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Research Article

EVALUATION OF DRUG RELEASE RETARDANT POTENTIAL OF *OCIMUM TENUIFLORUM* LINN. SEED MUCILAGE ISOLATED BY DEFATTING METHOD

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ABSTRACT

Sustained release dosage forms are advantageous as they reduce frequency of administration and side effects of drug and thus improve patient compliance. The present study aimed to evaluate the drug release retardant potential of *Ocimum Tenuiflorum* Linn seed mucilage isolated by defatting method. Diltiazem HCl a calcium channel blocker, freely water soluble drug having $t_{1/2}$ 3-5 h was selected and matrix tablet formulations were prepared. The release retardant polymer under study was used alone and in combination with povidone a commercially used release retardant polymer in 1:1 ratio. The matrix tablet formulations were evaluated for various parameters and in vitro drug release profile. The drug release kinetics profile from prepared formulations was compared with drug release profile of marketed sustained release formulation of diltiazem HCl. Out of seven formulations prepared F1, F3, F4, F5 were found to sustained drug release for more than 7 h. All the formulations except F6 and F7 showed extended drug release for more than 6 h. All the formulations when fitted to drug release kinetics showed Hixon-Crowel pattern. The seed mucilage of Ocimum Tenuiflorum Linn has shown good release retardant potential when used in combination with povidone.

Keywords: Diltiazem HCl, Seed mucilage, Release retardant, Matrix tablet.

INTRODUCTION

Natural polymers remain attractive primarily because they are inexpensive, readily available, capable of multitude of chemical modifications and potentially degradable and compatible due to their origin. Various natural gums and mucilages have been examined as polymers for sustained drug release, in the last few decades. The physical and structural properties and the drug release mechanisms and kinetics of these sustained release preparations determine the in vivo performance of these dosage forms[1].

Diltiazem is a calcium channel blocker widely used for its peripheral and vasodilator properties. It is also used for lowering blood pressure and has some effect on cardiac induction. It is given as oral dosage form in the treatment of angina pectoris and the management of hypertension. Its short biological half life (3-5 h), high aqueous solubility, and frequent administration (usually three to four times a day) make it a potential candidate for sustained release preparations[2].

The present study investigates Ocimum mucilage as a suitable, natural, low-cost hydrophilic matrix material for the formulation of sustained release tablets. Modulations of Diltiazem release from its matrix tablet using mucilage as well as release mechanism were also assessed.

MATERIALS AND METHODS

Materials

Diltiazem HCl, Povidone were obtained as gift samples from Cipla Ltd. Mumbai. Microcrystalline cellulose was donated by Maple Biotech, Bhosari, Pune. Magnesium stearate was procured from LR-Hexon Laboratories, Pune.

Methods

Isolation of the mucilage from *Ocimum Tenuiflorum* Linn seeds

The *Ocimum Tenuiflorum* Linn seeds were blended and defatted in Soxhlet apparatus using petroleum ether as defatting agent. After defatting the material was soaked in distilled water for 12 h. The swollen mass was spread on a tray and dried in an oven at 60^0C. The dried mass was then passed through sieve # 30. The mucilage was winnowed and again passed through sieve # 60. The mucilage obtained was stored in desicator until use[3].

Drug-excipient compatibility studies by Fourier Transform Infrared (FTIR)

The samples of drug, mucilage and their mixture were prepared in the form of potassium bromide pellets and subjected for scanning from 4000 cm^{-1} to 400 cm^{-1} using FT-IR spectrophotometer (FT-IR-M4100, Jasco)[4].

Drug-excipient compatibility studies by Differential scanning calorimetry (DSC)

The compatibility study was carried out by using Differential Scanning Colorimeter (Mettler). Different parameters like onset of peak, peak, & end-set of peak values of drug-seed mucilage mixture were measured & compared with the pure drug[5].

Preparation of Sustained Release Matrix Tablet Formulation

All the ingredients were weighed accurately and mixed properly in mortar. The mucilage and povidone were used as drug release retardant agent in the formulation. The coherent mass was produced by adding sufficient quantity of purified water. The wet mass was then passed through the sieve #16 to form the uniform granules. The granules were then dried in the oven at 60 ^{0}C [6].

The dried granules were placed in the die cavity of (8 mm) and compressed using round flat punch on 8-station rotary tabletting machine (CIP, D8 Lab press, Ahmadabad). The hardness was kept between 9.5 to 10 kg/cm^2. Table 1 shows the formulation details.

EVALUATION

Pre-compression parameters

The granules so obtained were evaluated for flow properties viz. bulk density[7], tapped density[8], compressibility index[8], Hausner's ratio[9].

Post-compression parameters

The formulated tablets were evaluated for uniformity in thickness[10], uniformity in weight[11], hardness[12], friability[11], drug content[11] and in vitro drug release[12].

Drug content

Randomly three tablets were weighed and powdered. A quantity equivalent to 5 mg of diltiazem hydrochloride was placed a 100 ml volumetric flask and dissolved in Distilled water, sonicated for 5 minutes and made up the volume up to the mark and filtered through membrane filter. After appropriate dilutions with solvent, the drug content was determined by UV spectrophotometer at 237 nm (Shimadzu 1800, Tokyo, Japan) against suitable blank using standard plot equation[11].

In vitro drug release studies

Release of diltiazem HCl from the prepared tablet formulations and marketed formulations was studied using USP Dissolution Test Apparatus Type- II (Electrolab TDL 08, Mumbai, India). The drug release study was performed in 900 ml phosphate buffer (pH 6.8) with paddle rotating at 100 rpm and temperature maintained at 37^0C ± 0.5^0C. At predetermined time intervals samples were withdrawn and replenished with fresh medium. Amount of drug in sample was assessed by determining absorbance using UV-Spectrophotometer (Jasco V530) at 237nm after suitable dilution against blank[12].

RESULT AND DISCUSSION

Fig. 1 and 2 shows the spectra of FTIR and DSC studies for determining compatibility. The result indicated compatibility between drug and mucilage. Table 2 shows results of pre and post compression evaluation of prepared matrix tablets of diltiazem HCl. Seven formulations were prepared. The mucilage and povidone were used in 1:1 ratio in F1-F5 formulations with increasing concentration from 2.5-12.5 % while F6 contained only mucilage and F7 contained 1.25 % w/w of povidone to compare effectiveness of release retardant polymer when used alone. The use of mucilage and povidone in combination and alone was made to give comparison between the two polymers. The tablets were prepared by wet granulation method. The results of evaluation of granules indicated good flow properties. The hardness and thickness of the tablets were found to be 10 Kg/cm^2 and 3.5 mm respectively. The friability of the formulation was in the range of 0.21 – 0.27 % indicating good mechanical strength. The drug content of the formulations was found to be between 98.16 – 99.31 %.

Table 3 shows in vitro drug release of prepared matrix tablet formulations and marketed formulation of diltiazem HCl. Fig 3 shows the drug release profile of the prepared and marketed formulation of diltiazem HCl. It was observed that when Ocimum seed mucilage was used alone in 1.25 % w/w concentration it could sustain drug release only up to 2 h. Also povidone when used alone in same concentration could extend drug release only up to 2.5 h. But when these two polymers were used in combination in 1:1 ratio, an excellent control on drug release was observed. The concentration of the polymer mixture was increased from 2.5 % - 12.5 % w/w from F1 to F5, all the formulations (except F2) have shown extended drug release for more than 7 h. while F2 showed release upto 7 h. The marketed formulation had shown extended drug release only up to 4 h. The best fit model for drug release profile was found to be the Hixon-Crowel model.

CONCLUSION

From the above observations we conclude that seed mucilage alone does not give the desired release retardant effect but in combination with povidone shows excellent release retardant potential.

Table 1: Matrix tablet formulations containing mucilage and povidone

S. No.	Ingredients	Formulations (mg)						
		F1	F2	F3	F4	F5	F6	F7
1	Diltiazem HCl	30	30	30	30	30	30	30
2	Mucilage	2.5	5	7.5	10	12.5	2.5	0
3	Povidone	2.5	5	7.5	10	12.5	0	2.5
4	Microcrystalline cellulose	160	155	150	145	140	162.5	162.5
5	Magnesium stearate	5	5	5	5	5	5	5
Total		200	200	200	200	200	200	200

Table 2: Pre and Post compression evaluation of prepared matrix tablet formulations

Evaluation of Granules							
Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Bulk density (g/cc)	0.47	0.44	0.44	0.45	0.43	0.46	0.45
Tapped density (g/cc)	0.53	0.51	0.53	0.52	0.53	0.53	0.51
Compressibility index (%)	11.4	11.8	15.1	16.3	15.6	11.3	16.2
Hausner's ratio	1.1	1.13	1.17	1.2	1.2	1.1	1.2
Evaluation of matrix tablets							
Weight Variation (mg)	**Within acceptable limit**						
Friability (%)	0.26	0.24	0.27	0.21	0.21	0.23	0.22
Drug Content (%)	98.99	98.7	99.31	98.46	98.87	98.77	98.16

Table 3: In vitro drug release

Time (min)	F1	F2	F3	F4	F5	F6	F7	Mktd Tab.
30	25.29	24.86	22.69	22.32	25.43	20.35	25.67	21.45
60	38.06	35.74	33.93	33.02	37.73	53.28	43.23	30.55
90	50.10	48.09	43.92	42.29	46.09	87.23	67.09	42.76
120	60.91	59.19	54.12	51.78	56.68	98.78	89.43	56.70
150	69.31	67.61	61.62	57.98	64.40	_	99.01	70.11
180	76.68	75.76	69.46	64.67	71.92	_	_	82.32
210	82.94	82.18	75.53	69.96	78.17	_	_	91.75
240	86.24	86.82	80.27	73.62	82.50	_	_	99.67
270	88.70	89.94	83.44	76.83	86.24	_	_	_
300	91.87	93.10	86.8	80.03	89.8	_	_	_
330	92.59	95.22	87.14	84.00	92	_	_	_
360	94.07	96.95	90.42	86.60	94.41	_	_	_
390	95.47	98.86	92.73	90.96	96.53	_	_	_
420	96.7	99.79	94.21	95.41	98.08	_	_	_
450	98.86	_	97.01	98.10	98.25	_	_	_
480	_	_	99.35	_	_	_	_	_

Table 4: Coefficient of Determination for optimized formulations

Run	Zero order	1st order	Matrix	Peppas	n-Value	Hixon Crowel
F1	0.793	0.612	0.713	_	1.3127	0.933
F2	0.623	0.778	0.478	_	1.0123	0.873
F3	0.812	0.812	0.792	_	0.8764	0.851
F4	0.691	0.743	0.493	_	1.1012	0.952
F5	0.771	0.831	0.581	_	0.9589	0.851

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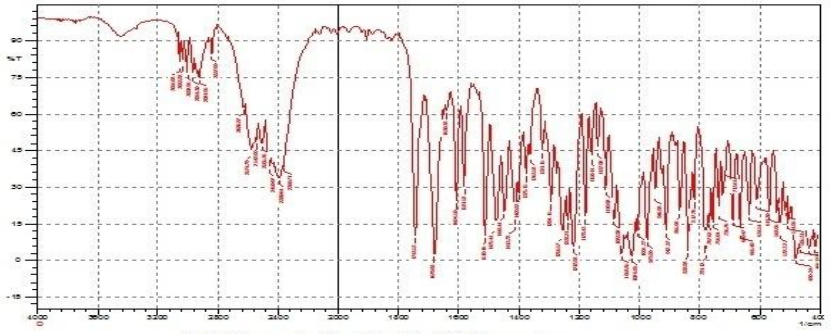
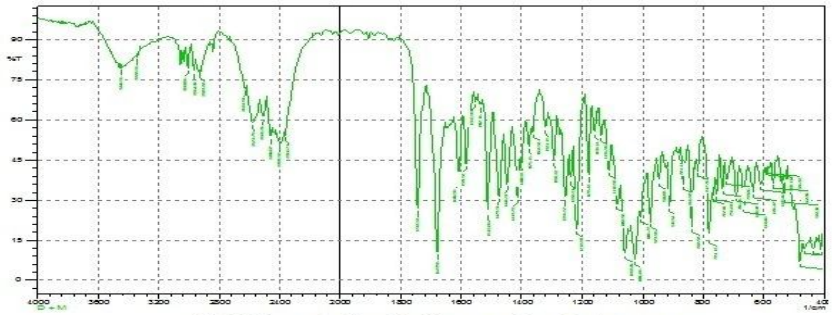
FIGURES



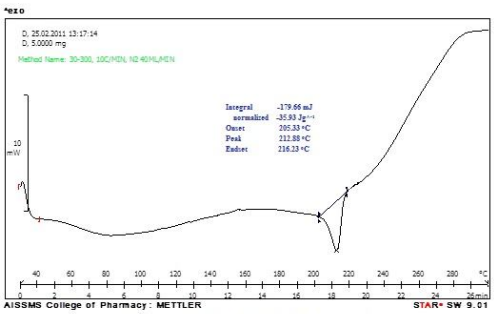
a) Diltiazem hydrochloride FTIR spectra



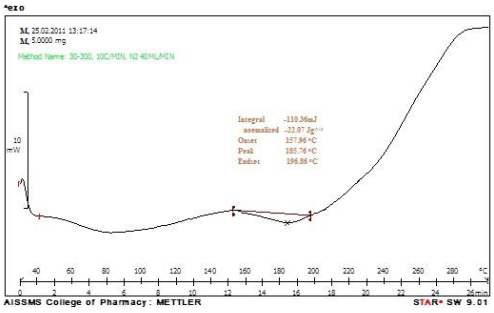
b) Diltiazem hydrochloride + mucilage FTIR spectra

Parameters	Frequency	Functional group
Diltiazem HCl	1743.53	Ester
	1679.88	Amide
	1606.58	C=C Benzene ring
Diltiazem HCl + Mucilage	1743.53	Ester
	1677.96	Amide
	1606.60	C=C Benzene ring

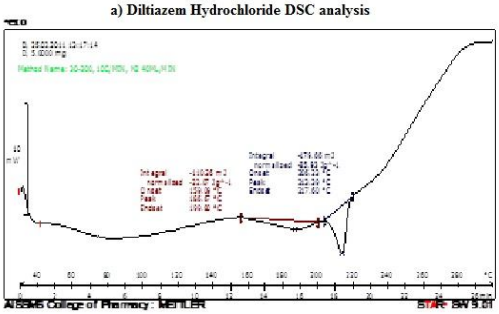
Fig 1 FTIR spectra (a) Diltiazem HCl (b) Diltiazem HCl + mucilage



a) Diltiazem Hydrochloride DSC analysis



b)Mucilage DSC analysis



c) Diltiazem HCl + Mucilage DSC analysis

Drug	Temperature (^{0}C)		
	Onset	Peak	Endset
Diltiazem HCl	205.33	212.88	216.33
Diltiazem HCl + Mucilage	206.23	213.39	217.60

Fig 2 DSC thermograms (a) Diltiazem HCl (b) Mucilage (c) Diltiazem HCl + mucilage

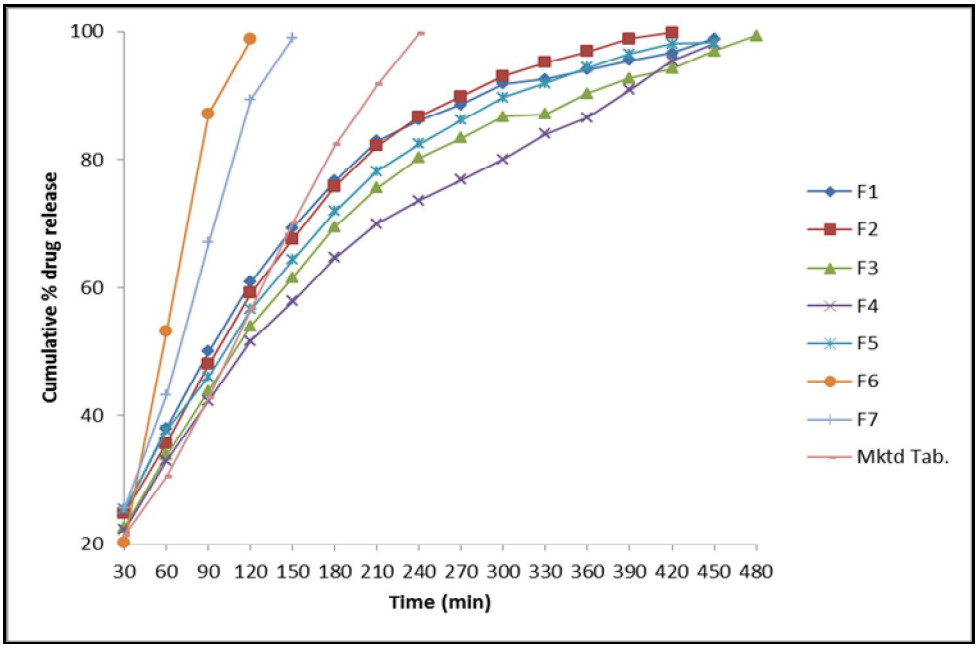


Fig 3 Cumulative % drug release graphical representation