were mixed thoroughly in a mortar by following geometric dilution technique. The binder solution (chloroform) was added and mixed thoroughly to form a dough mass. The mass passed through the mesh no. 12 to obtain wet granules. The wet granules were dried at 60 (for 2 h. The dried granules were passed through the mesh no. 16 to break the aggregates. The lubricants talc (2%) and magnesium stearate (2%) were passed through the mesh no. 100 onto the dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary multi-station tablet punching machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 8 - 10 kg/sq. cm using 9 mm round and flat punches.

EVALUATION OF TABLETS

Estimation of Diltiazem in Tablets:

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 50 mg of the medicament was taken into the boiling test tube and extracted with 4 x 10 ml quantities of methanol. The methanolic extracts were collected into 50 ml volumetric flask and the volume was made up to 50 ml with methanol. The solution was subsequently diluted and assayed for the drug content by the method discussed earlier.

Hardness: Hardness of the tablets was tested using a Monsanto Hardness Tester.

Friability: Friability of the tablets was determined in a Roche Friabilator.

Disintegration time: Disintegration times were determined in Thermionic Tablet Disintegration Test Machine using dissolution fluids 0.1 N HCl, distilled water, pH 7.4 phosphate buffers (Table2).

In vitro Dissolution studies

Drug release from the CR tablets prepared was studied using 6 station dissolution test apparatus (Electro lab) employing a paddle stirrer at 50 rpm and at 37±1°C. Distilled water (900 ml) used as dissolution fluid. Samples of 5 ml of each were withdrawn at different time intervals over a period of 24 h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 240 nm by using an Elico double beam UV - spectrophotometer. Prepared Diltiazem CR tablets compared with Diltiazem SR and DTM 90 SR Tablets (commercial) were also studied. The drug release experiments were conducted in triplicate.

RESULTS AND DISCUSSION

Matrix tablets of each containing 90 mg of Diltiazem HCl prepared by employing the EC and EVA as matrix formers and using chloroform (solvent for the polymer) as granulating fluid. The polymer (EC or EVA) was used at 2,5,10 % concentrations in the formula. The tablets were prepared by the wet granulation method. Hardness of the tablets was in the range 8-10 Kg/Sq.cm. Weight loss in the friability test was less than 0.8 % in all the cases. All the matrix tablets prepared contained Diltiazem HCl within 100±4% of the label claim. All the tablets prepared were found to be Non-disintegrating in water and acidic pH-1.2 and alkaline pH-7.4 fluids. All the matrix tablets were prepared by employing the EC and EVA was of good quality with regard to drug content, hardness and friability. As the matrix prepared were non-disintegrating in acidic and alkaline fluids, they are considered suitable for oral controlled release. Drug release profiles of the matrix tablets and commercial sustained release formulation were given in Table 3, and shown in Fig 1-6. The

drug release parameters of all the tablets prepared are summarized in Table 5. Diltiazem release from the matrix tablets prepared was slow and spread over a period of 12 h depended on the polymer and its concentration used in the tablets. The release data were analyzed as per zero order, first order, and higuchi and peppas equation models. The correlation coefficient values Obtained in different models shown in Table 4. Based on r^2 values of zero order, first order models indicated that the drug release from the majority of matrix tablets followed zero order kinetics. Higuchi plots were found to be linear (r^2 > 0.9524) with all the matrix tablets indicating that the drug release follows a diffusion controlled. When the release data were analyzed as per peppas equation ,the release exponent 'n' was found in the range 0.2857 – 0.4695 with all the tablets prepared employing EVA indicating Fickian diffusion as the mechanism from these tablets. Whereas in the case of tablets prepared with EC, the 'n' value was in the range 0.9527 -0.9725 indicating Non-Fickian (anomalous) diffusion as the release mechanism from the tablets prepared with EC.

CONCLUSIONS

Diltiazem HCl matrix tablets were prepared by the wet granulation method using Ethyl cellulose (EC) and Ethyl vinyl acetate (EVA) as matrix formers and using chloroform (solvent for the polymer) as granulating fluid. The polymer (EC or EVA) was used at 2, 5 and 10 % concentrations in the formulae. Diltiazem release from the matrix tablets was slow and spread over a period of 12 h and depended on the polymer and its concentration used in the tablets. Diltiazem HCl release from the matrix tablets was diffusion controlled and followed zero order kinetics. Fickian diffusion was the drug release mechanism from matrix tablets prepared with EVA and non-fickian diffusion in the case of tablets with EC. Among all the formulations CRF4 exhibited good release over 12 hours.

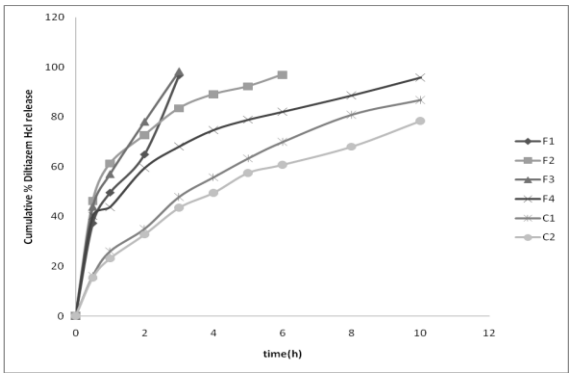

Fig.1: Drug release profiles of Diltiazem CR tablets prepared employing EVA and commercial tablets

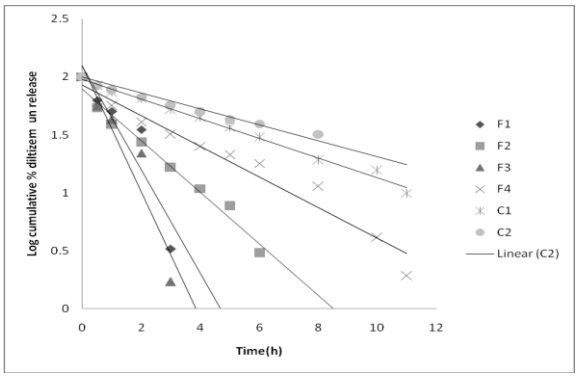

Fig.3: First Order Plots of Drug release from Diltiazem CR tablets prepared employing EVA and commercial tablets.

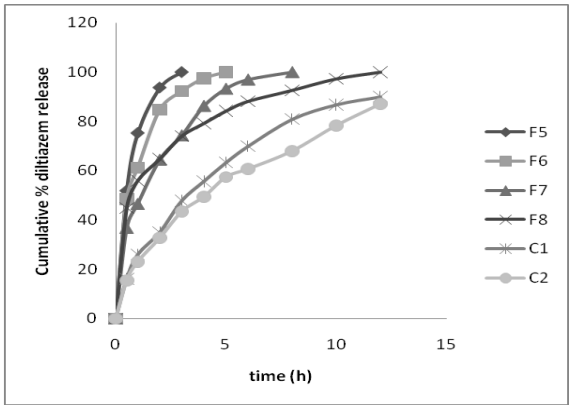

Fig.2: Drug release profiles of Diltiazem CR tablets prepared employing EC and commercial tablets

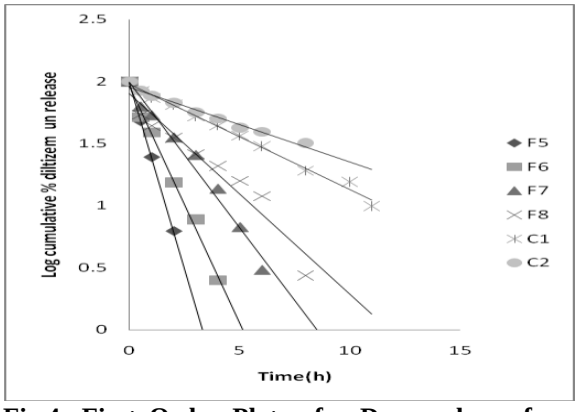

Fig.4: First Order Plots of Drug release from Diltiazem CR tablets prepared employing the EC and commercial tablets.

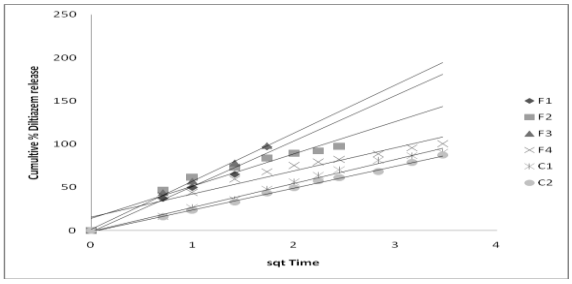

Fig.5: Percent released Vs Square Root Time Plots of Diltiazem CR tablets prepared employing EVA and commercial tablets.

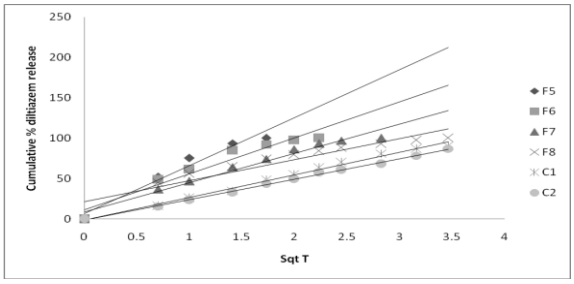

Fig.6: Percent released Vs Square Root Time Plots of Diltiazem CR tablets prepared employing EC and commercial tablets.

Table 1: Formulae of Diltiazem CR Tablets Prepared Employing EC, EVA

Name of the Ingredients(mg/tablet)	Formulation							
	CRF1	**CRF2**	**CRF3**	**CRF4**	**CRF5**	**CRF6**	**CRF7**	**CRF8**
Diltiazem HCL	90	90	90	90	90	90	90	90
Ethyl cellulose	-	-	-	-	4.2	10.5	21	10.5
Ethylene Vinyl acetate	4.2	10.5	21	10.5	-	-	-	-
Lactose	107.4	101.1	90.6	----	107.4	101.1	90.6	----
DicalciumPhosphate	----	----	----	101.1	----	----	----	101.1
Talc	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
Magnesium Stearate	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
Chloroform	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Weight of the tablet(mg)	210	210	210	210	210	210	210	210

Table2: Drug Content, Hardness, friability, and disintegration Time of the diltiazem CR Tablets Prepared Employing EVA, EC

Formulation	Diltiazem content(mg/tab)	Friability (%)	Disintegration Time	Hardness(KG/Sq.cm)
CRF_1	89.6	0.3	**	10.0
CRF_2	89.8	0.1	**	8.0
CRF_3	90.2	0.2	**	9.5
CRF_4	90.7	0.1	**	8.5
CRF_5	90.5	0.1	**	9.0
CRF_6	90.2	0.2	**	8.5
CRF_7	89.9	0.3	**	9.0
CRF_8	89.7	0.3	**	8.0

** Non-Disintegrating

Table 4: Correlation coefficient (r^2) values of Zero Order, First Order, Higuchi and Peppas Models of Diltiazem CR Tablets and commercial tablets

Formulation	'r^2' Values			
	Zero Order	First Order	Higuchi	Peppas
CR F1	0.9190	0.9685	0.9919	0.9757
CR F2	0.9801	0.8667	0.9524	0.9957
CR F3	0.9188	0.9472	0.9823	0.9984
CR F4	0.9684	0.8989	0.9635	0.9963
CR F5	0.9880	0.8968	0.9646	0.9922
CR F6	0.9958	0.8919	0.9547	0.9927
CR F7	0.9839	0.9282	0.9725	0.9972
CR F8	0.9701	0.8873	0.9527	0.9950
C1	0.9985	0.9471	0.9954	0.9939
C2	0.9919	0.9570	0.9989	0.9979

Table 5: Release Characteristics of Diltiazem CR Tablets and commercial tablets

Formulation	**Polymer concentration (%)**	**T_{50}(h)**	**T_{90}(h)**	**K_1 hr^{-1}**	**'n' in Peppas Equation**
CR F1	2	1.12	2.40	0.9452	0.4695
CR F2	5	1	4.30	0.5329	0.2857
CR F3	10	1	2.40	1.0732	0.4467
CR F4	5	2.0	8.40	0.2953	0.2974
CR F5	2	0.30	1.40	1.4193	0.3734
CR F6	5	0.50	2.30	0.8569	0.3640
CR F7	10	1.15	4.30	0.5679	0.3882
CR F8	5	0.45	6.50	0.3705	0.2965
C1	-	3.12	12	0.1920	0.4261
C2	-	4.96	13	0.1532	0.4825

Table 3: Cumulative % drug released of CRF1 to CRF8

Formulation	1hr	2hr	3hr	4hr	5hr	6hr	7hr	8hr	9hr	10hr	11hr	12hr
CRF_1	49.58	64.92	96.72	100.0	---	---	---	---	---	---	---	---
CRF_2	61.35	72.76	83.51	89.10	92.30	96.98	100.0	---	---	---	---	---
CRF_3	57.00	78.03	98.29	100.00	---	---	---	---	---	---	---	---
CRF_4	43.79	59.51	68.11	74.78	78.89	82.09	85.75	88.67	91.51	95.90	98.09	100.00
CRF_5	75.28	93.72	100.0	---	---	---	---	---	---	---	---	---
CRF_6	61.17	84.67	92.24	97.50	100.0	---	---	---	---	---	---	---
CRF_7	46.53	64.45	74.33	86.28	93.26	96.96	100.0	---	---	---	---	---
CRF_8	55.95	64.72	74.05	79.17	84.19	88.13	92.61	97.27	100.0	---	---	---
C1	25.98	35.02	47.86	55.74	63.32	69.93	74.5	80.90	83.8	86.84	88	90.05
C2	23.09	32.72	43.45	49.45	57.45	60.72	65.7	67.99	72.1	78.36	85.6	87.08

C1 and C2 are market products.

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