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FORMULATION AND INTRO EVALUATION OF DIETHYL CARBAZAMINE CITRATE TABLETS FOR COLON SPECIFIC DRUG DELIVERY SYSTEM

Miss.Afreen Banu,Dr. Teelavath Mangilal, Mrs.T. Sowmya, Mr.K.Tharun Kumar, Mrs. Farheen Kouser.

Smt.Sarojini Ramulamma College of Pharmacy,Seshadri Nagar,Mahabub Nagar-509001,Telangana,India.

Abstract:

In the present research work sustained release matrix formulation of diethyl carbamazine citrate targeted to colon by using various polymers developed. To achieve PH independent drug release of Diethyl carbamazine citrate.PH modifying agents (buffering agents)were used .Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different Ph dependent polymers. Ethyl cellulose ,Eudragit RLPO and S100 were used as enteric coating polymers. The precompression blend of all formulation was subjects to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests. Among all the formulations F6 formulation was found to be optimized as it was retarded the drug release up to 12 hours and showed maximum of 98.45% drug release. It followed Zero order kinetics mechanism.

Keywords: *Diethyl carbamzine citrate,colon targeting Delivery system,Ethyl Cellulose ,Eudragit RLPO,Eudragit S100*

Corresponding Author:

Miss. Afreen Banu,

Assistant Professor

Smt.Sarojini Ramulamma College of Pharmacy,

Seshadri Nagar,Mahabub Nagar-509001,Telangana,India.

Email.id: *afreenbanu2618@gmail.com,+918179617559.*

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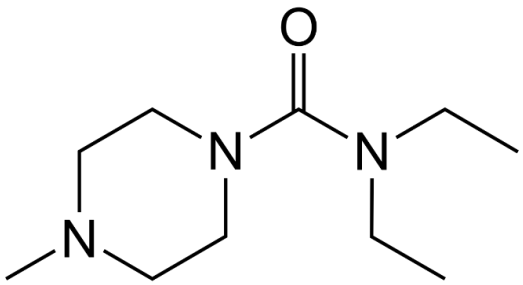
INTRODUCTION:

The aim of the present research work was to develop sustained release matrix formulation of Dieth carbamazine citrate targeted to colon by using various polymers and in vitro drug release study.

The obejective of this study was to prepare Diethyl carbamazine citrate as a colon targeted tablet. Diethly carmazine citrate matrix tablets containing several retarding agents. Separately were used in order to extend the release of drug over the desired period of time.[1]



Structure of Diethylcarbamazine

Diethylcarbamazine is a medication used in the treatment of filariasis including lymphatic filariasis, tropical pulmonary eosinophilia, and loiasis. It may also be used for prevention of loiasis in those at high risk. While it has been used for onchocerciasis (river blindness), ivermectin is preferred. It is taken by mouth.[2]

Common side effects include itching, facial swelling, headaches, and feeling tired. Other side effects include vision loss and dizziness. It is a recommended treatment in pregnancy and appears to be safe for the baby. The World Health Organization; however, recommends waiting until after pregnancy for treatment when feasible. It is made from 4-methyl-piperazine. IUPAC Name is N, N-Diethyl-4-methylpiperazine-1-caroxamide dihydrogen citrate with a molecular formula C10H21N3O.C6H8O7 and a molecular weight 391.4g/mol.it soluble in water and Hot alcohol. Pharmacokinetics studies indicates that peak plasma concentration is achieved at 1 to 2 hours eliminated mainly through feces (4to5%) elimination half-life approximately within 48 hours.[3]

MATERIALS AND METHODS:

The preparation of diethyl carbamazine citrate tablets involves a variety of ingredients sourced from reputable suppliers. The active pharmaceutical ingredient, diethyl carbamazine citrate is supplied by Natco Labs. Excipients such, Eudragit RLPO, Eudragit L100, Cross carmellose sodium, magnesium stearate, micro crystalline cellulose and talc are procured from Merk specilaity PVT Ltd ,Mumbai, India. as Ethyle cellulose is supplied by Signet chemical corporation, Mumbai. India The manufacturing process utilizes several key pieces of equipment. An electronic weighing balance from Wensar ensures accurate measurement of ingredients. A Roche Friabilator from lab India, Mumbai, tests tablet friability. Compression of tablets is performed using a CMD (Cadmach) compression machine. The Pfizer hardness tester from Monsanto[4]

India measures tablet hardness, while the Lab India UV 3000+ UV spectrophotometer is used for analytical purposes. The Electro lab TDT-08L dissolution apparatus evaluates the dissolution profile of the tablets. Finally, Vernier calipers (model CD-6”CS) are employed for precise measurement of tablet dimensions.

Methodology

Analytical Method Development

Determination of absorption maxima :A solution containing the concentration of 10µg/ml was prepared in 0.1n HCL ,7.4 PH and phosphate buffer 6.8 PH respectively ,UV spectrum was taken using double beam UV/VIS spectrophotometer .The solution was scanned in the range of 200-400NM.[5]

Preparation of calibration curve

10 mg of drug accurately weight and dissolved in 10 ml of 0.1N HCL ,7.4PH and 6.8OH in 10 mal volumetric flask ,to make 1000µg/ml standard stock solution (1) .Then 1ml stock solution(1) was taken in another 10ml volumetric flask to make (100µg/ml) standard stock solution (2),Then again 1ml of stock solution(2) was taken in another 10ml volumetric flask and then final concentration were prepare 2,4,6,8,10,12,14,16,18 and 20 µg/ml with 0.1N HCL ,7.4 PH and 6.8PHThe absorbance of standard solution was determined by using UV /VIS spectrometer at 273nm .linearity of standard curve was assayed from the square of correlation coefficient(r2) which determine by least square linearity regression analysis.[6]

Preparation of Tablets

Di ethyl carbamazine citrate tablets were prepared using the direct compression method. Ingredients include Diethyl carbamazine citrate , croscarmellose sodium (CCS), Talc, magnesium stearate and l MCC pH 102,. Tablets were compressed using 9 mm flat surface punches using 8 station tablet punching machine with the hardness of 4-4.5 kg/cm, each weighing 75 kg/cm².[7]

Formulation Composition

INGREDIENT NAME	F1	F2	F3	F4	F5	F6	F7	F8	FP9
Ethyl Cellulose (mg)	50	100					50		50
Eudragit RLPO (mg)			50	10			50	50	
Eudragit L 100(mg)					50	100		50	50
Magnesium Stearate (mg)	3	3	3	3	3	3	3	3	3
TALC (mg)	3	3	3	3	3	3	3	3	3
MCC PH 102 (mg)	Q,s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
TOATAL WEIGHT	200	200	200	200	200	200	200	200	200

Formulation Composition

Evaluation of Tablets

The formulated Tablets were evaluated for the following quality control studies & In vitro drug r dissolution studies.

Pre formulation studies

Angle of Respose

The frictional force in a loose powder can be measured by the angle of response .It is defined as ,the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile ,it slides down the slides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of response. A funnel was secured with its tip at a given height (h), above a graph that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. the angle of response was calculated using the following formula;

Tan o= h/r Tan o =Angle of response

h=Height of the cone ,r=radius of the cone base [8]

Angle of Repose

Angle of response	Nature of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk Density (BD)

Measure the mass of powder and its bulk volume without compaction to calculate bulk density using the formula

Bulk density = M/V0

Tapped density

Measure the mass of powder and its volume after tapping to minimum volume using a tap density tester calculate tapped density using

Tapped density = M/V [9]

Compressibility Index Limits

Carr's Index	Properties
5-15	Excellent
12-16	Good
18-21	Fait to possible A
2-35	Poor
33-38	very poor
>40	very very poor

Post compression Parameters

General Appearance

Evaluate tablets for shape, color, texture, and odor.

Average Weight/Weight Variation

20 tablets were taken and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (individual weight -Average weight/ average weight)*100 [10]

Pharmacopoeial Specifications for Tablet Weight Variation

Average weight of Tablet (mg) (I.P)	Average Weight of Tablet (mg) (USP)	Maximum Percantage Difference Allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Thickness

Measure tablet thickness is important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Hardness Test

Measure tablet hardness using a Monsanto hardness tester and the average is calculated and presented with deviation.

Friability Test

Roche friabilator was used to determine the friability by following procedure .pre weighed tablets were placed in the friabilator. The tablets were rotated at 25rpm for 4 minutes (100 rotations). At the end of test the tablets were re weighed loss in the weight of tablet is the measure of friability and is expressed in percentage as

%Friability = [(W1 - W2) / W1] x 100.

Determination of Drug Content

Both compression coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tabelet weight of Diethyl carbamazine citrate were accurately weighed transfererd to a 100ml volumetric flask containing 50ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV-Visible Spectrophotometer. The drug concentration was calculated from the calibration curve.

***In- Vitro* Dispersion Time**

In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of 0.1N HCL. Tablets from each formulation were randomly selected and in vitro dispersion time was performed.

Water Absorption Ratio (%)

A piece of tissue paper folded twice was placed in a small petridish (Internal diameter=6.5 cm) containing 6ml of water. A tablet was placed on the paper and the time required for complete wetting was then measured. The water absorption ratio (R) was determined using the following equation.

$$\boldsymbol{Water\ absorption\ ratio\ (R)} = \frac{\boldsymbol{Wa - Wb}}{\boldsymbol{Wb}} * \boldsymbol{100}$$

Where, Wb is the weight of the tablet before water absorption and is the weight of the tablet after absorption.

***In-Vitro* Dissolution Study**

Dissolution studies were performed using the USP-II apparatus (Paddle method). A total of 900 ml of 0.1N HCl was placed in the dissolution vessel, which was equilibrated to 37±0.5℃. A tablet was placed in the vessel and the apparatus was operated at 50 rpm for 30 minutes. Drug release studies were conducted in simulated gastric fluid (SGF, PH 1.2) for the first20 hours as the average gastric emptying time is about 2 hours. Then the dissolution medium was repaced with enzyme free simulated intestinal fluid (SIF,PH 7.4) and tested for drug release for 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme free stimulated intestinal fluid (SIF,PH 6.8) was used upto 12hours to mimic colonic ph conditionl .Drug release was measured from compression coated Diethylcarbamazine citrate tablets added to 900ml of dissolution medium. 5mlof sample was withdrawn every time and replaced with fresh medium, samples withdraw at various time intervals were analyzed spectrophotometrically at 275nm and 270nm respectively. All dissolution runs were performed for six batch. The results were given with deviation.[11]

Dissolution Parameters

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1N HCL
Volume	900 ml
Speed	50rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	2, 4, 6, 8, 10, 15, 20 and 30mins
Analytical method	Ultraviolet Visible Spectroscopy
λmax	270nm

Release Kinetics

The release kinetics of the drug from the matrix system were analyzed by fitting the dissolution data to several release models: zero-order, first-order, and diffusion models.

Zero-Order Release

It defines a linear relationship between the fraction of drug release

$F=k_o\ t$

F= is the drug release at time, t and ko is the zero order release rate constant.

A plot of % drug release versus time is linear.

First-Order Release Kinetics: The release rate data are fitted to the following equation

Log(100-F) = kt

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model

T**o** study the Higuchi release kinetics, the release rate data were fitted to the following equation..

$$\mathbf{F=k_t 1/2}$$

Korsmeyer and peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug release versus log

time according to Korsmeyer-peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight line

$$Mt/M=K\,t^{n}$$

Hixson-crowell release model:

$$(100-Q_t)1/3=1001/3-KHC.t$$

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly srosion.

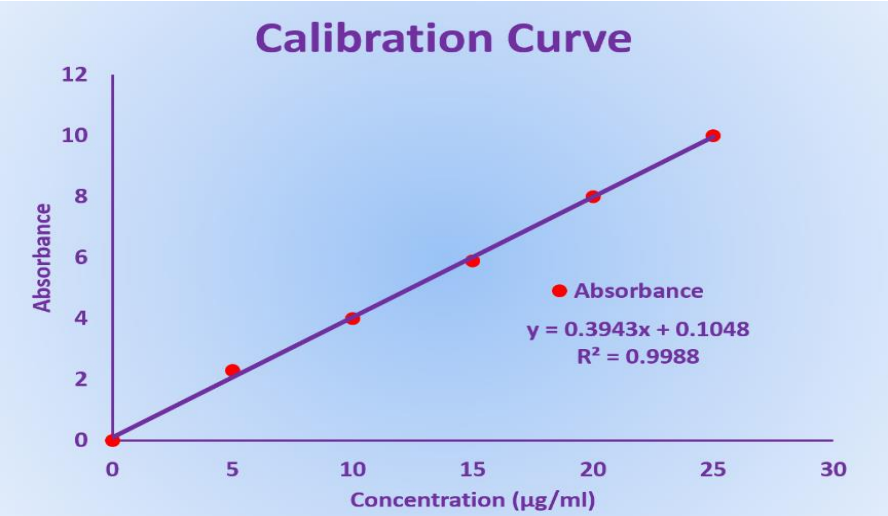
Results and Discussion

Construction of Standard Calibration Curve of Diethylcarbamazine citrate0.1 N HCL

The absorbance of the solution was measured at 275nm, using UV spectrometer with 0.1N HCL as blank. The values are shown in table. A graph of absorbance Vs Concentration was plotted which indicated in compliance In the concentration range 2 to 12 µg/ml

Observation for Graph of Diethylcarbamazine Citrain 0.1N Hcl (275nm)

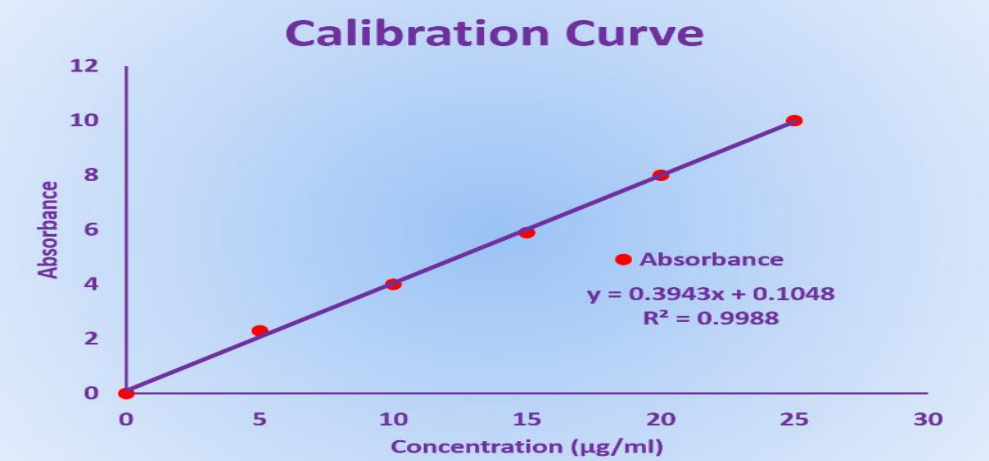
Concentration (mg/l)	Absorbance
0	0
2	0.138
4	0.256
6	0.376
8	0.461
10	0.582
12	0.824



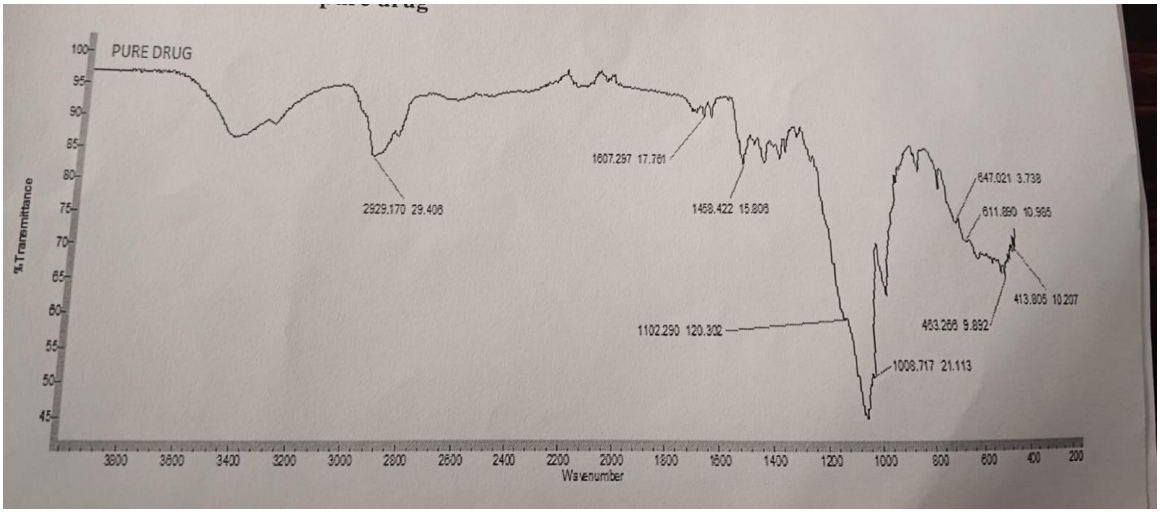
Observation for Graph of Diethylcarbamazine Citrain 0.1N Hcl (275nm)

Standard Graph of Diethylcarbamazine Citrate in 6.8pH

CONCENTATION (mg/l)	ABSORBANCE
0	**0**
1	**0.148**
2	**0.275**
3	**0.379**
4	**0.481**
5	**0.621**
6	**0.859**

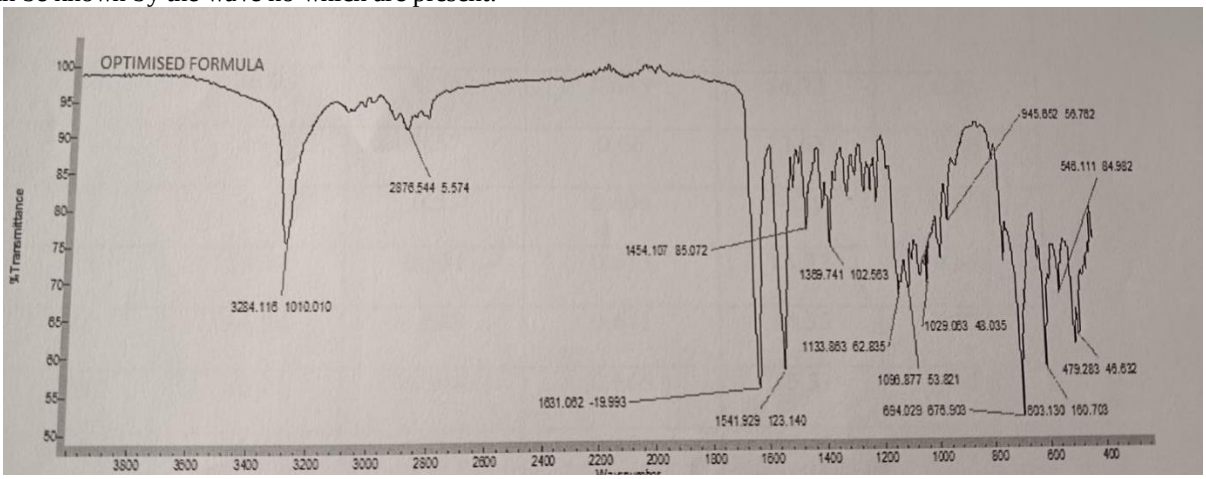


Standard Graph of Diethylcarbamazine Citrate in 6.8pH



FTIR -Spectrum of Pure Drug

The above figure is the FTIR spectrum of the pure drug by which the compatibility of drugs to all other Excipients can be known by the wave no which are present.



FTIR -Spectrum of optimized formulation

The above fig is the FTIR spectrum of the optimized formulation by which the compatibility of drug to all other excipients can be known by the waves no which are present.

Evaluation of Blend

Pre-Compression Studies of Diethylcarbamazine citrate

Formulation code	Bulk Density	Tapped Density	Cars Index	Hausner ratio	Angle of response
F1	0.55	0.645	14.72	0.85	36.01
F2	0.57	0.66	13.63	0.86	34.8
F3	0.53	0.606	14.19	0.838	36.05
F4	0.531	0.613	13.37	0.866	34.19
F5	0.549	0.641	14.35	0.856	36.24
F6	0.564	0.666	15.31	0.854	33.25
F7	0.581	0.671	13.41	0.865	37.08
F8	0.567	0.654	13.12	0.845	35.12
F9	0.571	0.689	13.28	0.855	35.45

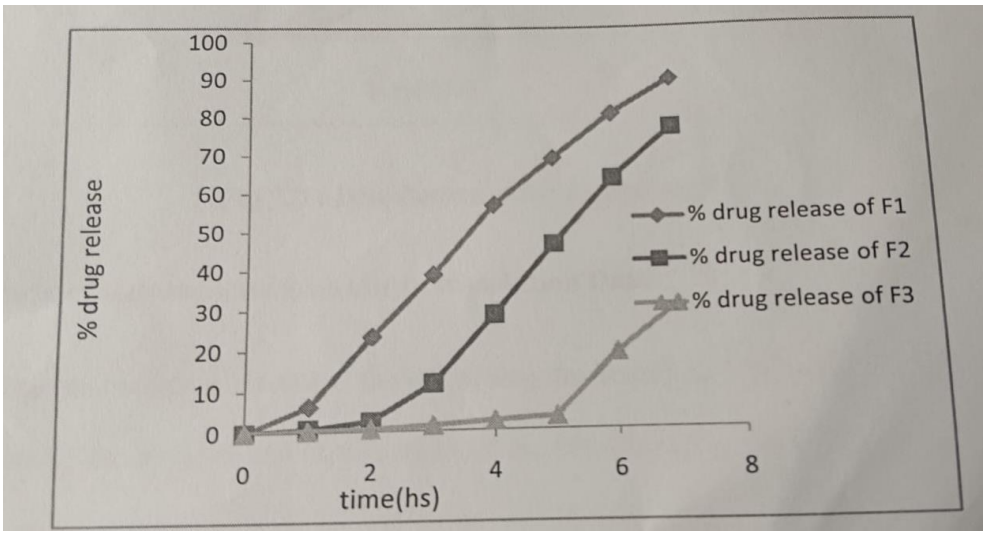
Post compression studies

***In-vitro* Quality control parameters for compression coated tablets**

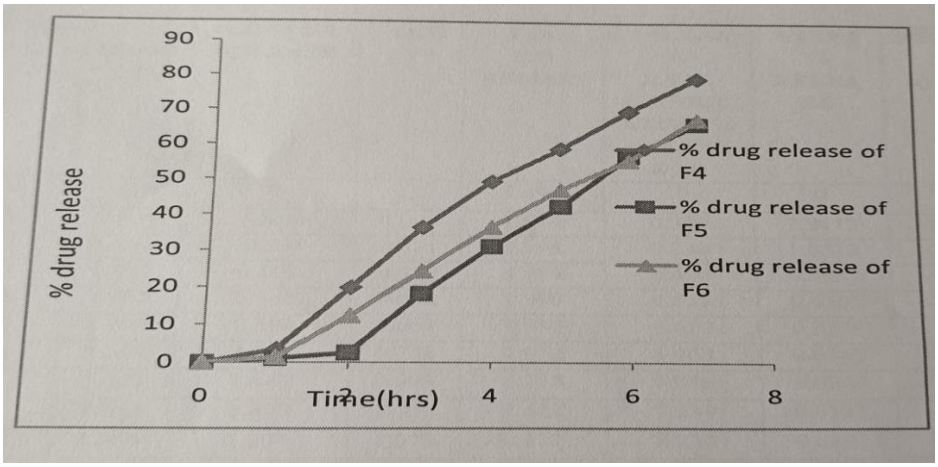
Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	312.5	4.5	0.52	4.8	99.76
F2	305.4	4.2	0.54	4.9	99.45
F3	298.6	4.4	0.51	4.9	99.34
F4	310.6	4.5	0.55	4.9	99.87
F5	309.4	4.4	0.56	4.7	99.14
F6	310.7	4.2	0.45	4.5	98.56
F7	302.3	4.1	0.51	4.4	98.42
F8	301.2	4.3	0.49	4.7	99.65
F9	298.3	4.5	0.55	4.6	99.12

***In-vitro* Drug Release profile for coated formulation**

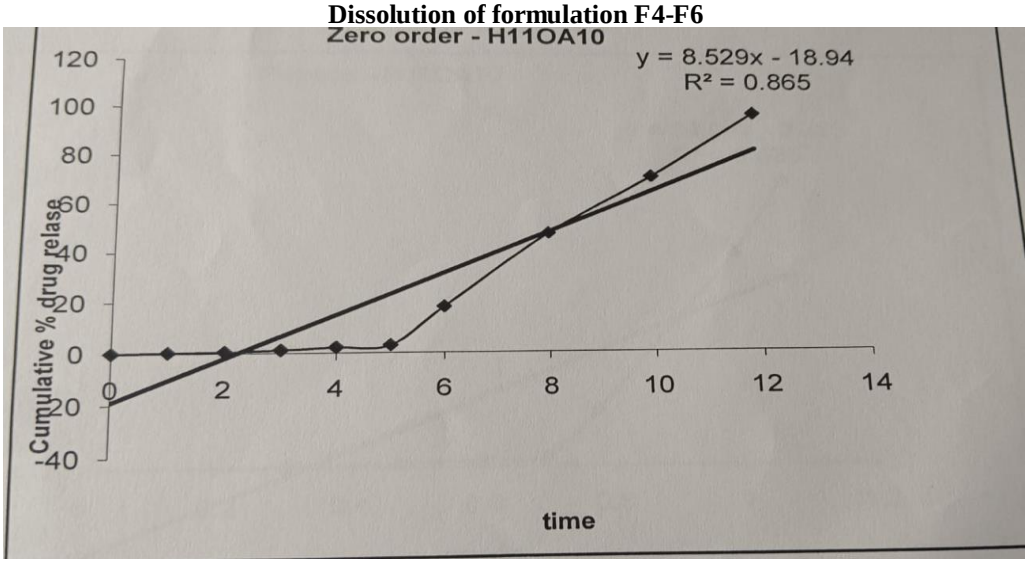
Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	6.19	0.73	0.34	3.39	1.11	1.44	8.06	2.65	1.32
2	23.16	2.46	0.54	19.88	2.49	12.30	20.46	10.23	1.74
3	38.49	11.46	1.26	36.45	18.19	24.44	34.46	19.19	3.67
4	56.34	28.19	2.22	49.59	31.19	36.61	48.41	31.57	9.57
5	68.44	45.79	3.05	59.01	42.46	47.30	68.76	43.08	19.48
6	80.16	62.87	18.41	69.85	56.78	55.68	76.73	58.74	31.88
7	89.16	76.19	30.05	79.46	66.19	67.53	94.23	65.13	52.47
8	98.14	85.16	48.69	86.19	79.46	78.72		78.45	62.46
9		92.78	55.38	99.14	91.46	83.34		85.67	73.47
10		97.73	72.34		96.19	90.67		98.45	83.44
11			87.56			96.12		98.12	92.47
12			93.69			98.45			96.44



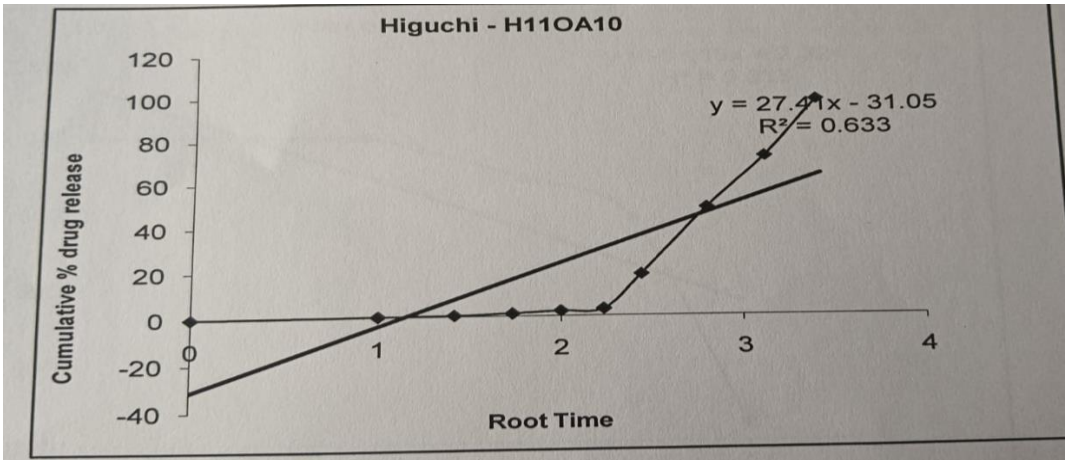
Dissolution of formulation F1-F3



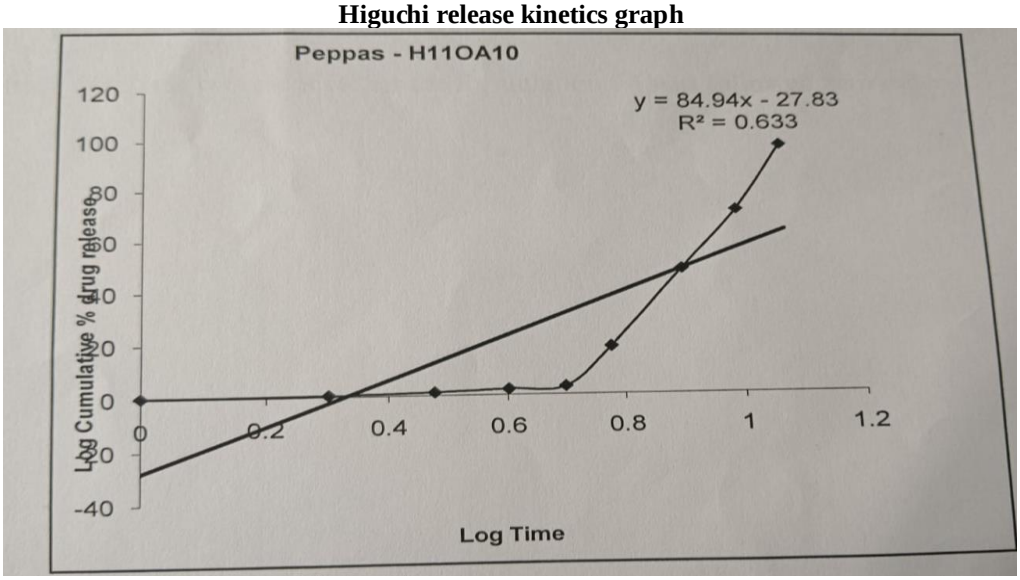
Dissolution of formulation F4-F6



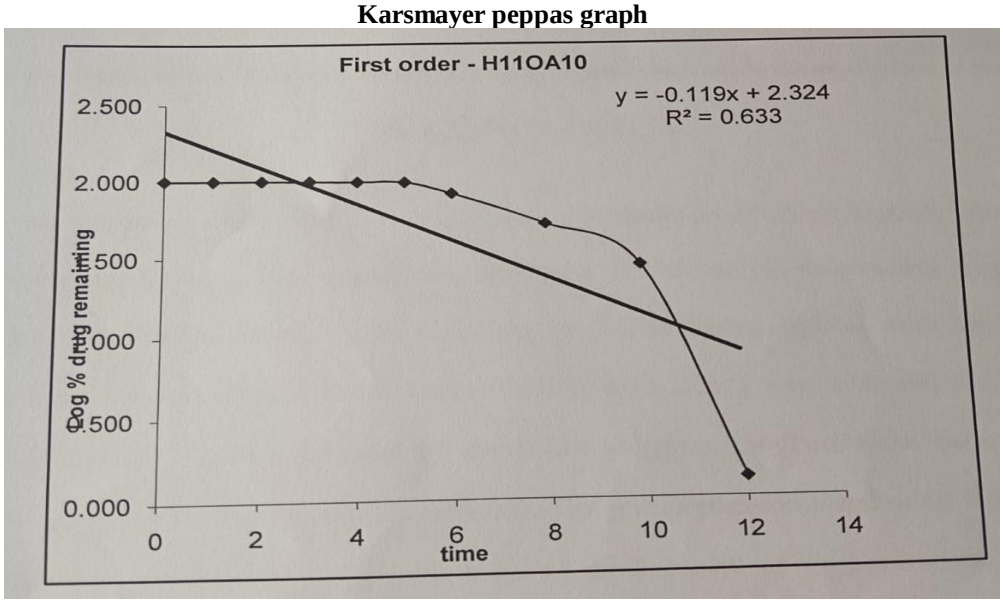
Zero order release kinetics graph



Higuchi release kinetics graph



Karsmayer peppas graph



First order release kinetics graph

CONCLUSION:

In the present work sustained release matrix formulation of Diethylcarbamazine citrate targeted to colon by using various polymers developed. To achieve ph-independent drug release of Diethylcarbamazine citrate, ph modifying (buffering agents) were used. Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different ph dependent polymers. Ethyl cellulose, Eudragit L100 and S100 were used as enteric coating polymers. The pre comprssion blend of all formulations was subjected to various flow property tests and all the formulations were passed the results. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all tests. Among all the formulation f6 formulation was found to be optimized as it was retarded the drug release upto 12 hours and showed maximum of 98.45% drug release. It followed zero order kinetics mechanism.

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