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Design and evaluation of Diltiazem hydrochloride matrix tablets by using gum olibanum

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ABSTRACT

The present study aimed to design and evaluate hydrophilic matrix tablets of diltiazem hydrochloride, to achieve a controlled and sustained drug release with reduced frequency of drug administration, reduced side effects and improved patient compliance. Matrix tablets of diltiazem hydrochloride were prepared by using natural polymer like Gum Olibanum, hydrophilic polymer like hydroxypropylmethylcellulose (HPMC K_4M) and different binders like starch, gelatin and polyethylene glycol (PEG-6000). All the batches were evaluated for weight uniformity, hardness, friability, drug content uniformity and in vitro drug release characteristics as per USP XXIV monograph. The drug release rates from matrix tablets were compared with marketed SR [Dilzem SR (Torrent Pharma Ltd, India)] formulations. The release kinetics and mechanism of drug release by regression coefficient analysis and higuchi constant and Peppas exponential release model equation were also investigated. It was observed that all the fabricated tablets delivered the drug following higuchi diffusion mechanism and the release mechanism of diltiazem hydrochloride from matrix tablets indicated Fickian transport mechanism. The binder's effect on drug release from the dosage form was investigated. The insitu interations between the drug, polymers and excipients during wet granulation process are also investigated by DSC examination.

Keywords: Diltiazem hydrochloride (DHL), hydroxypropylmethylcellulose (Methocel K_4M or HPMC K_4M), Gum Olibanum, Higuchi diffusion and Differential Scanning Calorimetry (DSC).

INTRODUCTION

Sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for extended period of time with minimum local or systemic adverse effects. Other advantages include economy and greater patient compliance. Sustained release dosage

forms would be most applicable for drugs having low therapeutic indices and short elimination half-life [1]. Sustained release can be achieved by formulating drugs as matrix devices using HPMC, Sodium CMC and other swellable polymer [2-4]. Combination of hydrophilic polymer like HPMC K_4M and natural polymer like gum olibanum as the polymer matrix resulted in first-order release.

Matrix tablets are easy to prepare and they are cost effective and exhibit predictable release behavior [5]. Diltiazem hydrochloride (DHL) is "a potent calcium channel blocker [6-7] used in the treatment of hypertension and angina (variant & classical angina)[8] and also used

in the management of angina pectoris, arrhythmia and hypertension." It has small plasma half-life ($t_{1/2}$ = 3.5 hrs) and usual dose is 30 mg thrice daily. As a result of its short half-life, the development of oral sustained release formulation of this drug is highly desirable, so as to improve therapeutic effects with minimum side effects and improved patient compliance [9]. So, the objective of the present study was to develop controlled and prolonged release formulation of DHL as matrix tablets by using natural polymer like gum olibanum. The drug release rates from matrix tablets were compared with marketed SR formulations. The release kinetics and mechanism of drug release by regression coefficient analysis, higuchi and peppas exponential release model equation i.e. $M_t/M_\infty = Kt^n$ [10-11] were also investigated. Various natural gums and mucilages have been examined as polymers for sustained drug release, in the last few decades. The use of natural polymers and their semi-synthetic derivatives in drug delivery continues to be an area of active research despite the advent of synthetic polymers. 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.

MATERIALS AND METHODS

Materials:

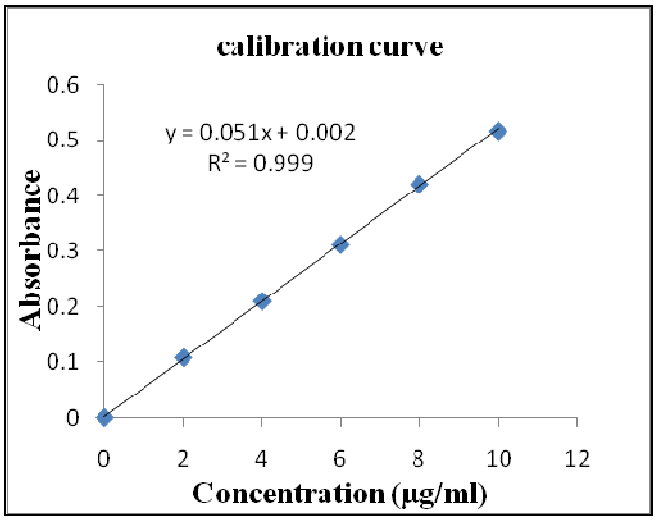
Diltiazem hydrochloride was obtained as gift sample from M/S. NATCO Pharmaceuticals Ltd, Hyderabad, India. Gum Olibanum was purchased from Girijan Corporation Ltd, Visakhapatnam, India. Hydroxypropylmethylcellulose (HPMC K_4M) was obtained as gift sample from M/S. Coloran asia Pvt Ltd, Mumbai, India. Binders like starch was obtained from Hi-pure fine chem. Industries, Chennai, gelatin was obtained from loba chemie Pvt Ltd, Mumbai and polyethylene glycol (PEG-6000) was obtained from central drug house (P) ltd, New Delhi, India. Other chemicals talc, magnesium stearate (S.D. Fine Chemicals, Mumbai, India) were obtained commercially and used as such.

Methods:

a. Diltiazem hydrochloride calibration curve:

Calibration curve of diltiazem hydrochloride was prepared using buffer pH 7.4 in the concentration range of 1 – 15 µg/ml. The drug was analyzed spectrophotometrically **(**Elico Double beam UV-Visible Spectrophotometer**)** at 237 nm (regression coefficient r^2 = 0.999 in buffer pH 7.4) and graph is shown in figure: I

Figure I: calibration curve of diltiazem hydrochloride



b. Fabrication of Dhl matrix tablets:

Drug (DHL), polymers (Gum Olibanum and HPMC K_4M), magnesium stearate and talc were passed through sieve no. 80 separately. Five different formulations with various polymer ratios were prepared i.e. 1:1, 1:1.5, 1:2, 1:1.5:0.5 and 1:1:1 by keeping Diltiazem hydrochloride at 90 mg constant with magnesium stearate 1% w/w, the composition is shown in Table I.

The compositions of diltiazem hydrochloride matrix tablets with different binders are shown in Table II.

Table I: Composition of diltiazem hydrochloride matrix tablets.

S.NO	INGREDIENTS (mg/tablet)	FORMULATIONS WITH CODE				
		F1	**F2**	**F3**	**F4**	**F5**
1	Diltiazem hydrochloride	90	90	90	90	90
2	Gum Olibanum	90	135	180	135	90
3	Methocel K_4M	--	--	--	45	90
4	Magnesium stearate	1.8	2.25	2.7	2.25	2.7
5	Ethanol	Q.S	--	--	Q.S	Q.S
6	Total weight (mg)	181.8	227.25	272.7	272.25	272.7

"--"indicates not present

1% w/w of magnesium stearate was present in each tablet

The matrix tablets of the above formulations were compressed in a single punch (Cadmach single punch tablet machine, Ahmedabad) tablet compression machine. A weighed amount of the powder was introduced in the die and the die capacity was adjusted as required. Compression force was adjusted to obtain the required hardness (7.5 kg/cm^2). A batch of 25 tablets was prepared for all formulations.

Table II: Composition of diltiazem hydrochloride matrix tablets with different binders

S.NO	INGREDIENTS (mg/tablet)	FORMULATIONS WITH CODE							
		F6	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
1	Diltiazem hydrochloride	90	90	90	90	90	90	90	90
2	Gum Olibanum	90	90	90	90	90	90	90	90
3	Methocel K_4M	90	90	90	90	90	90	90	90
4	Starch paste	27	54	81	--	--	--	--	--
5	Gelatin	--	--	--	27	54	81	--	--
6	Polyethylene glycol (PEG-6000)	--	--	--	--	--	--	27	54
7	Magnesium stearate	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7
8	Total weight (mg)	297	324	351	297	324	351	297	324

"--"*indicates not present*

1% w/w of magnesium stearate was present in each tablet

c. Drug-excipient interaction studies:

Pre-formulation studies are very important for the successful formulation of any dosage form. Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with polymers, binders and lubricants used in case tablet formulations. Positive interactions sometimes have a beneficial effect as far as desired release parameters are concerned. Therefore, in the present studies standard diltiazem hydrochloride, excipients and granules (obtained by wet granulation technique 1:1:1 ratio) was used and analyzed for compatibility studies.

d. Differential Scanning Calorimetry (DSC):

Differential Scanning Calorimetry (DSC) studies were carried out using "METTLER TOLEDO STAR^e System" (Thermal analysis center: IICT), United States. The instrument is very versatile as far interaction and compatibility studies at pre-formulation stage were concerned and used to evaluate melting point, enthalpy changes, interactions between the drug and polymers during wet granulation technique and glass transition temperatures of drug with excipients and polymers. Diltiazem Hydrochloride was mixed with the excipients and the DSC analysis of each sample under the analogous conditions of temperature range 25 – 400^o C, heating rate 10^{o}C/min, nitrogen atmosphere (30ml/min) and alumina as reference. Differential Scanning Calorimetry (DSC) was performed on pure drug (DHL), excipients and granules (obtained by wet granulation technique 1:1:1 ratio). DSC measurements were done on a METTLER TOLEDO STAR^e System and samples were heated at the rate of 10^{o}C min-1.The samples were heated in an aluminum cup up to 400^{o}C.

1. Evaluation of tablet formulations:

All the batches were evaluated for weight uniformity, hardness, friability and drug content uniformity as per USP XXIV monograph.

a. In vitro dissolution studies:

The studies were done using the USP XXIII dissolution rate test apparatus (type II) fitted with six rotating paddle type (Model Electrolab, India). All the batches of tablets were evaluated (3 runs for each batch) using 900 ml of sequential gastrointestinal release medium,i.e. 0.1N

hydrochloric acid (pH 1.2) for first two hrs and then pH 7.4 phosphate buffer for next 6 hr, maintained at 37 ± 0.5°C and stirred at 100 rpm. 5 ml of aliquots were withdrawn at different time intervals and an equivalent volume of medium (pre warmed at 37°C) was added to maintain constant volume. Withdrawn samples were analyzed spectrophotometrically at 237 nm using an Elico double beam UV-Visible Spectrophotometer.

b. Data Analysis

Different release kinetics is assumed to reflect different release kinetics mechanism. Therefore three kinetics models including zero order release equation (Eq.1), first order equation (Eq. 2) and Higuchi (Eq .3) were applied to process in vitro data to find the equation with the best fit.

$Q = K1t$ (Eq .1)
$Q = 100\ (1\text{-}e\text{-}K2t)$ (Eq. 2)
$Q = K_H t^{1/2}$ (Eq. 3)

Where Q is the release percentage at time t. K1, K2 and K_H are the rate constant of zero order, first order and Higuchi model respectively.

To investigate the mechanism of drug release the in vitro data were plotted as cumulative drug release verses square root of time as described by higuchi, when the linearity was observed in graph that indicates the diffusion controlled release mechanism of drug [12].

The dissolution data was further analysed to define the mechanism of release by applying the dissolution data following empirical equation proposed by peppas, $M_t/M_\alpha = Kt^n$ where M_t is drug release at time t, M_α is the total amount of drug in dosage form, M_t/M_α is the fraction of drug release up to time t, K is the kinetic constant and "n" is the release exponent indicative of the release mechanism of drug release from the formulation during dissolution process [13].

RESULTS AND DISCUSSION

In the present study an attempt has been made to formulate matrix tablets of Diltiazem hydrochloride using gum olibanum as hydrophobic matrix material. Over the last few years a large number of naturally obtained gums were evaluated as release retardants. Since they are of natural of origin (Burseraceae trees) they are non-toxic, biocompatible and cheaper. Gum olibanum is available in small tears or lumps of white-yellowish or yellow-reddish colour.

The matrix tablet formulations prepared by wet granulation method by using gum olibanum alone exhibited faster drug release over the other formulations. The matrix tablets containing drug, gum olibanum and HPMC K_4M at equal ratios (1:1:1) the drug released for prolong period of time up to 12 hrs. Among the matrix tablet prepared by wet granulation process, F5 was found to be suitable for controlling the drug release. Diltiazem hydrochloride matrix tablets were also prepared by wet granulation method with gum olibanum and HPMC K_4M by using starch, gelatin and PEG-6000 binder solutions as granulating agents.

a. Physical parameters of diltiazem hydrochloride matrix tablets

All the batches were evaluated for weight uniformity, hardness, friability and drug content uniformity as per USP XXIV monograph. The compositions of the matrix tablets and the results of the physical characterization of tablets are summarized in Table III.

Table III: Physical parameters of diltiazem hydrochloride matrix tablets

S.NO	FORMULATIONS WITH CODE	WEIGHT UNIFORMITY (mg)	*HARDNESS (kg/cm^2)	*FRIABILITY (%)	* DRUG CONTENT (mg/tablet)
1	F1	180	7.4±0.05	0.15±0.04	90.8±0.5
2	F2	225	7.5±0.05	0.18±0.04	90.5±0.4
3	F3	275	7.5±0.05	0.24±0.04	90.6±0.6
4	F4	275	7.4±0.05	0.16±0.02	89.8±0.3
5	F5	275	7.5±0.05	0.18±0.02	90.2±0.2
6	F6	300	7.5±0.05	0.14±0.02	90.5±0.5
7	F7	325	7.5±0.05	0.16±0.02	90.5±0.5
8	F8	350	7.5±0.05	0.12±0.04	89.7±0.2
9	F9	300	7.5±0.05	0.15±0.02	90.6±0.6
10	F10	325	7.5±0.05	0.20±0.02	90.8±0.6
11	F11	350	7.5±0.05	0.18±0.03	89.8±0.3
12	F12	300	7.5±0.05	0.14±0.02	90.2±0.4
13	F13	325	7.5±0.05	0.14±0.02	89.9±0.5

**All values are expressed as mean ± standard deviation, n =3*

Tablet friability was less than 0.25%, while hardness ranged from 7-7.5 kg/cm^2. Good uniformity in drug content was found among the various formulation batches was drug content was more than 89% in all cases with less than 0.6% standard deviation. Thus, all the tablet formulations showed acceptable physical characteristics.

b. In Vitro Release Kinetic Analysis

The release mechanism was evaluated using different kinetic models. The drug release rate constants (K) and regression coefficient (r^2) obtained from First order, Higuchi and Korsmeyer-Peppas models as shown in Table IV.

Table IV: Kinetics of in vitro drug release from different matrix tablets

S.NO	FORMULATIONS WITH CODE	FIRST ORDER RATE CONSTANT (hr^{-1})		HIGUCHI CONSTANT ($mg/hr^{1/2}$)		PEPPAS CONSTANT	
		K	r^2 value	K	r^2 value	"n" value	r^2 value
1	F1	0.351	0.8434	28.558	0.9970	0.300	0.9698
2	F2	0.333	0.9212	29.358	0.9930	0.303	0.9560
3	F3	0.277	0.8989	27.767	0.9902	0.300	0.9780
4	F4	0.340	0.9092	27.870	0.9868	0.248	0.9792
5	F5	0.184	0.9564	24.900	0.9964	0.234	0.9718
6	F6	0.156	0.9916	24.862	0.9925	0.181	0.9860
7	F7	0.104	0.9969	21.522	0.9969	0.161	0.9721
8	F8	0.075	0.9931	18.377	0.9902	0.134	0.9756

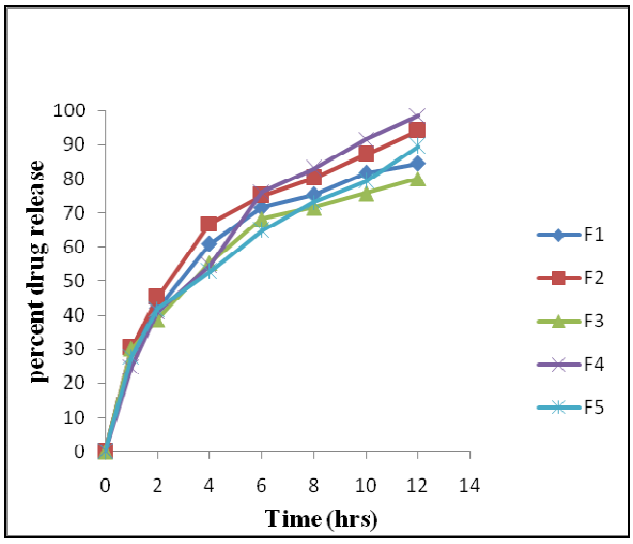
9	F9	0.127	0.9977	22.347	0.9978	0.219	0.9649
10	F10	0.157	0.9839	23.630	0.9994	0.238	0.9758
11	F11	0.186	0.9977	25.029	0.9848	0.246	0.9949
12	F12	0.132	0.9887	27.576	09952	0.226	0.9763
13	F13	0.097	0.9903	19.369	0.9957	0.217	0.9571

The first order plots drawn by log percent undissolved verses time for all the formulations were linear and followed first order release rate. The slope of the line and corresponding value of K can be calculated which is indicative of the release rate profile [14].

To investigate the mechanism of drug release the in vitro data were plotted as cumulative drug release verses square root of time as described by higuchi, for all matrix formulations were found to be linear, indicating the diffusion mechanism of drug release [12].

The percent drug release verses time profile were fitted in to the peppas equation. The “n” value of all the formulations was less than 0.5 that indicates formulations follow Fickian diffusion mechanism [13]. The percent drug release verses time profile plot are shown in figure II.

FIGURE II: In vitro release profile of diltiazem hydrochloride from matrix tablets.



c. Binders effect on release of drug from matrix:

Matrix tablets prepared by using starch mucilage and PEG-6000 as granulating agents, released the drug in highly steady state manner for a prolonged period of time. The release of drug from these formulations depends on the concentration of the starch mucilage and PEG-6000 added. As drug release from the matrix tablets were retarded due to high binding properties of starch and PEG-6000 expect Gelatin. Effects of starch and gelatin on in vitro release profile of diltiazem hydrochloride form matrix tablets are shown in figure III and figure IV**.** With gelatin as granulating agent, release the drug in a highly steady state manner for a prolong period of time. The release of drug from these formulations does not depend on the concentration of the gelatin added. As the concentration of gelatin increased, drug release from the matrix tablets was

increased due to rapid disintegration of gelatin at body temperatures which relaxes the polymer matrix for faster release of the drug. Effect of polyethylene glycol (PEG-6000) on in vitro release profile of DHL form matrix tablets is shown in figure V.

FIGURE III: effect of starch on release profile of diltiazem hydrochloride form matrix tablets.

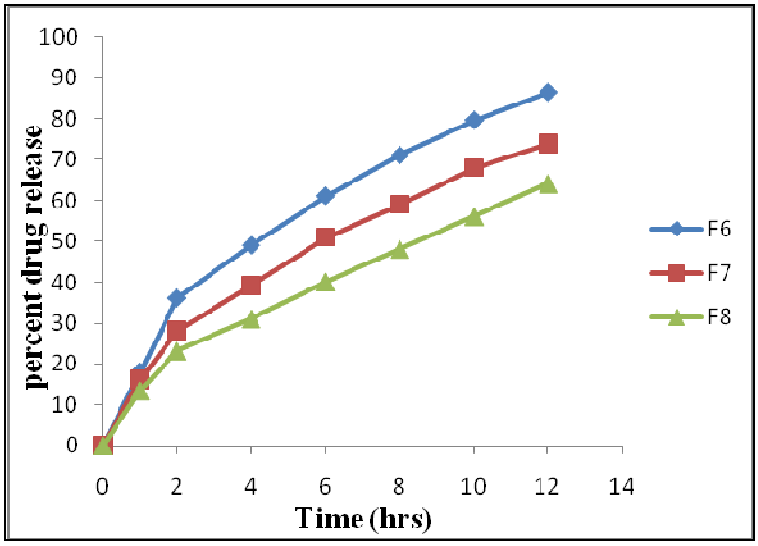


FIGURE IV: Effect of gelatin on release profile of diltiazem hydrochloride from matrix tablets

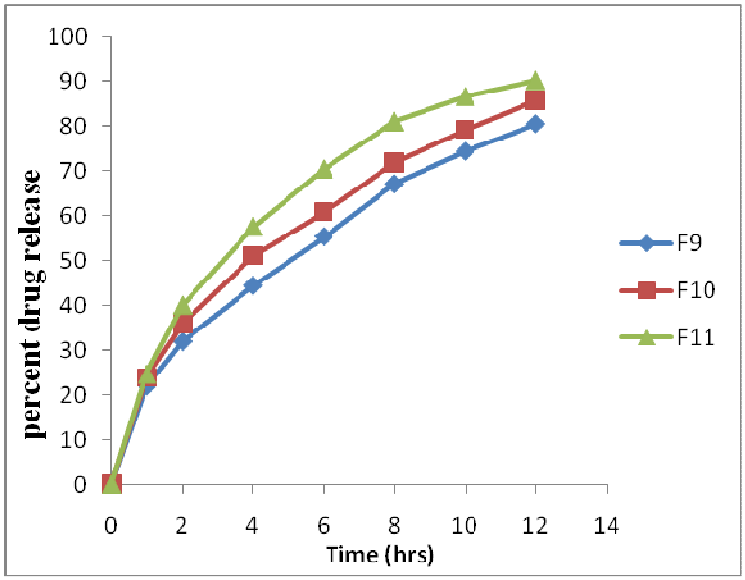
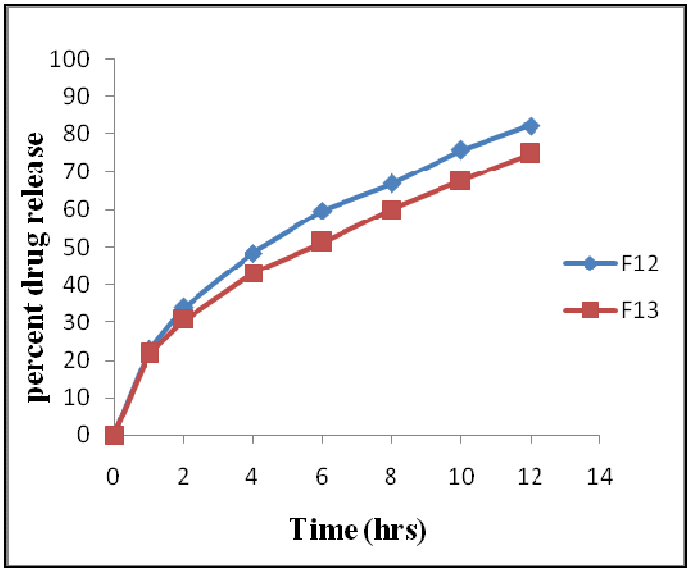


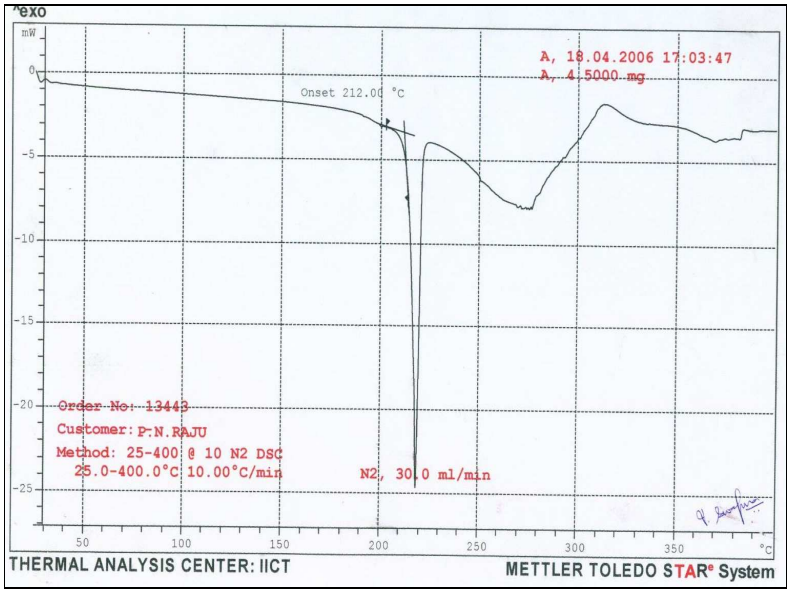
FIGURE V: Effect of polyethylene glycol (PEG-6000) on release profile of diltiazem hydrochloride form matrix tablets.



d. Drug excipient compatibility study:

Drug excipients compatibility studies were carried out to check whether any compatibility related problems are associated between drug and excipients used in the formulations.

FIGURE VI: DSC thermogram of pure diltiazem hydrochloride



e. Differential Scanning Calorimetry (DSC):

DSC results revealed that the physical mixture of Diltiazem hydrochloride with excipients showed superimposition of the thermograms. There is no considerable change observed in

melting endotherm. DSC study reveals that there was no interaction took place between the drug and the polymer. The DSC thermograms are shown in Figure VI to VIII.

FIGURE VII: DSC thermogram of granules prepared by wet granulation method (F5).

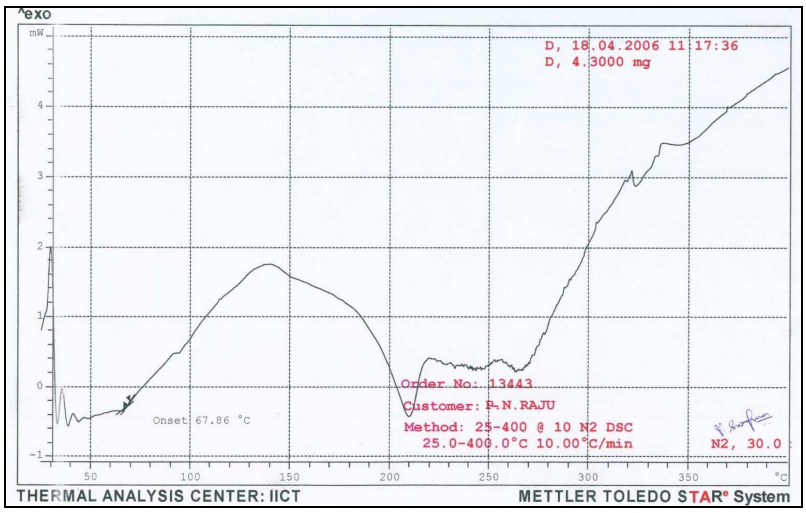
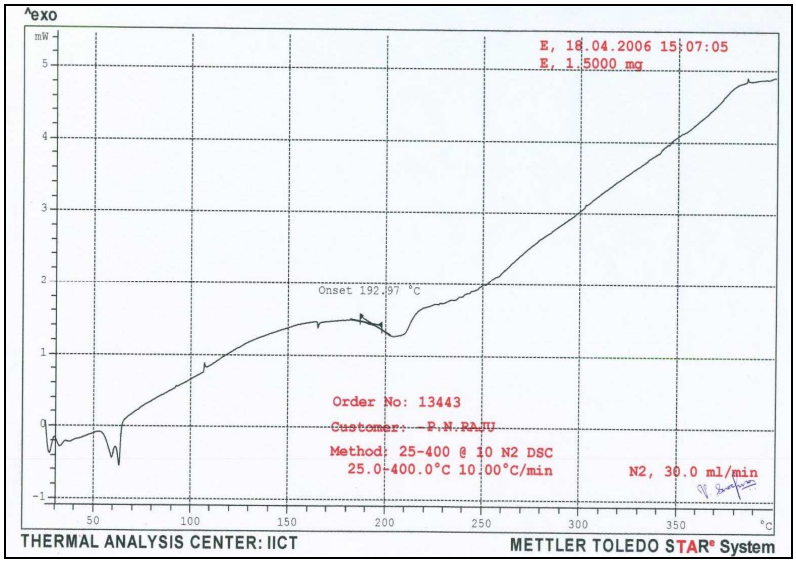


Figure VIII: DSC thermogram of granules prepared by wet granulation using PEG-6000 as binder (F12).

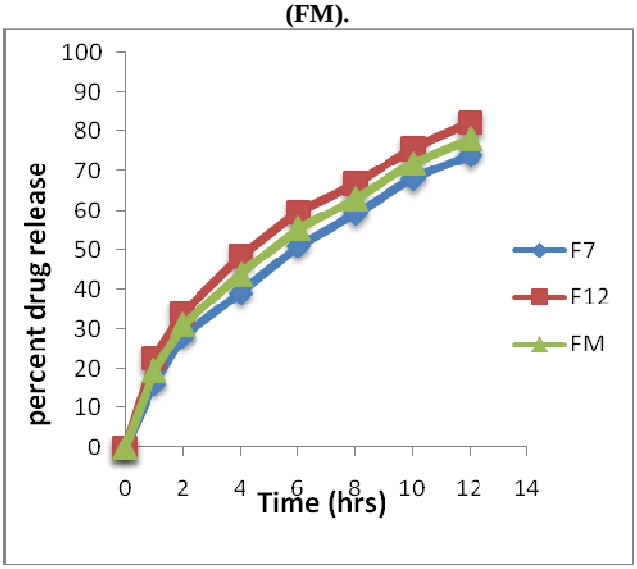


From the figure VI to VIII, it is clear that the characteristics peaks are seen in both pure diltiazem hydrochloride and gum olibanum without any change in their position, indicating no chemical interaction between gum olibanum and diltiazem hydrochloride.

The DSC analysis of diltiazem hydrochloride showed a single sharp endothermic peak at $212^{O}C$ due to melting point of the drug**.** Gum olibanum and HPMC K_4M did not show any characteristic peak and binder agent PEG-6000 showed respective peak at their melting point $53.31^{0}C$. The DSC curves shows that the endothermic peaks of diltiazem hydrochloride and excipients were

almost unchanged indicating the absence of strong interactions between the drug and excipients. DSC studies were performed on pure DHL, gum olibanum, granules prepared by wet granulation method (F5) and granules prepared by wet granulation method using PEG-6000 as binder (F12) Among the formulations prepared by wet granulation method, matrix tablets with starch 20 % (F7) and PEG-6000 10 %(F12) released the drug uniformly and meet the USP dissolution test profile-II for diltiazem hydrochloride extended release tablets. Comparison of in vitro release of optimized formulations (F7, F12) with market formulation is shown in figure IX.

FIGURE IX: comparison of in vitro release of optimized formulation (F7, F12) with market formulation (FM).



CONCLUSION

Based on the present study, it can be concluded that gum olibanum is an appropriate hydrophobic material that can be utilized as matrix forming agent to prolong the release of water soluble drug such as dilitiazem hydrochloride. Preparation of matrices by wet granulation method was found to be more effective in controlling the release of drug. Gum olibanum is widely available in India and is non-toxic, biocompatible and inexpensive. It can be used as substitute in place of currently marketed matrix forming polymers. The drug release from all the formulations mentioned above followed first order kinetics and the release mechanism of Diltiazem hydrochloride from matrix tablets indicated “Fickian transport mechanism”.

It was also concluded that the drug release was greatly influenced by the nature of the binder incorporated in the formulations. Finally to achieve a sustained release formulation of diltiazem hydrochloride matrix tablets by using gum olibanum, matrix tablets were developed to be capable to provide prolonged release patterns over 12 hrs. Formulation containing diltiazem hydrochloride, HPMC K_4M and gum olibanum having equal ratios (1:1:1) was found to satisfy the desired criteria when used in the quantity given for formulation F5.

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