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FORMULATION AND EVALUATION OF CITICOLINE SUSTAINED RELEASE TABLET

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Abstract

The effects of formulation variables on the release profile of Citicoline monosodium (CM) from hydroxypropylmethyl cellulose (HPMC) matrix tablets were studied. CM tablets were prepared by wet granulation methods and different ratios of HPMC were used. Physical properties of the prepared tablets and targeted commercial sustained release (SR) tablet and the drug release were studied in tablets that were placed in water for 12. In vitro studies showed that varying HPMC concentration in granulation and coating of SR formulation with with wet granulation method is the optimum formulation due to its better profile in terms of release. This formulation also exhibited the best-fitted formulation into the first order release kinetics and korsmeyer release kinetics. The precision and accuracy of the analytical method were also checked. The evaluation parameter of tablet were also checked.

Keywords: Citicoline monosodium; Sustained release; Hydroxypropylmethyl cellulose; Kinetics; Dissolution; Validation.

1. Introduction

An sustained release tablet allowing a twofold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form.¹ Continuous release systems is the systems release the drug continuously for prolonged period of time along the entire length of GIT with normal

transit time.² The many design goals that need to be achieved in a successful controlled delivery system the two important are (1) the achievement of a sufficient input flux of drug and (2) the achievement of a desired drug concentration-time profile. While both goals require the balancing of design parameters and biopharmaceutical properties of the drug, the first goal is governed primarily by system design, and the second is governed primarily by the physiology of the body. Therefore, it is not surprising that pharmacokinetics, which is the convolution of input and disposition, can be of great help in the design of controlled release delivery systems.³ Literature has studied solid dispersion system with ethylcellulose and HPMC.⁴ combination of moderate swelling properties of Eudragit with the plastic properties of the more hydrophobic Ethocel 100 on Didanosine release,⁵ the effect of HPMC used as an excipient for controlled release of drug, on release profile and bioavailability of poorly water soluble drug,⁶ new parameter obtained during preformulation stage by NMR experiment to understand better drug release mechanism. This study was carried out using Microcrystalline cellulose, HPMC and ethylcellulose,⁷ this study help to understand the release mechanism and also help to understand how the HPMC help for sustained and control release mechanism.

2. Materials and methods

2.1. Material

CM and Citelec OD were kindly provided by BDR and RANBAXY, Pharmaceutical Companies, respectively. HPMC K100M, microcrystalline cellulose (MCC) (Avicel pH 101) were supplied by Colorcon Asia Pvt. Ltd, Vijlak pharma Ltd.respectively. Magnesium stearate, Potassium hydroxide were supplied by Sunshine Organics, Techno Search respectively. Potassium dihydrogen phosphate, Sodium hydroxide were supplied by MERCK. All other reagents were analytical or pharmaceutical grade and deionised water was obtained by reverse osmosis. Citicoline sodium is also known as cytidine Diphosphate-choline (cdp-choline) and cytidine 5'diphosphocholine. With Crystalline powder White in Colour and odorless.See table no.2.1 for drug properties.⁸

Table No.2.1: For Drug Properties.

Molecular formula	:	C ₁₄ H ₂₅ N ₄ NaO ₁₁ P ₂
State	:	Solid
Molecular weight	:	510.31
Solubility	:	in water and 0.1 N HCl
Melting Point	:	233°C
pH	:	At 20°C - 6.5-7.5
Category	:	Cerebral Vasodialator
Appearance of solution	:	Solution is clear and colorless
Half life	:	4 to 6 hr
Storage	:	Store in tightly closed containers at room temp.

2.2. Preparation and characterization of SR tablets

Tablet formulations were prepared by wet granulation methods.

Table No. 2.2 different Batches Are A1 to A6.

Ingredients	A1	A2	A3	A4	A5	A6
Drug (mg)	1092	1092	1092	1092	1092	1092
HPMC K100M (mg)	366	360	350	340	326	300
Microcrystalline cellulose (mg)	22	22	22	22	25	40
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Lubrication						
HPMC K100M (mg)	40	46	52	52	60	60
Magnesium stearate (mg)	30	30	30	30	18	18

2.2.1. Wet granulation methods

A aqueous granulation process was adopted to prepare CM tablets. Granules of CM tablets containing HPMC were prepared as follows:

Manufacturing process include sifting Citicoline sodium through 20 #, S.S. security sieve. Then Sift Hydroxy Propyl Methyl Cellulose K100M and Avicel PH 102 through 40 #, S.S. security sieve. Mix the material of step 2 & 3 in rapid mixer granulator for 10 min at slow speed. Add purified water slowly to the dry mix of step 4 and granulate the material; add additional quantity of purified water, if required. Granulate for 6 - 8 mins with impeller and chopper at slow speed and for 2 min. with impeller and chopper at fast speed. Air dry the granules in FBD then, pass the wet mass through 3 mm screen using Cad mill & then dry the granules in FBD keeping 75-85°C as the inlet temperature and outlet temperature reaches to 55° to 65°C. Dry the granules till the LOD is between 3.0 – 4.0 % determined at 105°C for 5 min on IR moisture balance. Pass the dried granules through 16 #. Pass retained granules through 1.8/1.0 mm S.S. security screen knives forward at slow speed of cad mill and again pass through 16 #. Sift Hydroxy Propyl Methyl Cellulose K100M, Magnesium Stearate through 40 #, S.S. security sieve. Mix above material with dried granules in Cage blender for 10 min.(at 13 ± 2 RPM).

Compression – Load the granules of step (10) to the hopper of the tablet compression machine using 21.5X10.5 mm capsule shape punch and adjust the die fill Weight to 1510 ± 5.0 %. Commence the regular compression operations with following In-process checks.

The weight variations of the tablets were evaluated on 20 tablets with an electronic balance (CONTECH). Tablet hardness was obtained on 20 tablets using a hardness tester (Shivani scientific industries.Ltd). Friability was determined on 20 ◀tablets▶ with a Roche friabilator for 5 min at a speed of 25 rpm/min. The thickness and diameter of the tablets were measured on 20 ◀tablets▶ with a vernier caliper.

Different Batches are A1 to A6. See table no. 2.2

2.3. Tablet dosage forms assay procedure

Standard Preparation: Weigh accurately about 210 mg of Citicoline Monosodium working standard in a 100 ml volumetric flask. Add sufficient distilled water, Sonicate to dissolve and make up the volume with distilled water and mix. Dilute 1 ml of this solution to 100 ml with 0.1N hydrochloric acid and filter the solution through Whatman No.42 filter.

Sample Preparation: Weight accurately equivalent to 1000 mg of Citicoline form the mixed content of 20 crushed tablets into a 500 ml volumetric flask. Add 300 ml of distilled water, sonicated to dissolve and make the volume to 500 ml with distilled water and mix. Centrifuge the solution for 5 minutes and filter the solution through Whatman No.42 filter. Further dilute 1 ml of the filtrate to 100 ml with 0.1N hydrochloric acid. Absorbance were take at 280nm on UV spectrophotometer(1700, SHIMDZU UV).

2.4. In vitro dissolution studies⁹

Dissolution measurements were carried out in a USP dissolution test apparatus using paddle method (Electrolab). With 75 RPM. Sample absorbance taken at 1,4,8,12 h. Water(900) used as dissolution media.

The dissolution results were the average of determinations. The percentage released versus time data was assessed for the kinetics of release and dissolution. The data was tested according to different release and dissolution kinetics.

Zero order release

$$Q = K_0 t$$

First order release equation

$$\ln(100-Q) = \ln Q_0 - k_1 t$$

Higuchi square root equation

$$Q = K_H t^{1/2}$$

Korsemeier and Peppas equation

$$\frac{M_t}{M_\infty} = K t^n M_\infty$$

$$\text{Log} \left(\frac{M_t}{M_\infty} \right) = \text{Log} K + n \text{log} t$$

Where Q is the amount of drug released at time t, K_0 is zero order release constant, t is the time. R^2 near to 1 indicating Zero order release K_1 is first order release constant, Q is the amount of drug released at time t, R^2 obtained from the Log % amount of drug remaining to release vesses time. R^2 near to 1 indicating Zero order

release Where Q is the amount of drug released at time t , K_H Higuchi square root of time release constant.

Where M_∞ is the total amount of drug released in infinite time. M_t/M_∞ is fraction of drug released at time t . K is kinetic constant. n is diffusion exponent that characterize the mechanism of drug release.

3. Result and Discussion

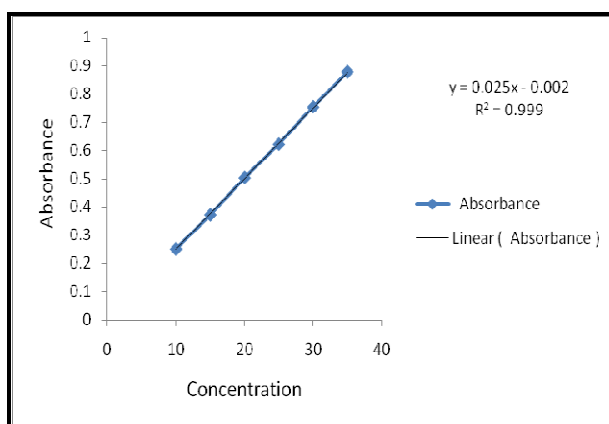
Citicoline linearity on 280nm.

For linearity study preparation of different parts per million solution (ppm) 10, 15, 20, 25, 30 and 35 were prepared and absorbance taken 280 nm. Shown in table no 3.1. fig 3.1.

Table-3.1: Citicoline accuracy and linearity on 280nm.

Concentration	Absorbance
35	0.877
30	0.753
25	0.621
20	0.503
15	0.371
10	0.251

Fig-3.1 Citicoline accuracy and linearity on 280nm.



Compatibility study: The Citicoline tablet showed the characteristic peaks as shown in fig 3.2 match with the characteristic peak of Citicoline working standard.

In all physical mixtures of drug and polymer, there was neither masking of single characteristic peak nor existence of additional peak in drug spectra fig.3.2-3.3 so we can proved that drug and polymers are compatible with each other.

Figure 3.2 IR spectrum of Citicoline standard.

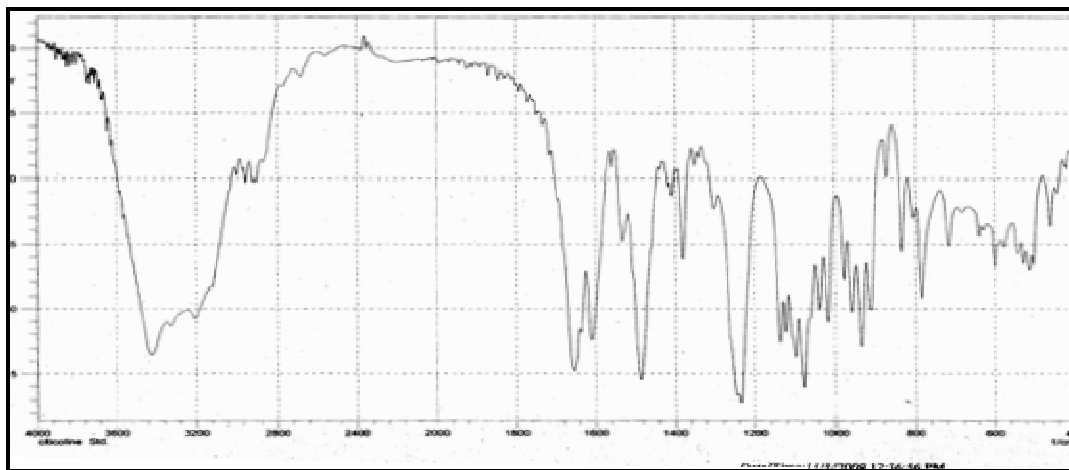
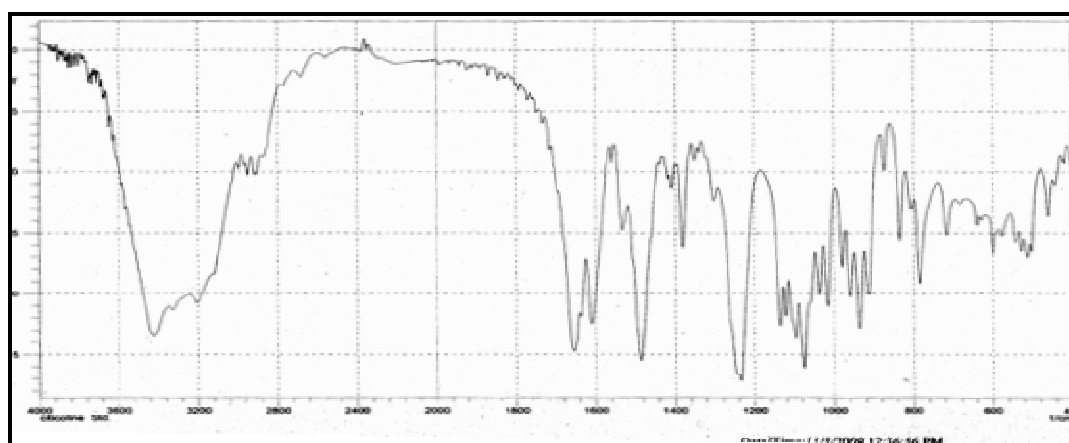


Fig.3.3 IR spectrum of Citicoline tablet.



3.3 Granule Properties of All Formulations

The angle of repose for all formulations fell within the range of 25-33⁰ indicating good flow properties. The angle of repose is a characteristic of internal friction or cohesion of the particles. If the value of angle of repose is high powder is cohesive and low powder is non cohesive. Granule properties of all formulations shown in table. No.3.2.

Table-3.2: Granule properties for different batches.

Sr. No.	Granule properties	Formulations					
		A1	A2	A3	A4	A5	A6
1	Angle of repose	30.1	28.44	29.47	26.56	26.13	27.47
2	Bulk Density(gm/cc)	0.3872	0.39	0.3854	0.386	0.395	0.381
3	True Density	0.3388	0.341	0.337	0.334	0.342	0.335
4	Haursers ratio	1.0	1.0	1.0	1.1	1.1	1.0
5	% compressibility	12.5	12.57	12.5	13.48	13.42	12.08

3.4 Tablet Properties before and after coating are shown in table. No.3.3 and 3.4.

Table-3.3: Tablet Properties before coating.

Formulation	Average weight (mg)	Thickness (mm)	Hardness (kg/cm ²)	Length (mm)	Width (mm)
A1	1509	7.4	23.93	21.5	10.5
A2	1510	7.3	23.55	21.5	10.5
A3	1513	7.4	23.79	21.5	10.5
A4	1515	7.5	22.52	21.5	10.5
A5	1510	7.6	22.23	21.5	10.5
A6	1510	7.4	22.05	21.5	10.5

Table-3.4: Tablet Properties after coating.

Formulation	Average weight (mg)	Thickness (mm)	Hardness (kg/cm ²)	Length (mm)	Width (mm)
A1	1545	7.4	23.93	21.5	10.6
A2	1540	7.5	23.55	21.6	10.5
A3	1555	7.8	23.79	21.5	10.5
A4	1545	7.5	22.52	21.7	10.6
A5	1544	7.6	22.23	21.5	10.5
A6	1555	7.4	22.05	21.5	10.5

4. Evaluation test for tablet.

In-Vitro Dissolution Study:-

Table No.3.5 shows Citicoline release from tablets formulations A1 to A6 containing different concentration of polymers. At lower concentration % release was more. As concentration of polymer increased the release rate was retarded.

Table-3.5: in-vitro release profile for different batches.

Time (Hrs)	Formulations (% Drug Release)					
	A1	A2	A3	A4	A5	A6
1	37.80	36.50	37.30	35.40	37.68	37.80
2	47.00	47.30	46.70	47.40	47.60	47.90
3	58.04	58.02	58.33	58.24	58.56	58.98
4	66.49	66.54	66.60	66.00	67.67	67.99
6	79.03	79.43	79.53	79.63	79.73	80.70
8	90.01	90.01	90.01	89.31	92.01	94.01
10	92.21	92.98	93.21	92.43	94.21	97.21
12	94.24	94.98	95.94	96.24	96.88	99.24

Table 3.5 depicts effect of HPMC K100M on Citicoline release from matrices, increasing concentration of HPMC in matrix showed linear retardation of drug release. Table 8.6 showed release of citicoline monosodium from HPMC vary with changing concentration of HPMC in both in granulation and lubrication.

Concentration of HPMC and MCC continuously changing in all batches to match the release profile with innovator sample. In A6 batch at particular concentration of HPMC and MCC show nearer drug release with innovator sample.

Release Kinetics Study:

A) Model Dependant Methods:

In kinetic assessment the data was plotted according to zero order, First Order, Higuchi and Krossemeyer equation.

See figure no.3.4 to 3.7. From the observations it was observed that all batches gave the release by first order and Korsmeyer release kinetics. To evaluate the orders by which tablets gave the release was also evaluated. The optimize batch gave drug release by first order diffusion dissolution controlled.



Figure3.4 zero order release kinetics

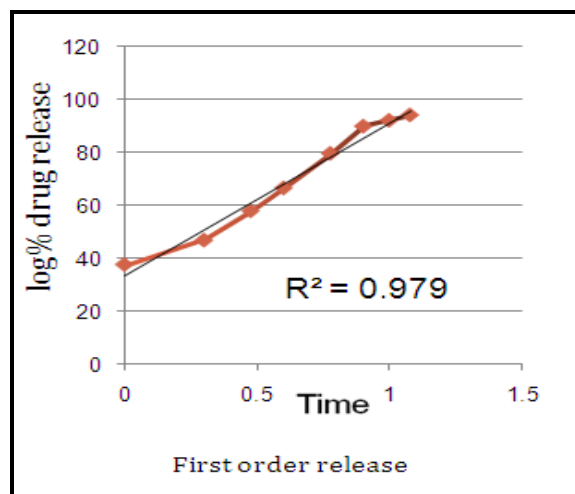


Figure3.5 first order release kinetics

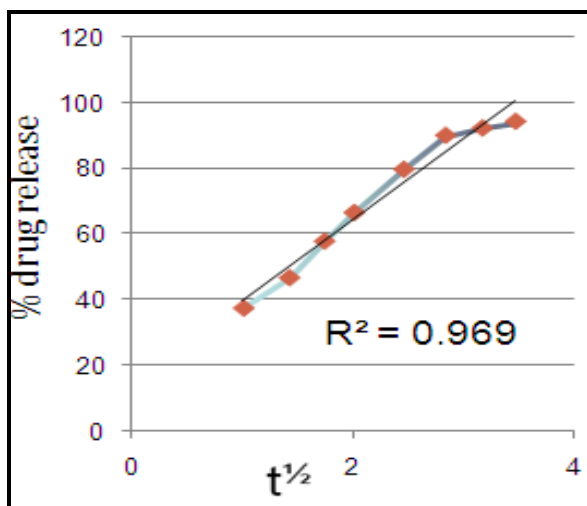


Figure 3.6 Higuchi release kinetic

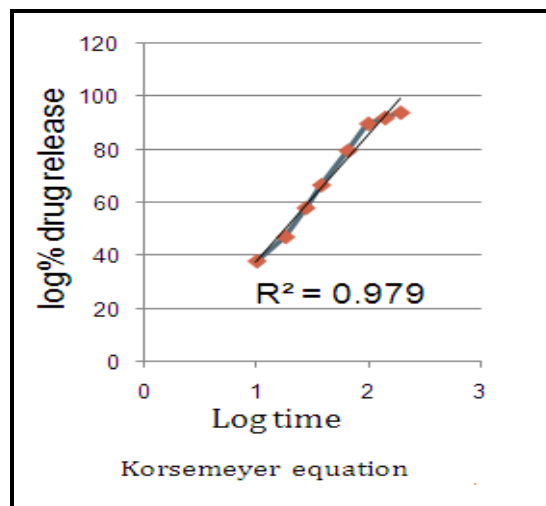
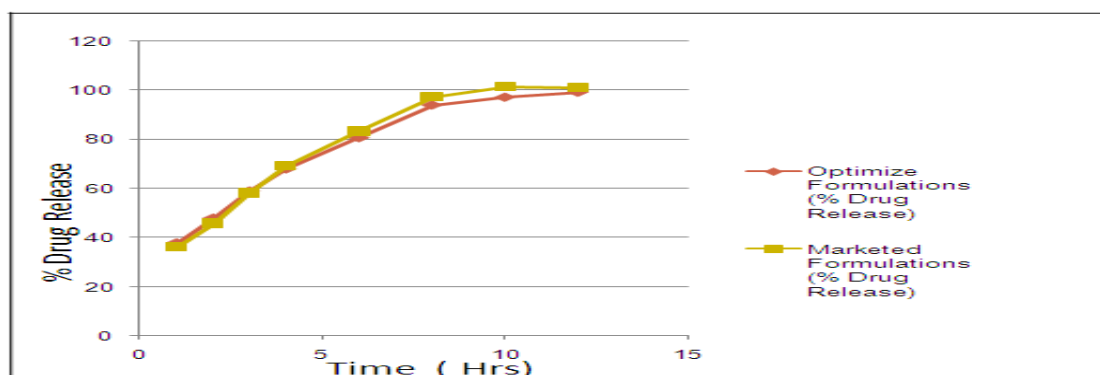


Figure 3.7 Korsmeyer release kinetics

Figure3.8: Comparison between innovator batch and optimized batch.

f_1 & f_2 value found to be in the range. f_1 value between 0 to 15 and f_2 value between 50 to 100.

B) Model Independent Methods:

Comparison between innovator sample and optimize batch: Table No.3.6 shows between the profiles, f_1 should be in the range of 0-10, and f_2 in the range of 50-100. f_1 and f_2 values are found to be in range.

Table 3.6: Table of %drug release comparison between optimized and innovator batch.

Time (Hrs)	Optimize Formulations (% Drug Release)	Marketed Formulations (% Drug Release)
1	37.80	36.28
2	47.90	45.78
3	58.98	58.18
4	67.99	69.31
6	80.70	83.27
8	94.01	97.26
10	97.21	101.35
12	99.24	101.02

Assay (By U.V.)

Sample preparation

Weight of 10 tablets is 14118.69 mg. Average weight is 1411.86 mg, (1000mg citicoline present in 1411.86 mg of crush tablet). 1411.86 mg dissolve in 500 ml water and from this 1ml diluted to 100ml by 0.1N HCl.

Standard preparation

210mg of working standard diluted to 100ml by WFI and from this 1ml diluted to 100ml by 0.1N HCl.

Citicoline (mg/tablet) found to be

$$\begin{aligned} \text{Citicoline (mg/tablet)} &= \frac{A_T}{A_S} \times \frac{D_S}{D_T} \times \frac{P}{100} \times W \times \frac{488.32}{510.32} \\ &= \frac{0.4795}{0.4747} \times \frac{210.54}{705.93} \times \frac{95.99}{100} \times 1411.5 \times \frac{488.32}{510.32} \end{aligned}$$

Determination of content of Citicoline Mono sodium equivalent to citicoline found to be 97.67%.

Stability studies

Table 3.7 show the packed formulations were stored in stability chambers maintained at 40 °C and 75% relative humidity for two months are stable.

Table3.7: Accelerated stability study protocol.

Condition	40°C/75%RH		
	A6		
Batch No.			
Test	Initial	1 Month	2 Month
Time (Hour)	0	0	0
1	38.8	39.2	38.5
2	47.7	46.1	49.8
4	69.4	70.1	69.9
6	81.4	82.2	83.6
12	101.0	99.0	100.1
Assay	99.7%	99.5%	99.4%

5. Conclusion

In the present work, the incorporation of citicoline, an cerebral vasodilator agent was performed in inert HPMC. HPMC polymer in different concentration is used to achieve sustained release kinetic for drug. There was no chemical interaction between the drug and polymers as inferred primarily from FTIR. Thus HPMC with MCC in solvent result in formation of thick gel which give diffusion path for drug and give control release profile

Hydroxypropyl- methylcellulose proved useful as a rate controlling polymer to produce a controlled release formulation of citicoline using the diffusion-dissolution controlled mechanism.

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