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Design development and evaluation of citicoline controlled release tablets

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ABSTRACT

Citicoline sodium (citicoline) has a broad spectrum of therapeutic index, as a neuroprotectant or cerebroprotectant.Citicoline is useful in the treatment of ischemic stroke, head trauma and neurodegenerative disease. The present study was planned to develop controlled release tablets of citicoline. The effect of various hydrophilic and hydrophobic polymers on controlling release of the drug was studied by using Hydroxypropylmethyl Cellulose, Hydroxypropyl Cellulose, Methacrylic acid copolymers (Eudragit RSPO, Eudragit RLPO). Tablets were prepared by wet granulation method using non aqueous granulation fluid. Tablets were evaluated for physical, drug content and in-vitro release properties. Promising results were obtained with tablets prepared by using Eudragit RSPO in controlling the release of the drug for extended period of time. The drug release followed Zero order, Higuchi square root and Peppas & Korsmeyer kinetics with diffusion mechanism. Stability studies indicated the dosage form is stable for 3 months at accelerated condtions of 40°C± 2 °C&75%±5 % RH.

Key Words: Citicoline sodium, Eudragit RSPO, Eudragit RLPO, Hydroxy propyl methyl Cellulose and Hydroxypropyl Cellulose.

INTRODUCTION

Citicoline sodium is a chemically designate as Cytidine 5'-(trihydrogendiphosphate) P'-[2-(trimethylammonio) ethyl] ester monosodium salt, its molecular formula is $C_{14}H_{25}N_4NaO_{11}P_2$ and molecular weight is 510.31(salt) and 488.32 (base- $C_{14}H_{26}N_4O_{11}P_2$). It is a white crystalline, hygroscopic powder and readily soluble in water but practically insoluble in alcohol. Its melting point was 259 - 268°C and dissociation constant (Pka) was 4.4 [1]. Biopharmaceutical classification system (BCS) for Citicoline is Class – I (High solubility and High Permeability) [3]. Citicoline has a broad spectrum of therapeutic index, as a Neuroprotectant or Cerebroprotectant, in particular citicoline is useful the victims of ischemic stroke, head trauma and neurodegenerative disease. Citicoline is also used to treat unconsciousness resulting from cerebral thrombosis, hemorrhages, demyelinating diseases, cranial trauma and cerebropathies due to atherosclerosis [2].

Citicoline was originally developed in Japan for stroke. It was later introduced as a prescription drug in many European countries. In these countries it is now frequently prescribed for thinking problems related to circulation problems in the brain. In the US, citicoline is marketed as a dietary supplement [3].

Citicoline daily dosages may range from 250 mg to about 3000 mg and more preferably from 500 mg to about 2000 mg up to four or more times daily, duration of the treatment may vary from several weeks to several years, dosages may be varied over time depending on the severity of symptoms [4].

A controlled release dosage form is designed to maintain therapeutic levels of a drug in patient's bloodstream by releasing the drug over an extended period. This reduces the repeated chemical imbalance in the blood chemistry, which might be detrimental to the patient's health. Maintenance of constant blood levels of Citicoline in the bloodstream increases the therapeutic effectiveness of the drug, thereby controlling the condition more promptly. The use of Citicoline controlled Release tablets will reduce the frequency of dosage which is especially beneficial for patients.

Developing the oral controlled release matrix tablets for highly water soluble drugs with constant release rate has always been challenge to the pharmaceutical technologist.

The objective of the study was to formulate controlled release drug delivery systems of citicoline using hydrophilic and hydrophobic polymers. Hydroxypropylmethyl Cellulose (HPMC K100 M) and Hydroxypropyl Cellulose(HF) were selected as hydrophilic polymer HPMC K100 M is the most important hydrophilic polymer used at levels of 10-80% w/w to retard the release of drugs from the oral delivery systems [5]. Hydrophobic polymers, the most interesting acrylic polymers are high-permeable Eudragit RLPO and low-permeable Eudragit RSPO, both are neutral copolymers of poly (ethyl acrylate, methyl methacrylate) and trimethyl aminoethyl methacrylate chloride, and are insoluble in water and digestive juices; but they swell and are permeable, which means that drugs embedded in their matrices can be released by diffusion with independent of the pH of the digestive tract [6]. The degree of permeability depends on the relative proportion of quaternary ammonium groups in Eudragit. The proportion of functional quaternary ammonium groups in Eudragit RSPO and Eudragit RLPO is 5 and 10%, respectively [7].

MATERIALS AND METHODS

Citicoline monosodium was gift sample from Micro Labs, Bangalore, Eudragit RSPO, Eudragit RLPO and Colloidal Silicon Dioxide NF from Evonik, Mumbai, Hypromellose (Methocel K100 M) from Colorcon, Goa, Hydroxypropyl Cellulose from Ashland, SA, Microcrystalline Cellulose NF from Signet, Mumbai, Magnesium Stearate NF from Ferro corp, Mumbai, Talc from Luzenca Pharma , Italy, Titanium dioxide from Kronos, Germany, Triacetin from Merck ,Mumbai, Acetone and Isopropyl alcohol from Rankem , Mumbai. All other materials used were of pharmaceutical grade.

PRE-FORMULATIONS:

Preformulation studies were conducted with citicoline sodium and the important rate controlling polymers to evaluate their compatibility. The chemical incompatibility studies were conducted using Differential Scanning Calorimetry and Fourier Transform Infra-Red (FT-IR) spectroscopy.

Differential Scanning Calorimetry :(DSC)

The thermograms of pure citicoline sodium, alone and in combination (HPMC, HPC, Eudragit RSPO, Eudragit RLPO with Pure drug) were recorded using Differential Scanning Calorimetry (Mettler Toledo Star DSC1, USA) at a heating rate 10°C/min over a temperature range of 35-350° C under nitrogen flow of 25 ml min^{-1} for maintaining inert atmospheres. The sample was hermetically sealed in an aluminium crucible.

Fourier Transform Infra-Red (FT-IR) spectral analysis:

Infrared spectra of pure citcoline, alone, in combination (HPMC, HPC, Eudragit RSPO, Eudragit RLPO with Pure drug) and tablet formulation were recorded using Fourier–Transformed Infrared (FT–IR) spectroscopy, Perkin Elmer, spectrum-100, Japan. KBr was used as background and the scanning range was 400 to 4000 cm^{-1}.

PREPARATION OF MATRIX TABLETS

The tablets were prepared by wet granulation method by using non-aqueous solvent acetone. The composition of the tablet formulations studies are represented in the Table - 1The required amount of drug, polymers and other excipients were mixed in a SS container. Required amount of acetone was added and mixed thoroughly to form the wet mass. The wet mass was passed through 14# mesh to obtain wet granules. The wet granules were transferred into a tray and dried in hot air oven at 60 ± 5°C as inlet temperature until the LOD reaches below 3.0 %. The dried granules were sifted through 20# mesh. The dried granules were mixed with colloidal silicone dioxide (previously sifted through 40# mesh) and Magnesium stearate (previously sifted through 60# mesh) for 5 min. The tablets were compressed on compression machine by using 22 x 10 mm oval shape punch for the tablet weight of 1580mg and 20 x 10 mm oval shape punch for the tablet weight of 1280 to 1420 mg. All tablets were coated with Eudragit RLPO using acetone and isopropyl alcohol (1:1) as solvent.

EVALUATION OF GRANULES:

Flow property of the granules evaluated by using below methods [8],

Bulk Density = Weight of the powder (g) / Untapped volume (ml)

Tapped Density = Weight of the powder (g) / Final tapped volume (ml)

Compressibility Index (%) = (Tapped Density- Bulk Density) ×100/ Tapped Density

Hausner's Ratio = Tapped Density/ Bulk Density

The physical properties of granules were shown in Table - 4.

PHYSICAL EVALUATION OF TABLETS:

Weight variation

20 tablets from each formulation were weighed using an electronic balance (Mettler-Toledo,AB104, Germany) and mean and relative standard deviation of the weight were determined based on an official method.

Hardness and Thickness

The diametrical crushing strength test was performed on 10 tablets from each formulation.
10 tablets were tested using a Dr.Schleuniger, 6D, hardness tester.

The thickness of the tablets was measured with a Verniercaliper (Mitutoyo, CD-8 CSX).

Friability [9]

For each formulation, the friability of 20 tablets was determined using a friabilator (Electrolab EF-2W). 20 tablets from each formulation were weighed and tested at a speed of 25 rpm for 4 min. After removing of dust, tablets were re-weighed and friability percentage was calculated using the following equation:

% Friability = $(W_0\text{-}W)/ W_0 \times 100$.

(W_0= initial weight and W= Final weight)

DRUG CONTENT (ASSAY):

Standard Preparation:

Weigh accurately and transfer about 53 mg of Citicoline sodium (equivalent to 50 mg of Citicoline) into 100 mL volumetric flask. Add 50 mL of 0.1N hydrochloric acid and sonicate for 20 min. to dissolve and make up the volume with 0.1N hydrochloric acid.

Dilute 5 mL of the above standard solution to 50 mL volumetric flask and make up the volume with 0.1N hydrochloric acid and filtered through Whatman filter.

Sample Preparation:

Weighed powder of 10 crushed tablets equivalent to 100 mg of citicoline and transferred into a 200 ml volumetric flask. 100 ml of 0.1N hydrochloric acid added to it, sonicated to dissolve and made up the volume to 200 ml with 0.1N hydrochloric acid, mixed well and filtered through Whatman filter. 5 ml of the filtrate was taken and further diluted to 50 ml with 0.1N hydrochloric acid. Absorbances were taken at 270nm on UV spectrophotometer (Analytikjena Specord 210,).

***IN-VITRO* DRUG RELEASE STUDY:**

Preparation of standard solution:

57.5mg of Citicoline monosodium (equivalent to 55mg of Citicoline) was weighed, transferred in to 50mL of volumetric flask, dissolved and made up the volume with pH 6.8 Phosphate buffer. Further diluted 2 ml of this solution to 50 ml volumetric flask and make-up to the volume with pH 6.8 Phosphate buffer.

Table – 1: Composition of controlled release tablet formulations

S.No	Ingredients	mg/tablet															
		CTC/01	**CTC/02**	**CTC/03**	**CTC/04**	**CTC/05**	**CTC/06**	**CTC/07**	**CTC/08**	**CTC/09**	**CTC/10**	**CTC/11**	**CTC/12**	**CTC/13**	**CTC/14**	**CTC/15**	**CTC/16**
1	Citicoline Sodium	1045.00	1045.00	1045.00	1045.00	1045.00	1045.00	1045.00	1045.00	1045.00	1045.00	1045.00	1045.00	1045.00	1045.00	1045.00	1045.00
2	MCC	102.00	42.00	42.00	52.00	102.00	42.00	42.00	52.00	102.00	42.00	42.00	52.00	102.00	42.00	42.00	52.00
3	HPMC K 100 M	100.00	160.00	300.00	450.00	---	---	---	---	---	---	---	---	---	---	---	---
4	HPC HF	---	---	---	---	100.00	160.00	300.00	450.00	---	---	---	---	---	---	---	---
5	Eudragit RLPO	---	---	---	---	---	---	---	---	100.00	160.00	300.00	450.00	---	---	---	---
6	Eudragit RSPO	---	---	---	---	---	---	---	---	---	---	---	---	100.00	160.00	300.00	450.00
7	Acetone	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
8	CSD	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
9	Magnesium Stearate	18.00	18.00	18.00	18.00	18.00	18.00	18.00	18.00	18.00	18.00	18.00	18.00	18.00	18.00	18.00	18.00
Tablet Weight (Core)		**1280.00**	**1280.00**	**1420.00**	**1580.00**	**1280.00**	**1280.00**	**1420.00**	**1580.00**	**1280.00**	**1280.00**	**1420.00**	**1580.00**	**1280.00**	**1280.00**	**1420.00**	**1580.00**
10	Eudragit RLPO	12.25	12.25	12.25	12.25	12.25	12.25	12.25	12.25	12.25	12.25	12.25	12.25	12.25	12.25	12.25	12.25
11	Talc	5.10	5.10	5.10	5.10	5.10	5.10	5.10	5.10	5.10	5.10	5.10	5.10	5.10	5.10	5.10	5.10
12	Titanium Dioxide	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
13	Triacetin	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15	1.15
14	Acetone : Isopropyl Alcohol (50:50 %)	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Tablet Weight (Coated)		**1300.00**	**1300.00**	**1440.00**	**1600.00**	**1300.00**	**1300.00**	**1440.00**	**1600.00**	**1300.00**	**1300.00**	**1440.00**	**1600.00**	**1300.00**	**1300.00**	**1440.00**	**1600.00**

***MCC**-Microcrystalline Cellulose, **HPMC**- HydroxypropylMethyl Cellulose, **HPC**- Hydroxypropyl Cellulose, **CSD**- Colloidal silicone dioxide*

Preparation of Sample solution:
In-vitro drug release studies were carried out using 900 ml of pH 6.8 Phosphate buffer as dissolution medium using USP Apparatus-I Basket (EelctroLab,TDT- 08 L) at 100 rpm and the temperature was maintained at 37±0.5°C. The sampling points were 1,3,6,9, & 12 hours. 10ml of aliquot was withdrawn at regular interval and replaced with equal volume of fresh dissolution medium to maintain the volume constant. The samples were filtered, diluted the 2 ml of this solution to 50 ml volumetric flask and make-up to the volume with pH 6.8 Phosphate buffer and analysed for drug release. The amount of drug released was determined by UV at 270 nm.

Calculate the percentage of citicoline dissolved by the formula

$$= \frac{At}{As} \times \frac{Std.Wt.}{50} \times \frac{2}{50} \times \frac{900}{1} \times \frac{50}{2} \times \frac{100}{LC} \times \frac{488.32}{510.31}$$

At: Absorbance of citicoline in the Sample Solution
As: Average Absorbance of citicoline in Standard Solution
Std. wt.: Weight of citicoline standard
LC: Labelled amount of citicoline per tablet. (1000mg)
Citicoline molecular weight: 488.32
Citicoline monosodium molecular weight: 510.31

KINETICS OF DRUG RELEASE
The kinetic data for the *in vitro* release was estimated using different kinetic orders like zero-order, systems such as Higuchi's diffusion and Peppas & Korsmeyer model programs were used to calculate the kinetic treatments, kinetic parameters and kinetic data for the *in vitro* release.

STABILITY STUDY:
Stability study of selected formulation will test according to international conference of harmonization guidelines. The tablets will stored in Alu-Alu blister for 3 months in stability chamber at 40°C± 2°c&75% ± 5 % RH. Stability samples will be tested for Physical, drug content and in vitro dissolution.

RESULTS AND DISCUSSION

Table - 2: DSC characteristics of pure drug and Combination with Polymers

Parameters	Citicoline Sodium(API)	API+HPMC K100M	API+HPC HF	API+Eudragit RLPO	API+Eudragit RSPO
On Set (°C)	264.92	257.63	255.83	256.50	251.85
Peak (°C)	272.41	266.28	261.13	263.76	257.73
Area (mJ)	1620.00	782.54	452.35	696.28	226.92
Delta H (J/g)	403.97	195.63	113.09	174.07	56.73

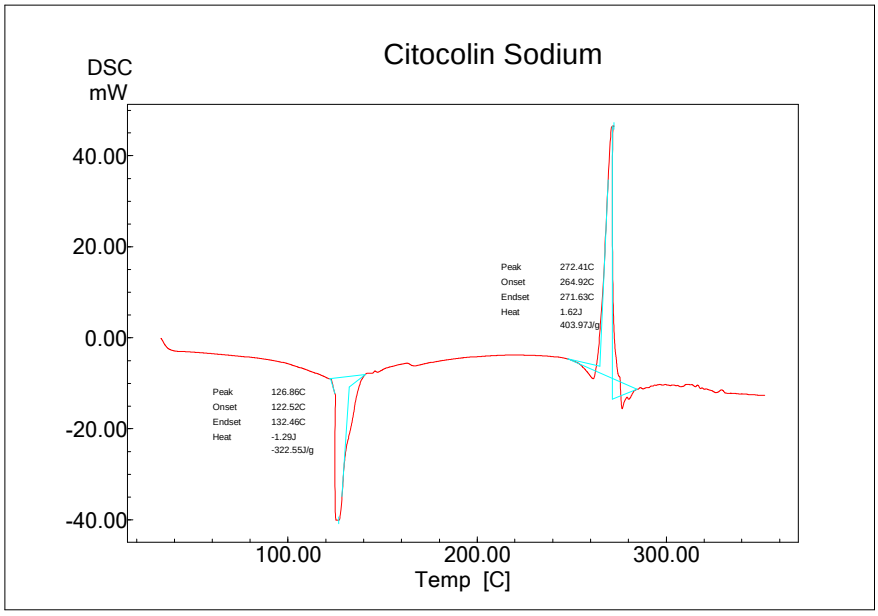

Figure – 1: DSC Thermo graph of Citicoline Sodium

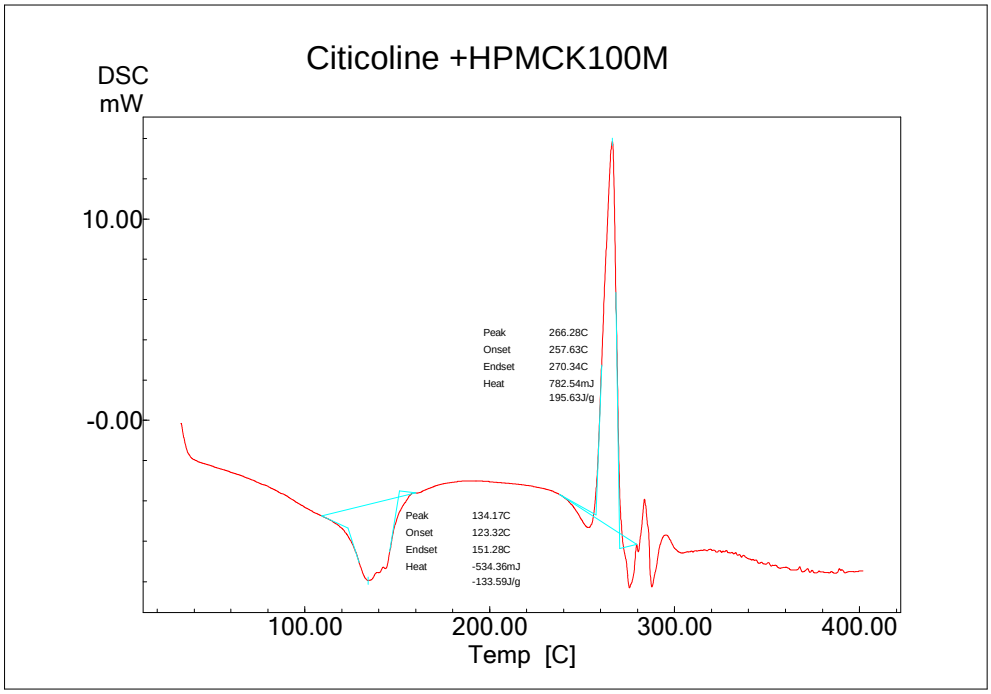

Figure – 2: DSC Thermo graph of Citicoline Sodium with HPMC K100M

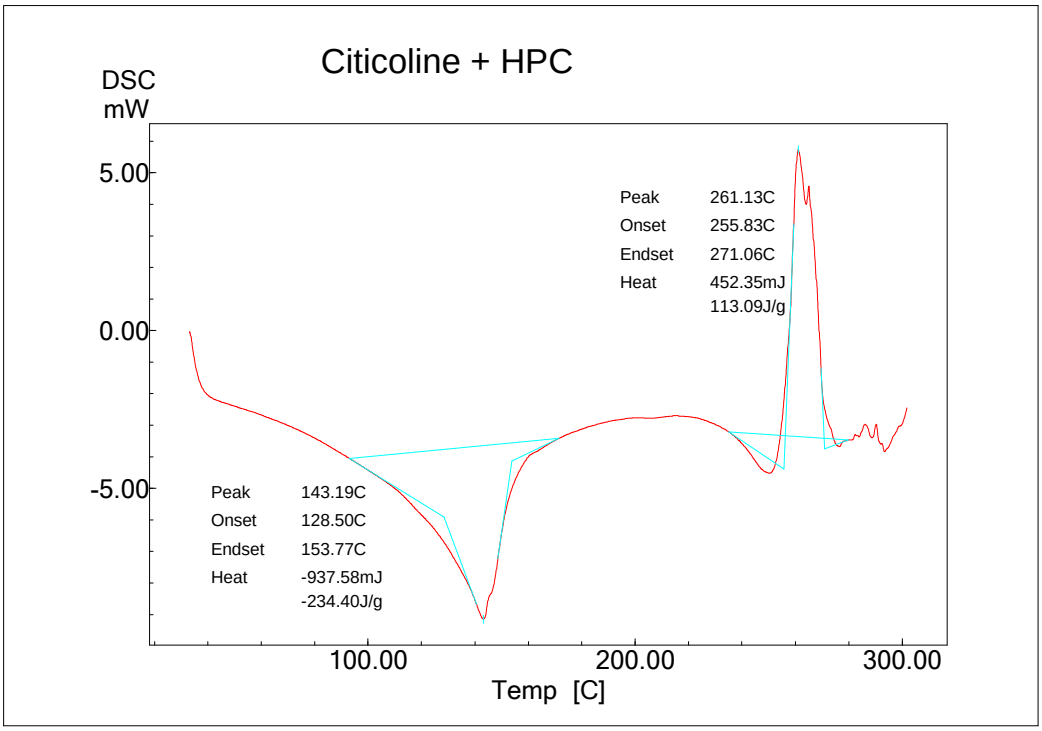

Figure – 3: DSC Thermo graph of Citicoline Sodium with HPC HF

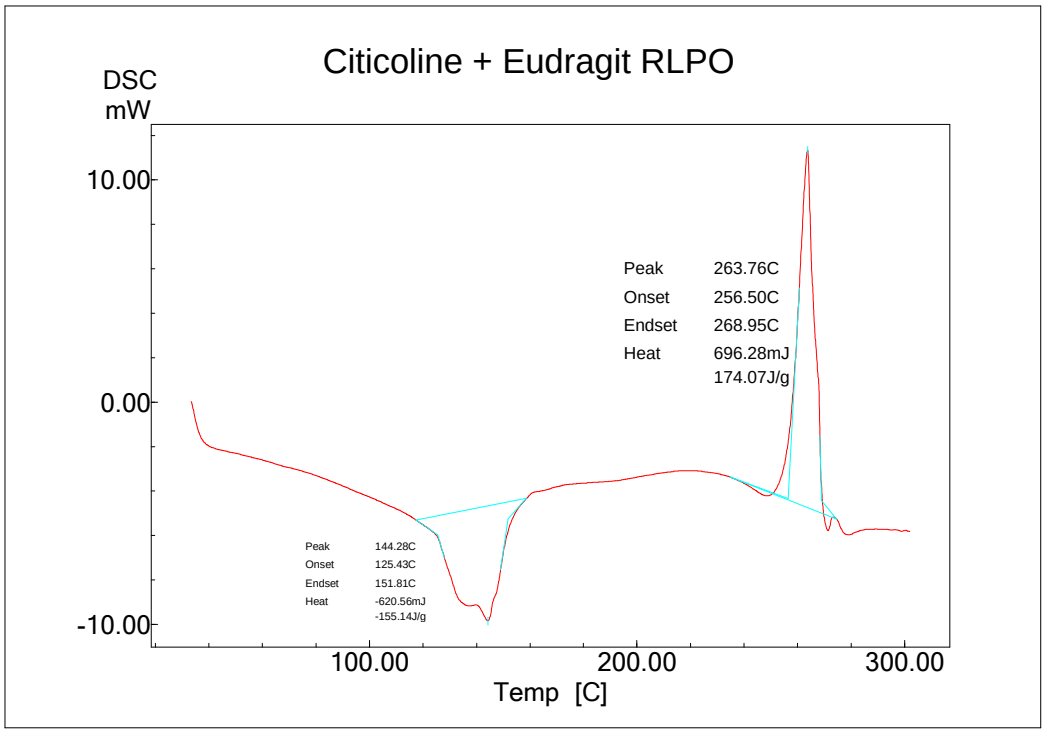

Figure – 4: DSC Thermo graph of Citicoline Sodium with Eudragit RLPO

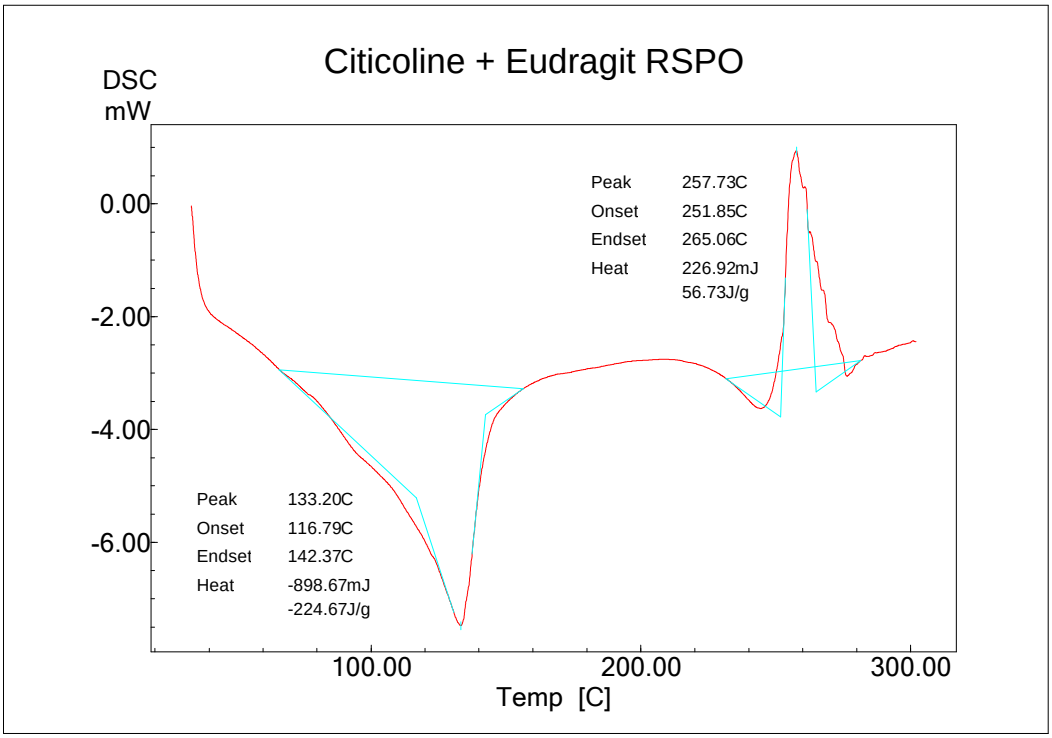

Figure - 5: DSC Thermo graph of Citicoline Sodium with Eudragit RSPO

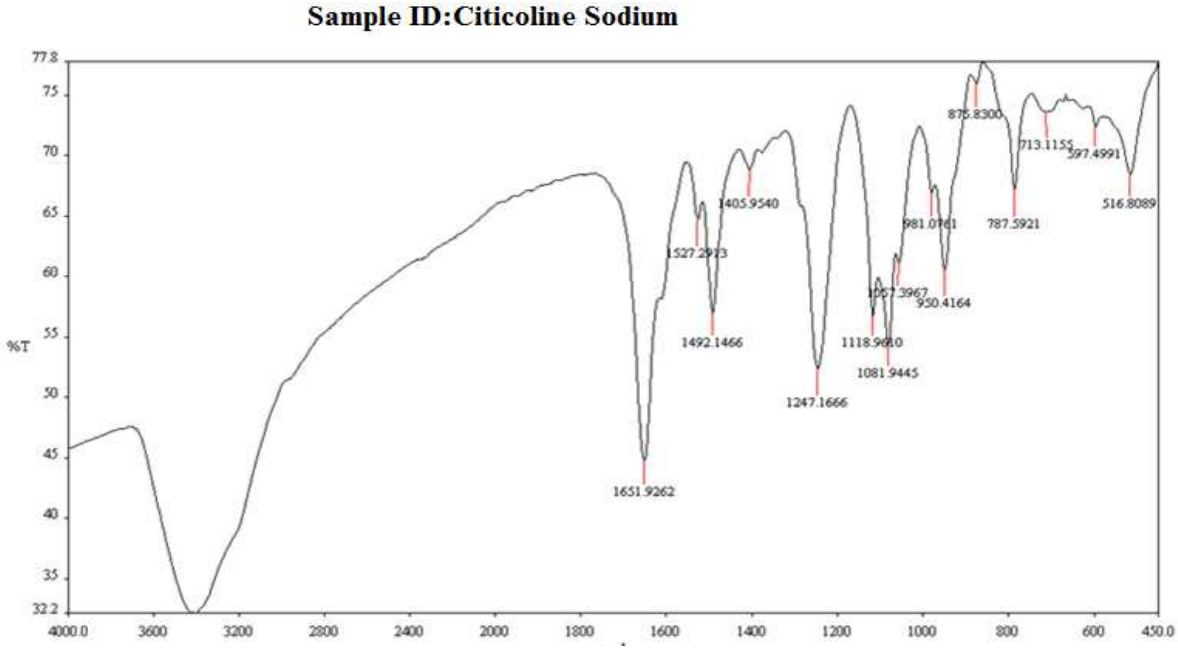

Figure - 6: FTIR Spectrum of Citicoline Sodium

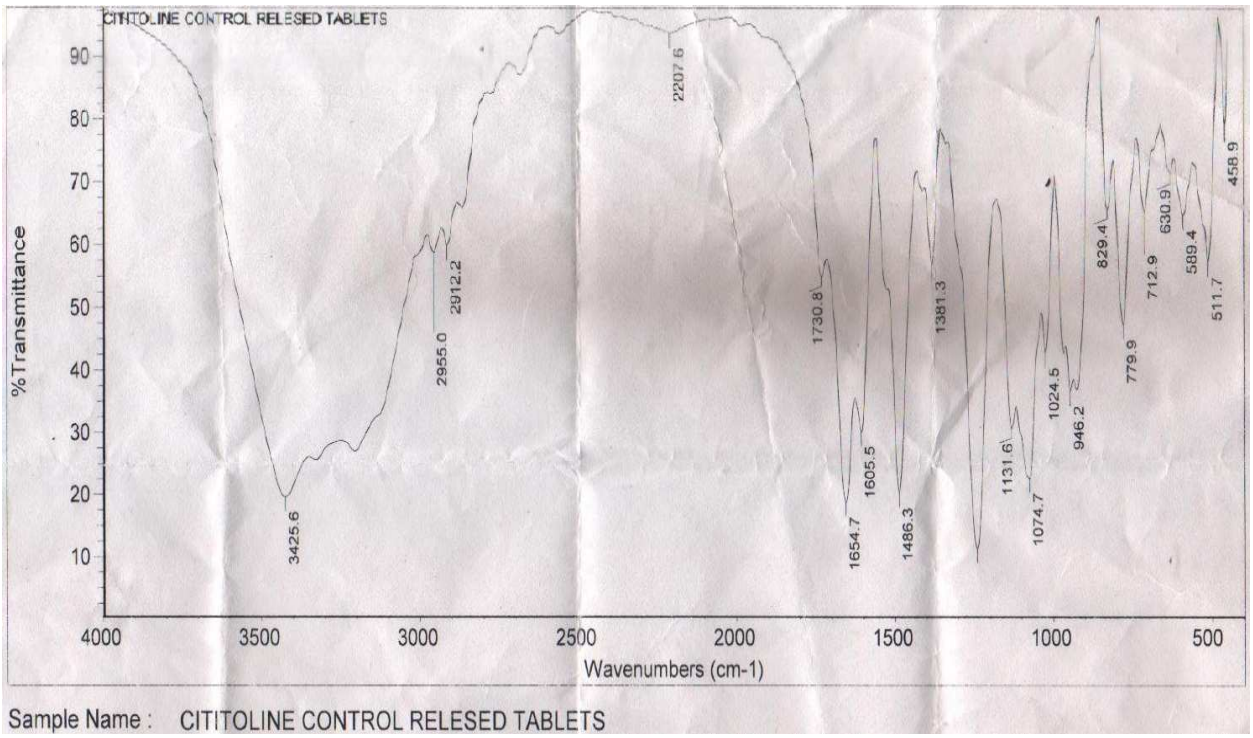

Figure - 7: FTIR Spectrum of Citicoline Sodium controlled Released Tablets

Table – 3: Characteristic peaks of Citicoline Sodium and Citicoline Sodium Controlled Release Tablets:

Functional group	Frequency (cm^{-1})	
	Citicoline Sodium	Citicoline Sodium Controlled Release Tablets
Stretching of RCOR' in Pyrimidine ring	1651	1654
Free amine present $–NH_2$ in Pyrimidine ring	3400	3425.6
Stretching of C-N in Pyrimidine ring	1247.1	1250
Stretching of C=N in Pyrimidine ring	1605	1492-1527
Stretching of C-O in Tetra Hydro Furan	1081-1118	1131.6
Stretching of C-N in Tertiary Amine	1247	1250
Stretching of C-C in Tertiary Amine	1600	1605

Compatibility studies

The compatibility between the citicoline sodium and polymer evaluated by DSC analysis performed with the ration of 1:0.5(drug: polymer). It reveals that there was no interaction between the citicoline and polymer.

FTIR also performed and checked using peak matching method. Spectrum of citicoline sodium was not interacted by polymers in the tablet formulation, which represents that the no chemical interaction between the citicoline sodium and polymer.

Physical Parameters of the Granules

Table - 4: Physical Parameters of the Granules

Batcn.No	Parameter			
	Bulk density(gm/ml)	Tap density (gm/ml)	Carr's index (%)	Hausners ratio
CTC/01	0.435	0.607	28.33	1.39
CTC/02	0.327	0.422	22.51	1.29
CTC/03	0.347	0.448	22.54	1.29
CTC/04	0.366	0.578	36.67	1.57
CTC/05	0.380	0.500	24.00	1.31
CTC/06	0.318	0.406	21.67	1.28
CTC/07	0.348	0.429	18.88	1.23
CTC/08	0.366	0.440	16.81	1.20
CTC/09	0.348	0.445	21.79	1.27
CTC/10	0.487	0.634	23.18	1.30
CTC/11	0.568	0.679	16.34	1.20
CTC/12	0.458	0.589	22.24	1.28
CTC/13	0.361	0.425	15.05	1.17
CTC/14	0.495	0.625	20.80	1.26
CTC/15	0.521	0.659	20.94	1.26
CTC/16	0.500	0.571	12.43	1.14

The bulk density and tapped density were found to be in the range of 0.318 to 0.568g/ml and 0.406 to 0.679g/ml respectively. A Hausner ratio was within the range of 1.14 to 1.57, lesser than 1.25 is considered to be an indication of good flow property. The compressibility index was within the range of 12-36 % hence falls within the good range.

Physical Evaluation of Tablets (Uncoated Tablets):

Table - 5: Physical evaluation of Tablets (Uncoated)

Batch No.	Parameters						
	Description	Tooling	Wt. of 10 tablets (gm)	Wt. of individual tablets(mg)	Hardness (N)	Thickness (mm)	Friability (%w/w)
CTC/01	White to off white, oval shaped, uncoated coated tablet	D-Tooling ,20 x 10 oval shaped punch(CTC/01, 02, 03, 05, 06, 07, 09, 10, 11, 13, 14 and 15) D-Tooling, 22 x 10 oval shaped punch(CTC/04, 08, 12 and 16)	12.790	1245-1315	360 - 390	6.75 - 6.83	0.14
CTC/02			12.825	1252-1313	379 - 399	6.74 - 6.82	0.21
CTC/03			14.110	1382-1440	363 - 392	6.82 - 6.93	0.19
CTC/04			15.780	1535-1625	345 - 397	6.86 - 6.94	0.15
CTC/05			12.815	1248-1314	347 - 401	6.73 - 6.81	0.13
CTC/06			12.824	1250-1310	355-402	6.74 - 6.81	0.10
CTC/07			14.135	1385-1442	349-405	6.81 - 6.92	0.10
CTC/08			15.805	1538-1623	359 - 386	6.85 - 6.94	0.10
CTC/09			12.809	1247-1313	358 - 385	6.71 - 6.84	0.14
CTC/10			12.805	1245-1316	369 - 387	6.72 - 6.80	0.21
CTC/11			14.135	1390-1437	365 - 389	6.81 - 6.94	0.19
CTC/12			15.822	1537-1627	348 - 395	6.87 - 6.94	0.15
CTC/13			12.765	1243-1310	343 - 371	6.72 - 6.80	0.14
CTC/14			12.795	1244-1314	344 - 376	6.74 - 6.82	0.16
CTC/15			14.135	1389-1438	342 - 372	6.82 - 6.94	0.12
CTC/16			15.812	1539-1623	340 - 386	6.85 - 6.93	0.11

Physical Evaluation of Tablets (Coated Tablets):

Table - 6: Physical evaluation of Tablets (Coated Tablet)

Batch No.	Parameters			
	Wt. of 10 Tablets (gm)	Wt. of individual tablets (mg)	Hardness (N)	Thickness (mm)
CTC/01	13.014	1264-1336	360 - 390	6.78 - 6.85
CTC/02	13.035	1273-1334	379 - 399	6.73 - 6.84
CTC/03	14.310	1401-1461	363 - 392	6.85 - 6.95
CTC/04	16.085	1554-1663	345 – 397	6.89 - 6.97
CTC/05	13.015	1267-1336	347 - 401	6.77 - 6.84
CTC/06	13.015	1271-1332	355-402	6.78 - 6.84
CTC/07	14.335	1406-1461	349-405	6.85- 6.93
CTC/08	16.020	1559-1645	359 - 386	6.89 - 6.96
CTC/09	13.005	1266-1335	358 - 385	6.76 - 6.85
CTC/10	13.015	1266-1337	369 - 387	6.77 - 6.83
CTC/11	14.345	1411-1458	365 - 389	6.85 - 6.97
CTC/12	16.020	1556-1648	348 – 395	6.92 - 6.97
CTC/13	12.975	1264-1331	343 - 371	6.77 - 6.83
CTC/14	12.995	1263-1336	344 - 376	6.78 - 6.83
CTC/15	14.345	1410-1459	342 - 372	6.86 - 6.96
CTC/16	16.010	1560-1642	340 - 386	6.89 - 6.96

All the batches were evaluated for the physical, dug content and in-vitro release of tablets. All the batches were shown the satisfactory flow characters. Physical properties of core tablets and coated tablets were shown in Table - 5 and Table – 6 respectively. Weight variation, hardness, thickness and friability of all batches core tablets were found satisfactory.

In-vitro release profile:

In-vitro release profile citicoline from all the prepared formulations was as shown in Table - 7

In case of HPMC K100M concentration varies from 100,160,300 and 450 mg in the formulation CTC/01, CTC/02, CTC/03 and CTC/04 respectively. Obtained results shows that the high amount of HPMC K100M is required to retard the release rate and also increase the tablet size respectively which is difficult to swallow the patient. Concentration varies from 100mg, 160mg, 300mg and 450 mg of HPC HF in the formulation CTC/05, CTC/06, CTC/07 and CTC/08 respectively. Since it is not shown the better performance than HPMC K100M but it is shown the similar results with HPMC K100M. Finally high amount of HPC HF required to control the release rate and also increase the tablet size respectively which is difficult to swallow.

Formulations prepared with Eudragit RLPO are unable to control the initial release of the drug even at maximum concentration of 450 mg. More than 50% of the drug released in 1 hour. Hence Eudragit RLPO is considered to be failed in the design of controlled release citicoline. The release of citicoline from tablets containing Eudragit RSPO was well controlled. The release is extended for about 12 hours. The formulation showed satisfactory in-vitro results at concentration of 160 mg/tablet. There is not much variation in controlling of drug release with increasing the concentration of Eudragit RSPO such as 300mg, 450mg. The optimum concentration is found to be 160mg for formulation CTC/14. For comparison commercial Citicoline controlled release tablets were also evaluated for dissolution. Commercial tablets could extend the release of the drug for about 12 hours. The release of the drug from commercial formulation was compared with all the prepared formulations and calculated similarity factor and difference factor. The values indicated formula CTC/14 containing Eudragit RSPO is best formula among all.

IN-VITRO RELEASE PROFILE OF THE ALL FORMULATIONS

Table - 7: In-Vitro release profile of the all formulations

Trial. No	Cumulative % Drug Release				
	1hr	3hr	6hr	9 hr	12 hr
CTC/01	64.10	85.60	98.60	99.70	100.20
CTC/02	60.21	80.52	98.34	99.05	99.19
CTC/03	57.01	75.58	95.86	99.08	99.48
CTC/04	33.70	80.60	95.50	98.90	99.80
CTC/05	66.60	93.30	99.00	99.60	99.80
CTC/06	65.56	87.17	99.15	99.21	99.37
CTC/07	59.63	80.67	96.62	99.01	99.04
CTC/08	44.40	74.60	90.60	97.50	99.40
CTC/09	62.70	82.80	98.20	98.80	98.80
CTC/10	59.86	79.13	96.06	99.16	99.29
CTC/11	56.62	75.09	93.28	99.04	99.09
CTC/12	50.30	72.80	89.90	96.60	98.20
CTC/13	44.90	56.70	76.20	95.30	99.10
CTC/14	30.18	47.25	58.83	80.38	99.71
CTC/15	31.90	47.90	56.60	82.00	99.20
CTC/16	34.10	45.30	63.60	84.00	99.70

Graphical presentation of In-Vitro Release Profile of the all formulations:

HPMC K100M:

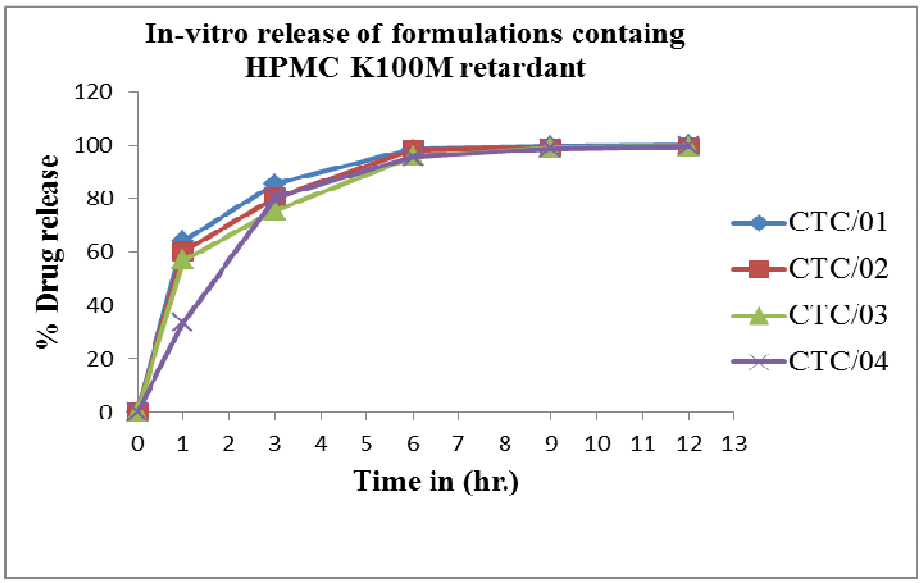

Figure - 8: In- Vitro release of formulations containing different concentration of HPMC K100 M.

With HPC(HF):

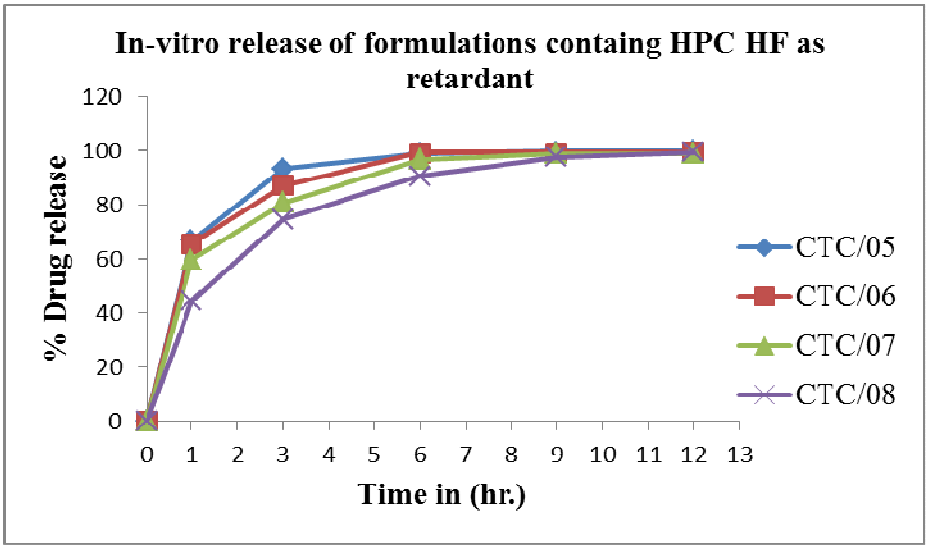

Figure - 9: In- Vitro release of formulations containing different concentration of HPC HF.

With Eudragit RLPO:

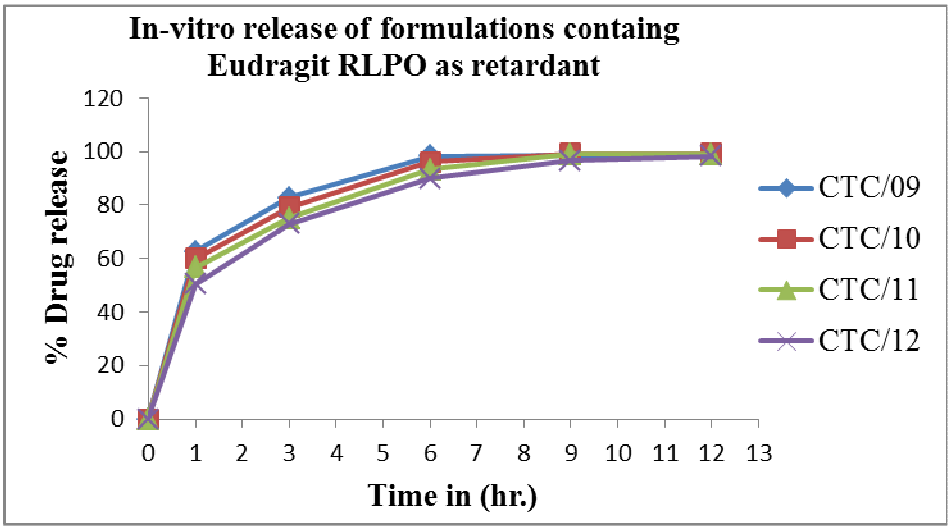

Figure - 10: In- Vitro release of formulations containing different concentration of Eudragit RLPO.

With Eudragit RSPO:

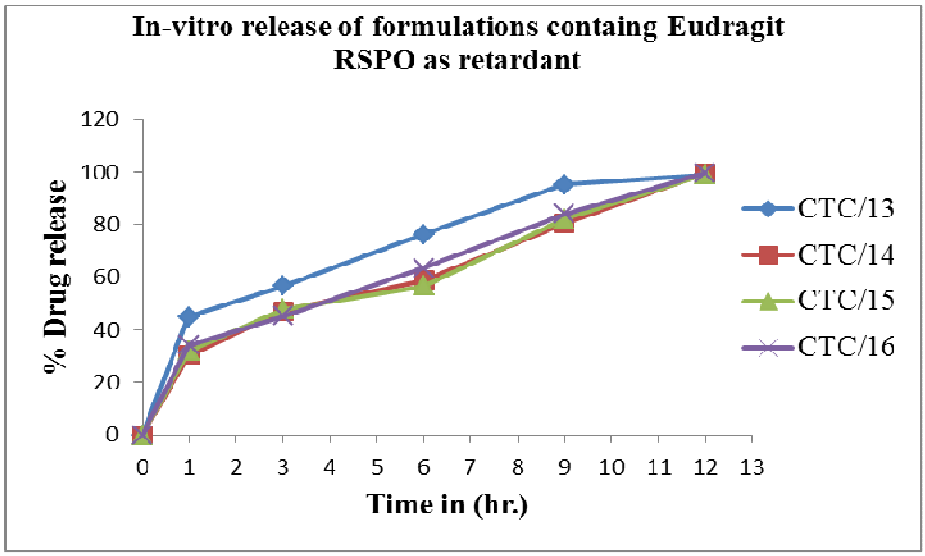

Figure - 11: In- Vitro release of formulations containing different concentration of Eudragit RSPO.

Table – 8: Comparison of in-vitro release of CTC/14 with Marketed Product

Time points	Marketed Product	CTC/14
1 hour	32.0	30.2
3 hour	53.1	47.3
6 hour	64.5	58.8
9 hour	84.7	80.4
12 hour	98.4	99.7
F2 value	**68.01**	
F1 value	**4.9**	

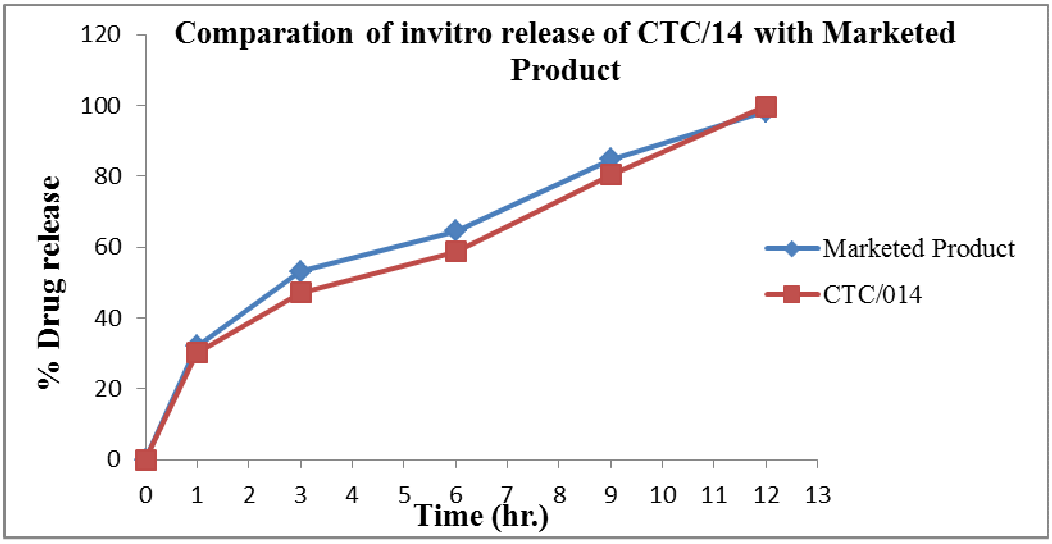

Figure - 12: Comparison of in-vitro release of CTC/14 with Marketed Product

KINETICS OF DRUG RELEASE

Table – 9 : Release Kinetics of Citicoline Sodium tablets

Formulation	Zero order			Higuchi square root			Peppas & Korsmeyer	
	r2	t1/2	K	r2	t1/2	K	r2	Kp
CTC/014	0.991	4.037	14.130	0.966	1.843	62.894	0.943	0.285

Kinetic release of CTC/14 was complied with above modelling systems.

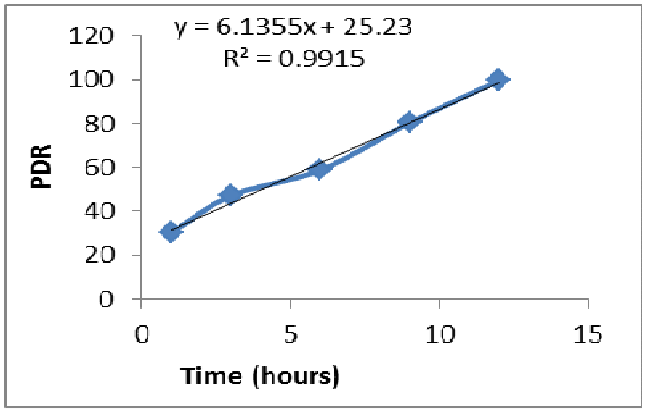

Figure – 13: Zero Order of Citicoline

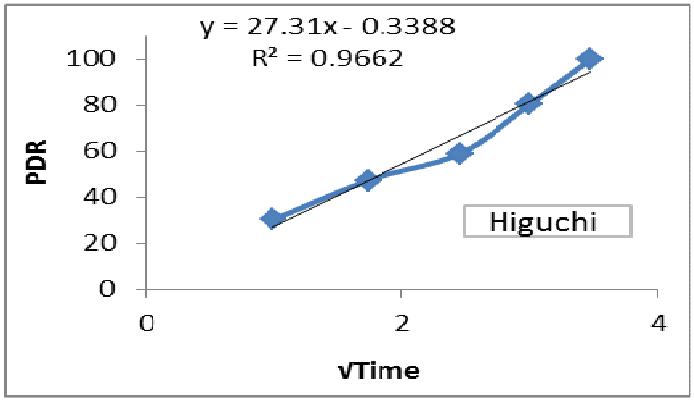

Figure – 14: Higuchi square root of Citicoline

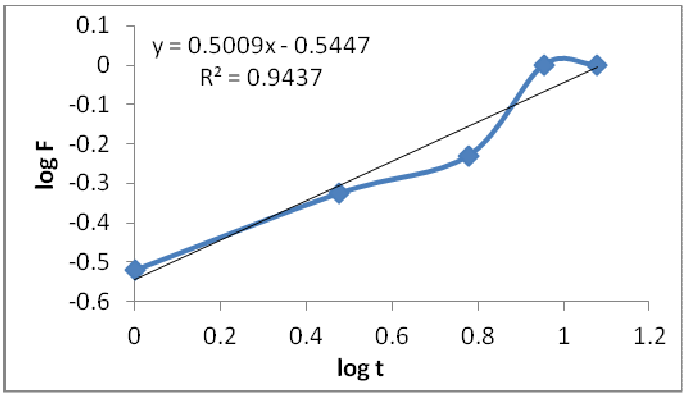

Figure – 15 Peppas & Korsmeyer of Citicoline

Stability Study:

The selected batch (CTC/14) was kept at 40°C± 2°&75%±5 % RH , the samples were withdrawn at 30, 60 and 90 days and tested for physical , Drug content and *in vitro* evaluation of drug release. The results indicated no significant change in the test product before and after subjecting to accelerated conditions. This indicates that the formulation CTC/14 is stable. The results are as below,

Table – 10: Compilation of stability data of Citicoline controlled release tablets

Time	Tests						
	Description	Drug Content	Cumulative % Drug Release				
			1hr	3hr	6hr	9hr	12hr
30 Days	Complies	99.7	30.49	47.86	56.93	81.24	99.54
60 Days	Complies	99.2	31.54	47.92	57.83	82.31	99.62
90 Days	Complies	99.5	31.89	46.98	57.99	81.26	99.34

CONCLUSION

Matrix tablet containing Citicoline was prepared successfully by wet granulation method using non aqueous granulation. All the tablets possessed good physical properties such as hardness, friability, weight variation. The drug content was uniform indicating the suitability of the process of manufacturing. The in vitro drug release from all the dosage forms was controlled and extended over period of 12 hours. Among all the formulations, the formulation which prepared using Eudragit RSPO found to be effective in controlling the drug release up to 12 hrs. Incompatibility study revealed that there was no interaction between the drug and other ingredients used. Stability studies revealed that there was no significant change in appearance, drug content and In-vitro release of selected formulation (CTC/14). The formulation CTC/14 was also showed comparable results with that of commercial tablets as indicated by similarity and difference factors.Results of the present study demonstrated that the hydrophobic polymers i.e. Eudragit RSPO could be successfully employed for formulating controlled release matrix tablets of Citicoline.

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