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CONTROLLED RELEASE FORMULATION DEVELOPMENT AND EVALUATION OF FELODIPINE MATRIX TABLETS BY USING HYDROPHOBIC POLYMERS

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ABSTRACT

Felodipine is a long-acting 1, 4-dihydropyridine calcium channel blocker, used to control hypertension by selective action on peripheral resistance. The conventional felodipine tablet gives a rather high peak and comparatively low trough levels, due to rapid absorption and distribution. More sustained plasma concentrations might thus produce a more even effect on blood pressure. The main aim of the study was to improve dissolution rate of the dosage form in a controlled manner over extended period of 24 hrs. Matrix tablets were prepared by direct compression method,using hydrophobic polymers like Glyceryl monostearate and Carnauba wax. The prepared formulations were evaluated for hardness, thickness, weight variation, friability and *in-vitro* dissolution studies. Among all the formulations F8 was selected as optimized formulation based on the evaluation parameters and in-vitro release profile of 100% drug release for 24 hrs. The FTIR and DSC results of optimized formulation showed no drug-excipient interaction. For optimized formulation(F8), the drug release mechanism was explored and explained by zero-order (r^2=0.984), first-order (r^2=0.947), Higuchi (r^2=0.967) and Korsmayer-peppas (r^2=0.982 & n=0.855) equations, which explained the drug release follows zero-order and is fit for Higuchi equation & mechanism was anomalous diffusion i.e diffusion and erosion.

INTRODUCTION: Oral solid formulations hold a high potential as they serve to be most convenient for the administration of drugs. More than 50% of drug delivery systems available in the market are oral drug delivery systems. They offer convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost [1, 2]. Controlled release (CR) technology has rapidly emerged over the past three decades as a new interdisciplinary science that offers novel approaches to the delivery of bioactive agents into the systemic circulation for a prolonged period at a predetermined rate. The choice of drug to be delivered, clinical needs, and drug pharmacokinetics are some of the important considerations in the development of CR formulations, in addition to the relationship between the rates of drug release from the delivery system to the maximum achievable rate of drug absorption in to the systemic circulation [3, 6, 15].

By achieving a predictable and reproducible bioactive agent release rate for an extended period of time, CR formulations can achieved optimum therapeutic responses, prolonged efficacy, and also decreased toxicity [9, 14].

Matrix system is widely used for the purpose of controlled release, which prolongs and controls the release of drug that is dissolved or dispersed [10, 15, 16]. By the controlled release method, therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time.

Felodipine is an antihypertensive calcium antagonist that lowers blood pressure (BP) by selective action on peripheral resistance. Because of early and high peak plasma concentration and rapid first-pass metabolism, the systemic bioavailability was 15%, need to formulate controlled release dosage form for extended period of time [12, 13].

The objective of the present study was to enhance bioavailability and prolong the release of the drug for a particular period of time in a controlled manner. By using Glyceryl monostearate, Carnaubawax, as hydrophobic polymers, which acts as a matrix forming and rate controlling polymers suitable for preparing a prolonged release dosage forms [17, 18].

MATERIALS AND METHODS:

Materials: Felodipine, Glyceryl monostearate, Carnaubawax, Lactose, Microcrystalline cellulose, Stearic acid.

Drug and polymer compatibility studies:

Compatibility study by FT-IR: This can be confirmed by carrying out with Infrared light absorption scanning spectroscopy (IR) studies. Infrared spectra of pure drug, polymer and physical mixture of formulations in ratio 1:1 was recorded by dispersing them in a suitable solvent (KBr) using Fourier Transform Infrared spectrophotometer [17, 18, 19]. A base line correction was made using dried potassium bromide and the spectra of the pure drug, polymer and the formulation mixture were recorded on FTIR. The data are represented in **Fig. 1 & 2**.

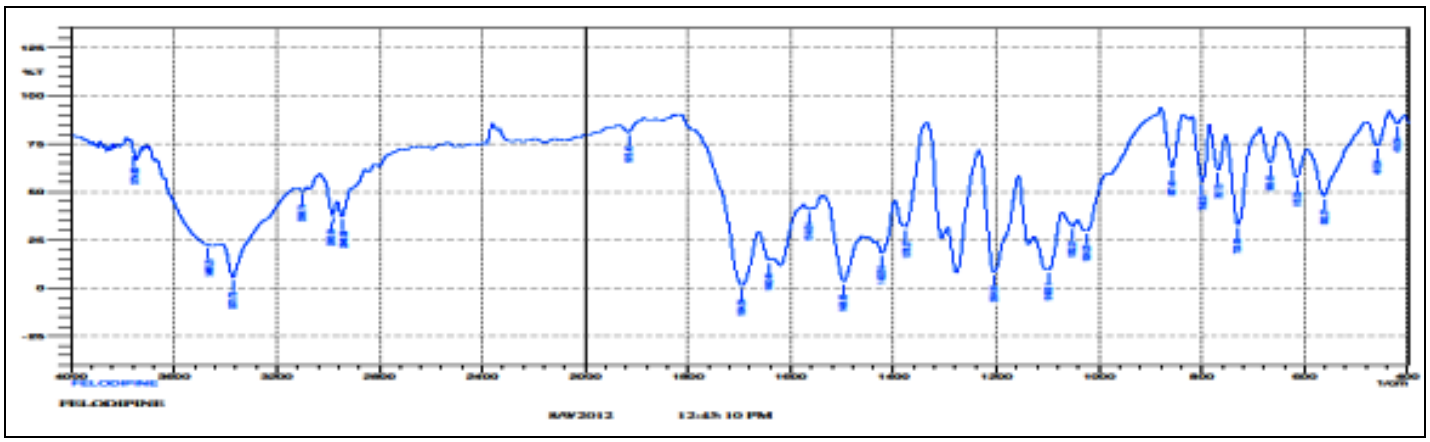


FIG. 1: IR SPECTRA OF FELODIPINE DRUG

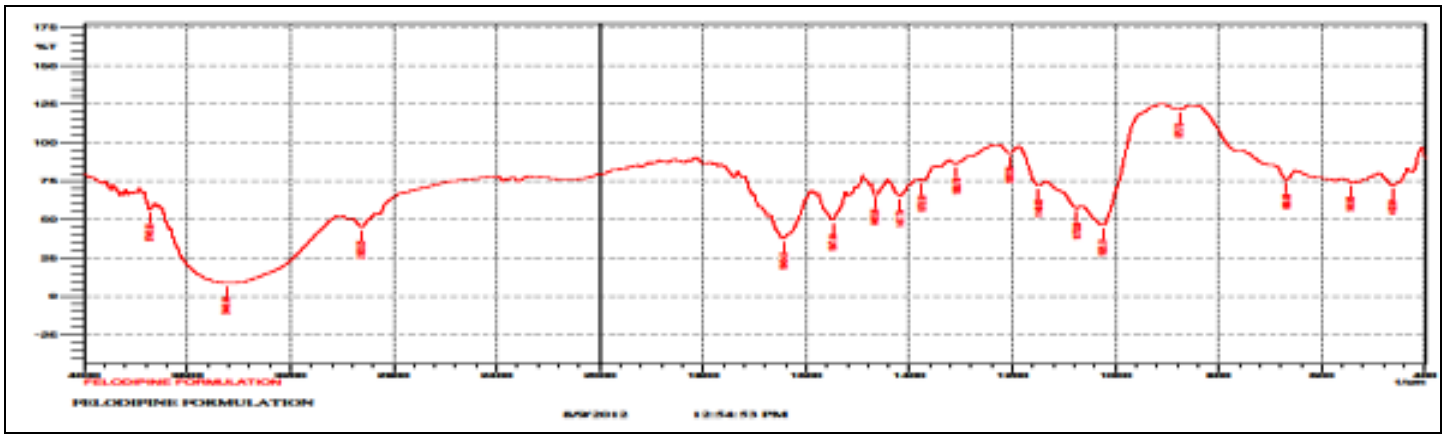
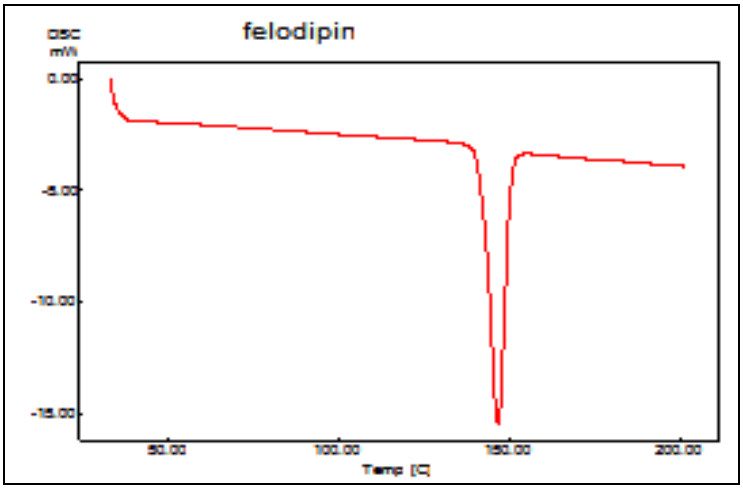


FIG. 2: IR SPECTRA OF FELODIPINE OPTIMIZED FORMULA

Compatibility study by DSC: Differential Scanning Calorimetry (DSC) was performed on pure drug, excipients and optimized formulation. DSC measurements were done on a Shimadzu DSC-60 and samples were heated at the rate of 10°C min in an aluminum cup. There is no considerable change observed in melting endotherm of drug in optimized formulation. It indicates that there is no interaction between drug and other excipients used in the formulation. The data are represented in **Fig. 4, 5 & 6.**



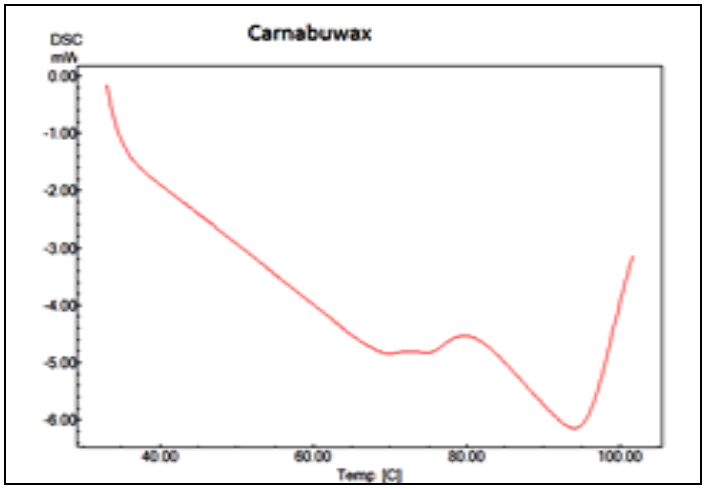


FIG. 4 & 5: DSC OF FELODIPINE & CARNAUBAWAX

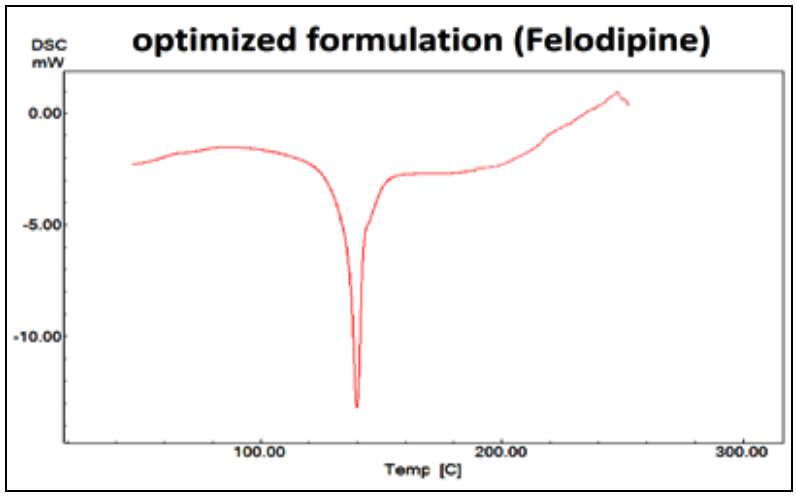


FIG. 6: DSC OF FELODIPINE OPTIMIZED FORMULATION

Methodology:

Preparation of Matrix Tablets: Tablets containing 10 mg of Felodipine were prepared by direct compression method and the formula are shown in **table 1.** The drug, polymer (Glyceryl monostearate or Carnauba wax), lactose, microcrystalline cellulose & stearic acid were individually passed through sieve # 60, mixed & blended for 15 minutes followed by compression.

TABLE 1: FORMULATION OF FELODIPINE CONTROLLED RELEASE MATRIX TABLETS

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Felodipine	10	10	10	10	10	10	10	10
Glyceryl monostearate	40	40	50	50	-	-	-	-
Carnauba Wax	-	-	-	-	40	40	50	50
Lactose	145	-	135	-	145	-	135	-
Microcrystalline cellulose	-	145	-	135	-	145	-	135
Stearic acid	5	5	5	5	5	5	5	5
Total	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Evaluation of Tablets:

Weight variation [9]**:** Twenty tablets were selected randomly and average weight was determined. Then individual tablets were weighed and was compared with an average weight. The results are shown in **table 2.**

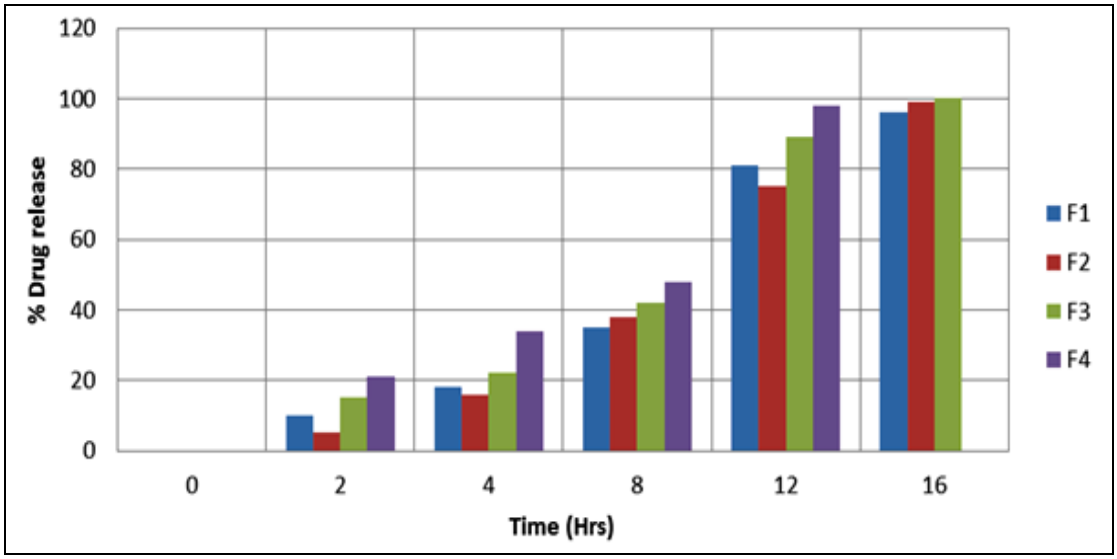
Hardness and Friability [7, 8]: Friability of the tablets was checked by using Roche Friabilator. This device subjects a number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a height of 6 inches with each revolution. Pre-weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. The results are shown in **table 2.**

Thickness: The thickness of the tablet was measured by using digital vernier callipers, twenty tablets from each batch were randomly selected and thickness was measured. The results are shown in **table 2.**

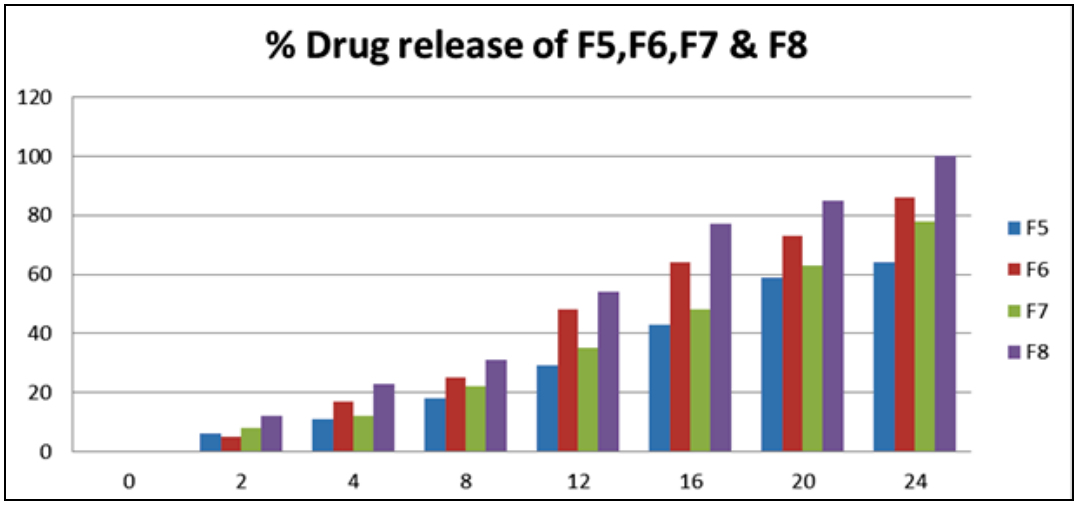
***In-vitro* Dissolution studies:** *In-vitro* dissolution test studies were carried out using USP 24 type-II dissolution test apparatus (Electrolab TDT-06P, Mumbai, India). A 900 ml of phosphate buffer pH 6.8 with 0.1% SLS used as media, thermo-stated at 37±0.5^{o}C and stirred at 100 rpm. Samples were collected periodically (2, 4, 8, 12, 16, 20 & 24 hrs) and replaced with fresh dissolution medium, then, the sample were analyzed using spectrophotometer at 361 nm. Results were shown in **graph 1 & 2.**

TABLE 2: EVALUATION OF FELODIPINE CONTROLLED RELEASE MATRIX TABLETS

Formulation	Hardness (Kg/cm^2)	Thickness (mm)	Weight variation (%)	Friability (%)
F1	3.8±0.21	3.88±0.11	0.25	0.152
F2	3.5±0.16	4.00±0.09	0.13	0.136
F3	3.9±0.19	3.92±0.05	0.20	0.133
F4	3.8±0.17	3.93±0.08	0.19	0.105
F5	3.6±0.15	3.81±0.06	0.08	0.109
F6	3.8±0.22	3.85±0.14	0.09	0.125
F7	3.7±0.19	3.85±0.20	0.15	0.102
F8	3.6±0.28	3.81±0.16	0.17	0.110

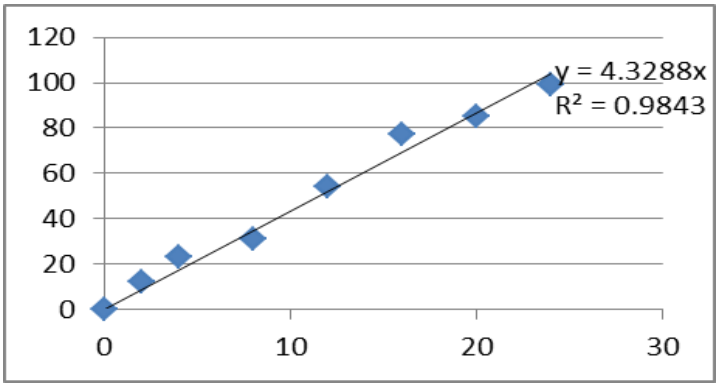


GRAPH 1: *IN-VITRO* DISSOLUTION PROFILE OF F1, F2, F3 & F4 FORMULATIONS

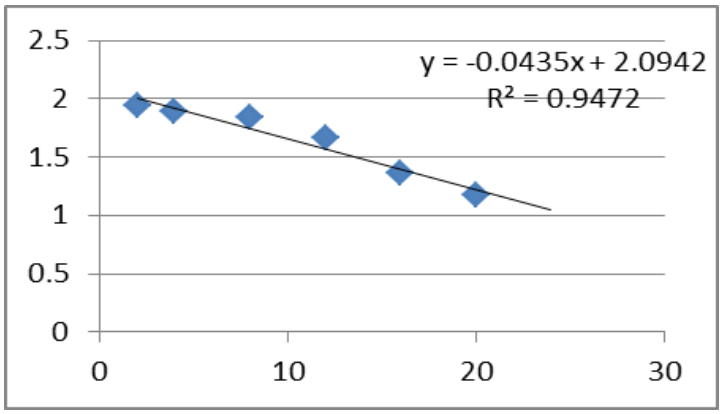


GRAPH 2: *IN-VITRO* DISSOLUTION PROFILE OF F5, F6, F7 & F8 FORMULATIONS

Kinetic mechanism of Drug Release: Kinetic mechanism of drug release was evaluated mathematically by Zero-order, First-order, Higuchi & Korsmayer-Peppas equations and values were shown in **table 3.**

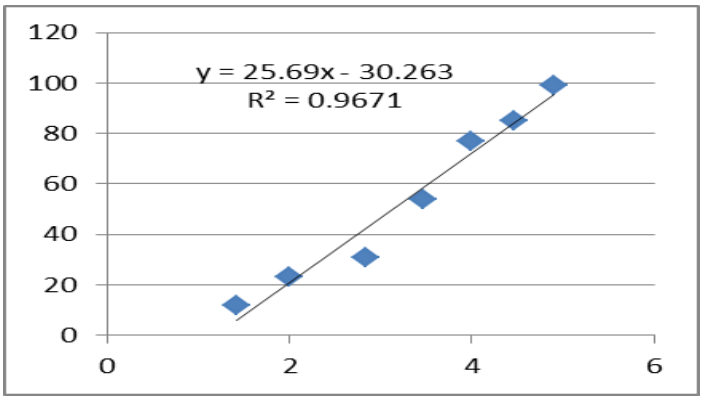


GRAPH 3: ZERO-ORDER

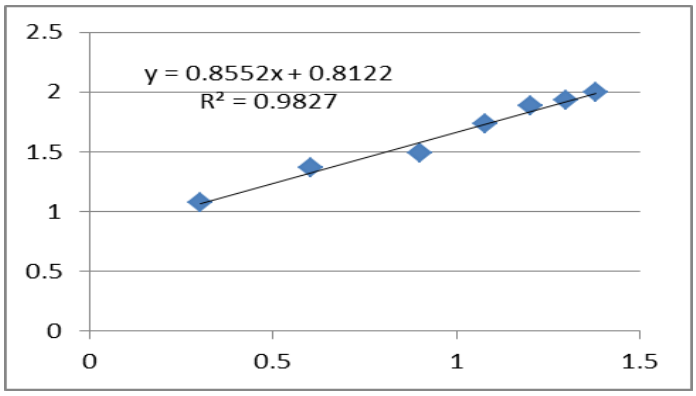


GRAPH 4: FIRST-ORDER

GRAPH 3 & 4: KINETIC DRUG RELEASE MECHANISMS ZERO & FIRST ORDER



GRAPH 5: HIGUCHI EQUATION



GRAPH 6: KORSMEYER-PEPPAS

GRAPH 5 & 6: KINETIC DRUG RELEASE MECHANISMS HIGUCHI & KORSMAYER-PEPPAS

TABLE 3: KINETICS OF DRUG RELEASE FOR OPTIMIZED FORMULATION (F5)

F5	R^2	n
Zero-order	0.984	4.328
First-order	0.947	0.043
Higuchi equation	0.967	25.69
Korsmayer-peppas	0.982	0.855

RESULTS & DISCUSSION: Drug polymer compatibility study was carried by FT-IR data was shown in Fig. 1 & 2 and DSC was performed on pure drug, excipient & optimized formulation and spectra was shown in fig. 4, 5 & 6, which indicates there is no interaction between drug & other excipients used in the formulation.

Compressed tablets were evaluated for thickness, hardness, friability & weight variation & results were shown in **table 2.** In all formulations, the hardness were 3.5-3.9 kg/cm^2 & fribility was less than 1%, indicates tablets has good mechanical strength & resistance.

In-vitro dissolution tests were carried out using USP type-II (Paddle) apparatus using 900 ml of phosphate buffer pH 6.8 with 0.1% SLS used as media, drug release study carried for 24 hrs, results were shown in **graph 1 (F1 to F4) & graph 2 (F5 to F8)**.

In formulations F1, F2 & F3 the 100% drug release was observed in 16 hrs & for F4 in 12 hrs. In F5 to F7, 65-85% drug release was observed in 24 hrs. In F8, 100% drug release was observed in 24 hrs and F8 was considered as optimized formulations.

The *in-vitro* release data was subjected to Zero-order, First-order, Higuchi & Korsmayer-Peppas in order to establish the drug release mechanism & kinetics of drug release from the matrix tablets. Results were shown in **Graphs 3-6 & table 3.**

CONCLUSION: Felodipine matrix tablets were prepared by using carnauba wax, a hydrophobic polymer with a concentration of 25% along with microcrystalline cellulose (F8) has released drug for extended period of time (24 hrs). FT-IR & DSC studies revealed that there was no drug-excipient incompatibility. The drug release mechanism was anomalous diffusion i.e diffusion and erosion.

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