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EFFECTS OF BINDERS, LUBRICANTS AND FILLERS ON DRUG RELEASE FROM DILTIAZEM HYDROCHLOIDE BI-LAYERED MATRIX TABLETS OBTAINED BY DIRECT COMPRESSION AND WET GRANULATION TECHNIQUE

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ABSTRACT
The present study is aimed to study and investigate the effects of binders, lubricants and fillers influencing the drug release from the Diltiazem hydrochloride bi-layered matrix tablets containing matrix components such as natural polymer (Gum Olibanum) and hydrophilic polymer (hydroxypropylmethylcellulose). The amount of drug loading did not affect the drug release which was influenced by the hydrodynamic force and the matrix composition. An increase in the binder concentration (eg: 10, 20 and 30%) correspondingly increased the release rate of drug from matrices except gelatin as a binder. Moreover, incorporation of soluble diluents in core or barrier could enhance the drug release. 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 DHL from matrix tablets indicated Fickian transport mechanism. The in-situ interactions between the drug, polymers and excipients (binders, lubricants and fillers, etc.,) during wet granulation process are also investigated by DSC examination. Most dissolution profiles of the prepared DHL bi-layered tablets provided a better fit to zero order kinetic than to first order kinetic and Higuchi's equation. All the batches were evaluated by physical parameters like "weight uniformity, hardness, friability, drug content uniformity" and in vitro drug release characteristics as per USP XXIV monograph. The binder's [starch, gelatin and polyethylene glycol (PEG-6000)] effect on drug release from the dosage form was also investigated.

Keywords: Diltiazem hydrochloride, Hydroxypropylmethylcellulose, Gum Olibanum, polyethylene glycol and Differential Scanning Calorimetry

INTRODUCTION

Tablets are the most commonly used dosage form. The ease of manufacturing, convenience in administration, accurate dosing and stability compared to oral liquids, tamper-proofness compared to capsules and safety compared to parenteral dosage forms makes tablets a popular and versatile dosage form[1]**.** The present study was Diltiazem hydrochloride as a model drug and matrix components are natural polymer like Gum Olibanum and hydrophilic polymer like HPMC K_4M are used to formation of DHL bi-layered matrix tablets. Diltiazem hydrochloride (DHL) is "a potent calcium channel blocker[2, 3] used in the treatment of hypertension and angina

(variant & classical angina)[4] 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 a 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[5]. 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. Sustained release dosage forms would be most applicable for drugs having low therapeutic indices and short elimination Half-life[6]. Sustained release can be achieved by formulating drugs as matrix devices using HPMC, Sodium CMC and other swellable polymer[7, 8]. 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[9]. Gum Olibanum is the dried, gummy exudate obtained from various species of Burseraceae trees. The main species are Boswellia carteri, Boswellia frererana, Boswellia papyrifera and many others. Main producing countries are Somalia, Ethiopia, Southeast Arabia, and India. The Olibanum trade knows three principal origins: Aden/Somalia, Eritrea, and India. Gum Olibanum is available in small tears or lumps of white-yellowish or yellow-reddish colour. It has a slight smell and is available in different qualities from dust, siftings, peasize, to tears. Gum Olibanum belongs to family Burseraceae. However, the rational choice of excipients is essential to obtain tablets with adequate properties. Filler, binders or diluents, disintegrating agents and lubricants are the major types of excipients and adjuvants used in formulations of tablets, which are present in almost all tablet formulations[10]. In order to obtain a good tablet formulation by direct compression or wet granulation technique, filler, binders[11, 12] as well as lubricants[13] must be carefully chosen. Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density. It is widely used as a lubricant in capsule and tablet manufacture at concentrations between 0.25-5%[14].

Lubricants are pharmaceutical excipients indispensable for improving the quality and manufacturing efficiency of tablets, mainly due to their characteristics to improve fluidity, filling properties, as well as to prevent powder adhesion to punch faces and minimize die-wall friction[15]. In a general way, hydrophobic lubricants are more efficient than hydrophilic lubricants. On the other hand, hydrophobic lubricants can also alter other physicochemical properties of tablets, such as hardness (tensile strength), disintegration time, and drug release[10]. Thus, the lubrication process is a combination of factors involving lubricant material, formulation to be lubricated and the mechanical process, which results in the final dosage form[15].

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

Fabrication of DHL bi-layered 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 Drug, 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 DHL matrix tablets were prepared by direct compression and wet granulation technique.

i. DHL matrix tablets prepared by direct compression: The materials individually passed through sieve No: 80 and mixed for 15 mints. The powdered mixer was lubricated with magnesium stearate (1%w/w) and compressed into tablets using a single punch [Cadmach single (Flat faced punch) punch tablet machine, Ahmadabad] tablet compression machine. The compositions of Diltiazem hydrochloride matrix tablets prepared by direct compression are shown in Table I.

ii. DHL matrix tablets prepared by wet granulation technique: A blend of all ingredients are mixed in a laboratory blender and granulated by using solvents (methanol or water) or granulating agents [Binders (starch, gelatin and polyethylene glycol)]. The wet mass was passed through sieve No: 16 and resulting granules were dried at 50^0C for 4 Hrs. the dried granules were passed through sieve No: 20 and the resultant granules were lubricated with suitable amount of lubricant such as magnesium stearate (1%w/w) by blending for few minutes. Then the lubricated granules were compressed as matrix tablets using a single punch [Cadmach single (Flat faced punch) punch tablet machine, Ahmadabad] tablet compression machine. The compositions of Diltiazem hydrochloride matrix tablets prepared by wet granulation technique and by using different binders are shown in Table II and Table III. The matrix tablets of the above formulations were compressed in a single punch tablet compression machine. A weighed amount of the powder or granules 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.

Drug-Excipients interaction studies: Pre-formulation studies are very important for the successful formulation of any dosage form. Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FT-IR) 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 of tablet formulations. Positive interactions sometimes have a beneficial effect as far as desired release parameters are concerned. Therefore, in the present studies standard DHL, excipients and granules (obtained by wet granulation technique 1:1:1 ratio with different binders) was used and analyzed for compatibility studies.

Differential scanning calorimetry: 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, polymers and binders during wet granulation technique and glass transition temperatures of drug with excipients and polymers". DHL was mixed with the excipients and the DSC analysis of each sample under the analogous conditions of temperature range 25 – 400º C, heating rate 10ºC/min, nitrogen atmosphere (30ml/min) and alumina as reference. DSC was performed on pure drug (DHL), excipients and granules (obtained by wet granulation technique 1:1:1 ratio by using different binders). DSC measurements were done on a METTLER TOLEDO STAR^e System and samples were heated at the rate of 10ºC min^{-1}.The samples were heated in an "Aluminum cup" up to 400ºC.

EVALUATION OF DHL MATRIX TABLETS

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

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 Electro lab, 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 2 hrs and then pH 7.4 phosphate buffer for up to 12hrs, 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.

Data analysis: Different release kinetics is assumed to reflect different release kinetics mechanism. Therefore four kinetics models including zero order release equation (Eq.1), first order equation (Eq. 2), Higuchi (Eq.3) and Korsmeyer-Peppas (Eq.4) equations were applied to process in vitro data to find the equation with the best fit.

$Q = K_1t$ (Eq.1)
$Q = 100\ (1\text{-}e\text{-}K_2t)$ (Eq. 2)
$Q = K_3t^{1/2}$ (Eq. 3)
$M_t/M_\alpha = K_4t^n$ (Eq. 4)

Where Q is the release percentage at time t. K_1, K_2 K_3 and K_4 are the rate constant of zero order, first order, Higuchi and Korsmeyer-Peppas model respectively.

To investigate the mechanism of drug release the in vitro data was 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[16]. The dissolution data was further analyzed to define the mechanism of release by applying the dissolution data following empirical equation proposed by Peppas, $M_t/M_\alpha = Kt^n$ (Eq.4) 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[17].

***Physical parameters of DHL bi-layered 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 Tables IV, V & VI. Tablet friability was less than 0.20%, while hardness ranged from 7-7.5 kg/cm^2. Good uniformity in drug content was found among the various formulation batches and drug content was more than 89% in all cases with less than 0.5% standard deviation. Thus, all the tablet formulations showed acceptable physical characteristics.

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 tables VII, VIII and IX. The first order plots drawn by log percent un-dissolved 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 [18]. 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[15]. 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 plots are shown in figure I & II.

Binders effect on release of DHL from bi-layered matrix tablets: 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 DHL form matrix tablets are shown in figure III and figure IV. With gelatin as granulating agent, release of the drug is 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 PEG-6000 on in vitro release profile of DHL from matrix tablets is shown in figure V.

Drug excipients compatibility study: Drug excipients compatibility studies were carried out to check whether any compatibility related problems are associated between drug and excipients [binders (starch, gelatin and polyethylene glycol), lubricants and fillers, etc,] used in the formulations.

Differential scanning calorimetry: 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, polymer and excipients. The DSC Thermograms are shown in figures VI to X. From the Thermograms [figure VI to X], it is clear that the characteristics peaks are seen in both pure DHL and Gum Olibanum without any change in their position, indicating no chemical interaction between Gum Olibanum and DHL. The DSC analysis

of DHL showed a single sharp endothermic peak at $212^{O}C$ [Figure VI] due to melting point of the drug. Gum Olibanum and HPMC K_4M did not show any characteristic peak and binder like PEG-6000 showed respective peak at their melting point $53.31^{0}C$ [Figure X]. The DSC curves shows that the endothermic peaks of DHL and excipients (binders, lubricants and fillers) 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 technique by using Starch (F12), PEG-6000 (F17) and Gelatin (F18) as a binder. Among the formulations prepared by wet granulation method, matrix tablets with starch-20 % (F12) and PEG-6000 10 % (F17) released the drug uniformly and met the USP Dissolution Test Profile-II for DHL extended release tablets. Comparison of in vitro release of optimized formulations (F12, F17) with market formulation (FM) is shown in figure XI.

CONCLUSION

This study was to investigate the effects of binders, lubricants and fillers influencing the drug release from the DHL bi-layered matrix tablets containing matrix components are natural polymer like Gum Olibanum and hydrophilic polymer like HPMC K_4M. The amount of drug loading did not affect the drug release from the DHL bi-layered matrix tablets. Diltiazem hydrochloride release from the matrix tablets was studied in distilled water medium over a period of 12 hrs. The matrix tablet formulations prepared by direct compression by using Gum Olibanum alone exhibited faster drug release over the other formulations. The matrix tablets containing DHL, Gum Olibanum and HPMC k_4 M at equal ratios (1:1:1) prepared by direct compression process, released the drug for prolong period of time up to 12 hrs. Among the matrix tablet prepared by direct compression 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 water, starch, gelatin and PEG-6000 binder solutions as granulating agents. Matrix tablets prepared by wet granulation method by using water as a granulating fluid were released the drug in a non uniform manner due to irregular hydration of the hydrophilic polymers. Matrix tablets prepared by using starch mucilage as granulating agent, released the drug in a 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 added. As drug release from the matrix tablets were retarded due to high binding properties of starch. Matrix tablets prepared by using Gelatin as granulating agent, release the drug in a highly steady state manner for a prolonged 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. Matrix tablets prepared by using PEG-6000 as granulating agent, release the drug in a highly steady state manner for a prolonged period of time. The release of drug from these formulations depends on the concentration of the PEG-6000 added. As drug release from the matrix tablets were retarded due to high binding properties of PEG-6000. Among the formulations prepared by wet granulation method matrix tablets with starch 20% and PEG-6000 10%

were release the drug uniformly and met the USP Dissolution Test Profiles-II for DHL extended release tablets. From the DSC curves shows that the endothermic peaks of DHL and excipients (binders, lubricants and fillers) were almost "unchanged indicating the absence of strong interactions between the drug and excipients [figure VI to X]. All the formulations prepared by different methods following first order release mechanism and the r^2 values obtained were linear. Higuchi plots for all the formulations were linear in drug diffusion process and the r^2 values were also linear. The "n" values obtained for different formulations prepared were less than 0.45 which indicates the Fickian Diffusion Mechanism of all matrix tablets. The r^2 values for Peppas plots were highly linear and values are show in tables VII, VIII and IX.

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Table I: Composition of DHL Matrix Tablets Prepared By Direct Compression

INGREDIENTS (mg/tablet)	FORMULATIONS WITH CODE				
	F1	F2	F3	F4	F5
Diltiazem hydrochloride	90	90	90	90	90
Gum Olibanum	90	135	180	135	90
HPMC K_4M	--	--	--	45	90
Magnesium stearate	1.8	2.25	2.7	2.7	2.7
Total weight (mg)	181.8	227.25	272.7	272.25	272.7

Table II: Composition of DHL Matrix Tablets Prepared By Wet Granulation Technique

INGREDIENTS (mg/tablet)	FORMULATIONS WITH CODE				
	F6	F7	F8	F9	F10
Diltiazem hydrochloride	90	90	90	90	90
Gum Olibanum	90	135	180	135	90
HPMC K_4M	--	--	--	45	90
Magnesium stearate	1.8	2.25	2.7	2.7	2.7
Ethanol	Q.S	--	--	Q.S	Q.S
Total tablet weight (mg)	181.8	227.25	272.7	272.25	272.7

Table III: Composition of DHL Matrix Tablets Prepared By Wet Granulation Technique by Using Different Binders

INGREDIENTS (mg/tablet)	FORMULATIONS WITH CODE							
	F11	F12	F13	F14	F15	F16	F17	F18
Diltiazem hydrochloride	90	90	90	90	90	90	90	90
Gum Olibanum	90	90	90	90	90	90	90	90
HPMC K_4M	90	90	90	90	90	90	90	90
Starch paste	27	54	81	--	--	--	--	--
Gelatin	--	--	--	27	54	81	--	--
PEG-6000	--	--	--	--	--	--	27	54
Magnesium stearate	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7
Total tablet weight (mg)	299.7	326.7	353.7	299.7	326.7	353.7	299.7	326.7

"--"indicates not present

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

Table IV: Physical Parameters of DHL Bi-Layered Matrix Tablets Prepared By Direct Compression

†FWC	WEIGHT UNIFORMITY (mg)	*HARDNESS (kg/cm^2)	*FRIABILITY (%)	*#DCU (mg/tablet)
F1	180	7.4±0.05	0.12±0.02	90.4±0.5
F2	225	7.4±0.05	0.15±0.04	90.5±0.5
F3	275	7.5±0.05	0.20±0.02	90.2±0.4
F4	275	7.5±0.05	0.15±0.04	89.9±0.2
F5	275	7.4±0.05	0.12±0.02	90.2±0.3

Table V: Physical Parameters of DHL Bi-Layered Matrix Tablets Prepared By Wet Granulation Technique

†FWC	WEIGHT UNIFORMITY (mg)	*HARDNESS (kg/cm^2)	*FRIABILITY (%)	*#DCU (mg/tablet)
F6	180	7.4±0.05	0.15±0.04	90.8±0.5
F7	225	7.5±0.05	0.18±0.02	90.5±0.4
F8	275	7.5±0.05	0.20±0.02	90.6±0.5
F9	275	7.3±0.05	0.16±0.02	89.8±0.3
F10	275	7.5±0.05	0.18±0.03	90.2±0.2

Table VI: Physical Parameters of DHL Bi-Layered Matrix Tablets Prepared By Wet Granulation Method using different Binders

†FWC	WEIGHT UNIFORMITY (mg)	*HARDNESS (kg/cm^2)	*FRIABILITY (%)	*#DCU (mg/tablet)
F11	300	7.5±0.05	0.14±0.02	90.5±0.5
F12	325	7.5±0.05	0.16±0.02	90.5±0.5
F13	350	7.5±0.05	0.12±0.02	89.7±0.2
F14	300	7.5±0.05	0.15±0.04	90.6±0.5
F15	325	7.5±0.05	0.20±0.02	90.8±0.5
F16	350	7.5±0.05	0.18±0.03	89.8±0.3
F17	300	7.5±0.05	0.14±0.02	90.2±0.4
F18	325	7.5±0.05	0.14±0.02	89.9±0.5

"" All values are expressed as Mean ± Standard Deviation, n =3*
***"#** "DCU is drug content uniformity*
†FWC is formulations with code

Table VII: Kinetics of in vitro Drug Release Parameters for DHL Bi-Layered Matrix Tablet Obtained by Direct Compression

†FWC	FIRST ORDER RATE CONSTANT (hr^{-1})		RELEASE RATE CONSTANT ($mg/hr^{1/2}$)		PEPPAS CONSTANT	
	K	r^2 value	K	r^2 value	"n" value	r^2 value
F1	0.855	0.9926	34.861	0.9477	0.45	0.9834
F2	0.423	0.9719	32.366	0.9457	0.435	0.9845
F3	0.332	0.9884	29.932	0.9495	0.411	0.9876
F4	0.352	0.9218	27.520	0.985	0.280	0.9803
F5	0.207	0.9367	26.344	0.9852	0.215	0.9768

Table VIII: Kinetics of in vitro Drug Release Parameters for DHL Bi-Layered Matrix Tablet Obtained by Wet Granulation Technique

†FWC	FIRST ORDER RATE CONSTANT (hr^{-1})		RELEASE RATE CONSTANT ($mg/hr^{1/2}$)		PEPPAS CONSTANT	
	K	r^2 value	K	r^2 value	"n" value	r^2 value
F6	0.351	0.8434	28.558	0.997	0.3	0.9698
F7	0.333	0.9212	29.358	0.993	0.303	0.956
F8	0.277	0.8989	27.767	0.9902	0.30	0.978
F9	0.314	0.9092	27.870	0.9868	0.248	0.9792
F10	0.184	0.9564	24.900	0.9964	0.234	0.9718

Table IX: Kinetics of in vitro Drug Release Parameters for DHL Bi-Layered Matrix Tablet Obtained by Wet Granulation Technique Using Different Binders

†FWC	FIRST ORDER RATE CONSTANT (hr^{-1})		RELEASE RATE CONSTANT ($mg/hr^{1/2}$)		PEPPAS CONSTANT	
	K	r^2 value	K	r^2 value	"n" value	r^2 value
F11	0.156	0.9916	24.862	0.9925	0.181	0.986
F12	0.104	0.9969	21.522	0.9969	0.161	0.9721
F13	0.075	0.9931	18.377	0.9902	0.134	0.9756
F14	0.127	0.9977	22.347	0.9978	0.219	0.9649
F15	0.157	0.9839	23.630	0.9994	0.238	0.9758
F16	0.186	0.9977	25.029	0.9848	0.246	0.9949
F17	0.132	0.9887	27.576	0.9952	0.226	0.9763
F18	0.097	0.9903	19.369	0.9957	0.217	0.9571

†FWC is formulations with code

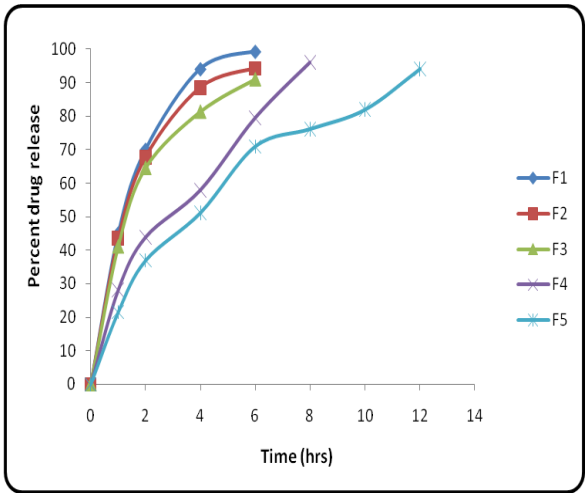

Figure I: In Vitro Release Profile of DHL Bi-Layered Matrix Tablets obtained by Direct Compression

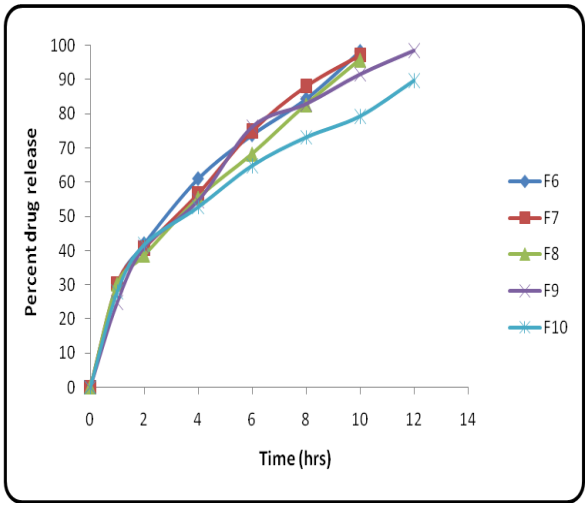

Figure II: In Vitro Release Profile of DHL Bi-Layered Matrix Tablets obtained by Wet Granulation Technique

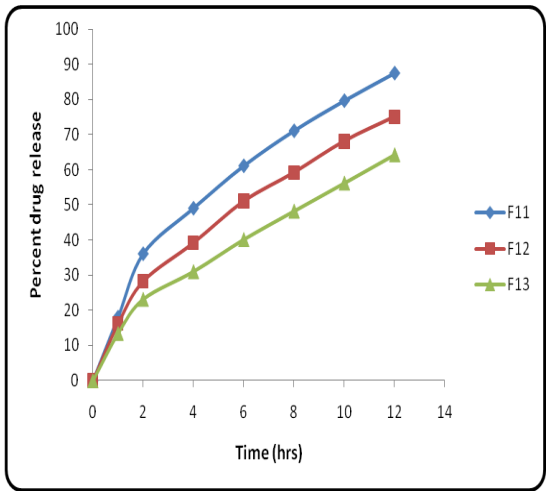

Figure III: Effect of Starch on Release Profile of DHL from Bi-Layered Matrix Tablets

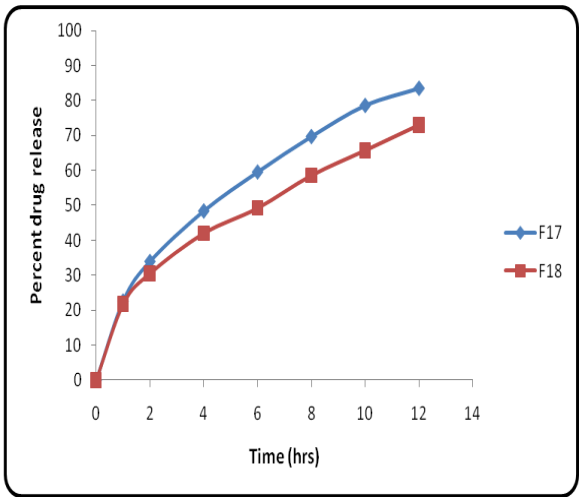

Figure V: Effect of PEG-6000 on Release Profile of DHL from Bi-Layered Matrix Tablets

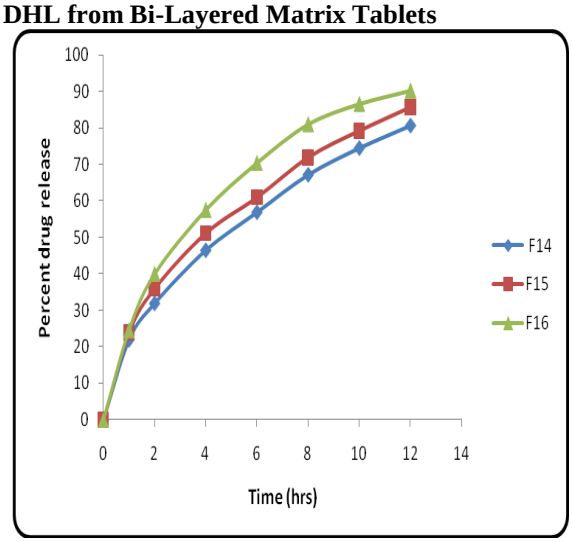

Figure IV: Effect of Gelatin on Release Profile of DHL from Bi-Layered Matrix Tablets

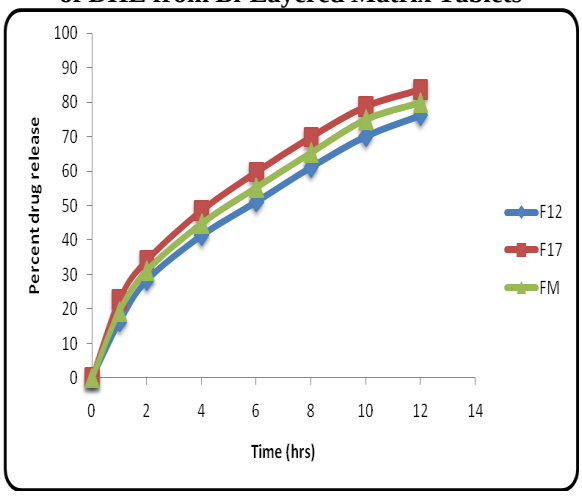

Figure XI: Comparison of In Vitro Release of Optimized Formulations (F12 & F17) With Market Formulation (FM)

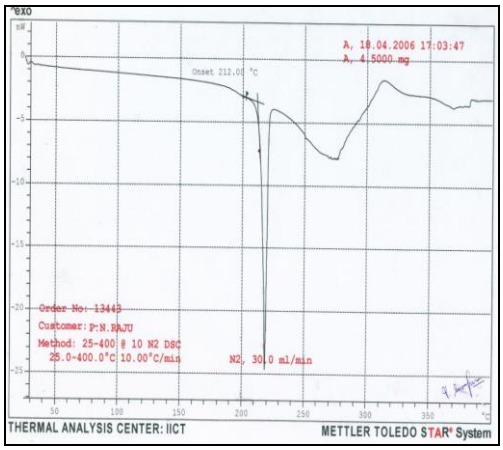

Figure VI: DSC Thermogram of Pure Diltiazem Hydrochloride

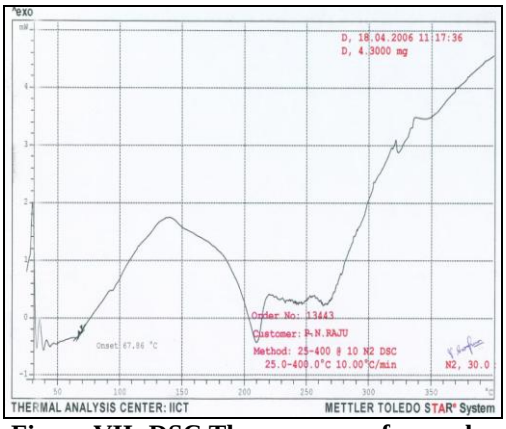

Figure VII: DSC Thermogram of granules prepared by wet granulation Technique (F5)

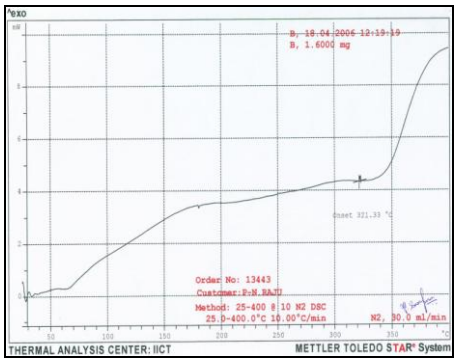

Figure VIII: DSC Thermogram of Granules Prepared By Wet Granulation Technique by Using Starch as a Binder (F12)

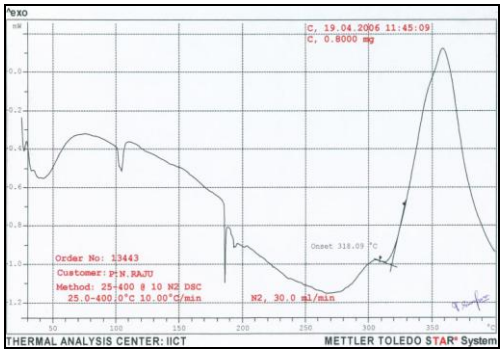

Figure IX: DSC Thermogram of Granules Prepared By Wet Granulation Technique by Using Gelatin as a Binder (F17)

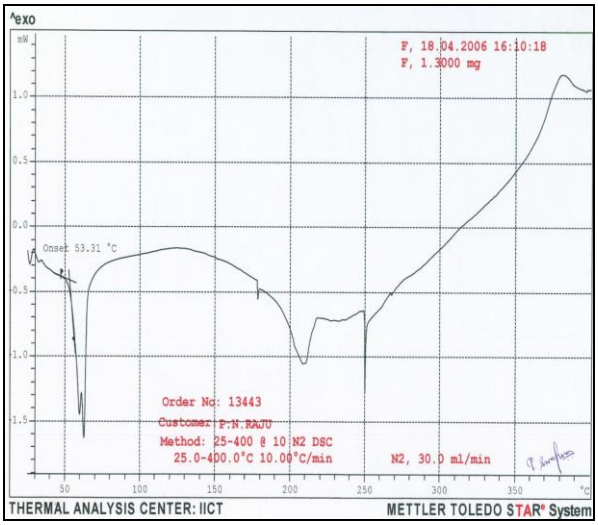

Figure X: DSC Thermogram of Granules Prepared By Wet Granulation Technique by Using PEG-6000 as a Binder (F18)

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