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Formulation and evaluation of Citicoline sodium bilayered tablet

Biswa Mohan Sahoo*, L. Mohan Krishna, Adasala Jahnavi

Department of Pharmacy, Vikas Group of Institutions, Nunna-521212, Vijayawada, AP, India.

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ABSTRACT: Background: Bi-layer tablets are made by compressing different granulations fed into a die in succession, one on top of another in layers. Each layer comes from a separate feed frame with individual weight control**. Aim:** The aim of present work was to formulate Bi-layer tablets of Citicoline Sodium so that synergistic effect of this combination could be used for the effective treatment of Alzheimer disease and other types of dementia, head trauma, cerebrovascular disease such as stroke, age-related memory loss, Parkinson's disease. **Methodology:** Wet granulation process was used for the formulation of both layers of Tablet and the final film coated tablets were evaluated for the thickness, weight variation, hardness, friability, disintegration time and dissolution study. **Results:** Among the formulation, tablets of batch A2 of Citicoline Sodium was taken as optimized formula due to its higher rate of dissolution and compiled all the other parameters with the official specifications of IP. The stability study of the selected formulations was done at 45 ˚C and 75 % RH for 1 month. **Conclusion:** It was concluded that Citicoline Sodium Bi-layer tablets can be prepared successfully as it satisfies all the criteria as a Bilayered tablet and would be alternative to the currently available conventional tablets.

Corresponding author*
Prof. (Dr.) Biswa Mohan Sahoo
Department of Pharmacy,
Vikas Group of Institutions,
Nunna-521212, Vijayawada, AP, India.
Tel: +91-9040442719
Mail ID: drbiswamohansahoo@gmail.com

Keywords: Alzheimer disease, Citicoline, tablet, stability study, wet granulation.

INTRODUCTIONS:

Bi-layer tablets are made by compressing different granulations fed into a die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control [1]. Rotary tablet presses can be set up for two or three layers. More are possible but the design becomes very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes [2,3]. Incompatible substances can be separated by formulating them in separate layers as a two-layer tablet or separating the two layers by a third layer of an inert substance as a barrier between the two. Two layer tablets may be designed for sustained release one layer for immediate release of the drug and the second layer for

extended release, thus maintaining a prolonged blood level. Various types of bi-layer presses have been designed over the years [4,5].

The simplest design is a single-sided press with both chambers of the double feeder separated from each other. Each chamber is gravity- or forced-fed with a different powder, thus producing the two individual layers of the tablet. When the die passes under the feeder, it is at first loaded with the first-layer powder followed by the second-layer powder [6,7]. Then the entire tablet is compressed in one or two steps. For drug substances which are weak acids it is very important to ensure a proper bioavailability of the drug substance already under acid conditions in order to have especially focused on compositions comprising a drug substance belonging to the class of drug substances normally denoted NSAIDs, but other drug substances having a low solubility in acidic medium and/or a pKa below about 5.5 may as well be suitable for use in a composition according to the invention [8].

Citicoline is a brain chemical that occurs naturally in the body. As a medicine, it is taken by mouth as a supplement or given by IV or as a shot. Citicoline is the generic name for synthetic CDP-choline (cytidine diphosphate choline), an organic molecule produced endogenously and found in all living cells. Citicoline is often called a “brain nutrient” because it increases levels of several important neurotransmitters including acetylcholine, dopamine and Noradrenalin. It helps maintain the integrity of neuronal cell membranes; and increases energy production in the frontal cortex. The chemical name for Citicoline is cytidine 5’-diphosphocholine (Figure 1). Citicoline is often called a “brain nutrient” because it increases levels of several important neurotransmitters including acetylcholine, dopamine and nor adrenaline. It helps to maintain the integrity of neuronal cell membranes and increases energy production in the frontal cortex [9].

Citicoline protects cholinergic neurons from auto cannibalism, a process in which membrane phospholipids are catabolised to provide choline for synthesis of acetylcholine. This occurs when choline supplies are depleted, necessitating sacrifice of membrane phospholipids to maintain neurotransmission.

Hydroxypropyl methylcellulose (HPMC) is the most important hydrophilic carrier material used for the preparation of oral controlled drug delivery systems. HPMC is an odorless, tasteless and inert hydrophilic polymer. It is manufactured from purified cellulose, which is obtained from cotton linters or wood basic or other electrolytic systems. HPMC polymers work well with soluble and insoluble drugs and at high and low dosage levels. The overall drug release mechanism from HPMC- based pharmaceutical devices strongly depends on the design (composition and geometry) of the particular delivery system [10].

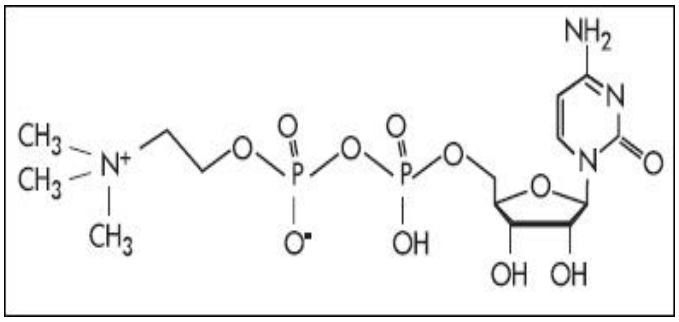

Fig 1. Structure of Citicoline.

MATERIALS AND METHODS:

Chemicals and reagents:

Citicoline was procured from Euticals spa, Italy and other materials from S. D. Fine Chemicals Ltd., Mumbai, India. All other chemicals and reagents used were analytical grade unless otherwise indicated.

Instrumentation:

The proposed work was carried out on a Shimadzu UV-visible spectrophotometer (Model UV-Pharmaspec 1700 series), which possesses a double beam double detector configuration. All weighing was done on electronic balance. A Fast clean ultrasonicate cleaner (India) was used for degassing the mobile phase.

Selection of Solvents:

On the basis of solubility study, suitable solvent was selected for dissolving Citicoline sodium. Citicoline sodium gives better solubility in water, 0.1 N HCl and 6.8 phosphate buffer so suitable for formulate the bi-layered tablet.

Table 1. Solubility Study of Citicoline Sodium.

Solvent	Solubility
Water	Freely Soluble
0.1N HCl	Freely Soluble
pH 4.5 Acetate Buffer	Soluble
pH 6.8 phosphate buffer	Soluble

Pre-formulation study:

Pre-formulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients [11,12]. Pre-formulation studies are the first step in the rational development of dosage form of a drug. The objectives of pre-formulation studies are to develop a portfolio of information about the drug substance, so that this information is useful to develop formulation (Table 1).

The Compressibility Index of the powder blend was determined by Carr's compressibility index (Table 2). It is a simple test to evaluate the bulk density (D_B) and Tapped Density (D_T) of a powder and the rate at which it packed down. The equation for Carr's Index (CI) and Hausner's ratio (HR), which is correlated to the flow ability of a powder or granular material (IP 1996) is given below.

$CI\ (\%) = [(D_T - D_B)/D_T] \times 100$ …. (1)

$HR = D_T / D_B$ ……..(2)

Table 2. Effect of carr's index and hausner's ratio on flow property.

Carr's index (%)	Flow character	Hausner's ratio
< 10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Calibration curve for API:

Preparation of Standard solution:

About 1000 mg of Citicoline Monosodium working standard was accurately weighed in a 100 ml volumetric flask. To the flask, sufficient water was added, Sonicated to dissolve and the final volume was made with water and mixed. About 1 ml of this solution was diluted with 100 ml with water and the solution was filtered through Whatman No.42 filter.

Sample preparation for assay:

About 20 tablets of Citicoline Monosodium were accurately weighed and the content was crushed in mortar pestle. From the poweder mixture, an equivalent weight of 100 mg of pure Citicoline Monosodium was taken in a 500 ml volumetric flask. To the flask, 300 ml of water was added, sonicated to dissolve and the volume was made up to 500 m with water and mixed. The solution was centrifuged for 5 min and the solution was filtered through Whatman No.42 filter. Further 1 ml of the filtrate was diluted to 100 ml with water. Absorbance were taken at 272 nm on UV spectrophotometer (1700, SHIMDZU UV) [13].

Preliminary trials for Immediate Release (IR) layer (For selection of polymer):

Composition of preliminary trials for selection of excipients was shown in Table 3. Tablets containing different super disintegrating agents were prepared by wet granulation. All the powders were passed through 40 mesh sieve. MCC added as diluents. Magnesium stearate was finally added as lubricant. PVP K30 used as binder and red oxide of iron as a colorant. The blend was compressed using Remiek mini press tablet machine. Citicoline 200 mg is equivalent to Citicoline sodium 223 mg [113,14].

Table 3. Preliminary trials for IR layer.

Ingra-dients	IR1 (mg)	IR2 (mg)	IR3 (mg)	IR4 (mg)	IR5 (mg)	IR6 (mg)	IR7 (mg)	IR8 (mg)
CS	223	223	223	223	223	223	223	223
MCC	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
CCS	2	4	6	8	---	---	---	---
SSG	---	---	---	---	2	4	6	8
ROI	2	2	2	2	2	2	2	2
PVP	2	2	2	2	2	2	2	2
MS	3	3	3	3	3	3	3	3

CCS - Cross Carmelose Sodium, ROI - Red Oxide of Iron, MS - Mg. Stearate, CS- Citicoline Sodium, PVP – Polyvinyl Pyrrolidine K30, MCC – Micro crystalline cellulose (pH 102) and q.s. – Quantity sufficient. The total tablet weight was 280 mg.

Preliminary trials for Sustained Release (SR) layer (For selection of polymer):

Tablets containing different matrix forming agents were prepared by wet granulation. All the powders were passed through 40 mesh sieve. MCC was added as diluents. Magnesium stearate was finally added as lubricant. The blend was compressed using Remiek mini press tablet machine. Each tablet contained 894 mg of Citicoline sodium and other pharmaceutical ingredients as listed in Table 5. Citicoline 800 mg is equivalent to Citicoline sodium 894 mg [13,14].

Drug Excipients Interaction Studies:

The possibility of Citicoline sodium (CTS) drug interaction with excipients, those were taken in formulation, was evaluated by DSC and FT-IR studies.

For the DSC Study, the peak of the CTS was found at 197 ^{0}C [15].

Table 4. Preliminary trials for SR layer.

Ingre-dients	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9
CTS	894	894	894	894	894	894	894	894	894
HPMC K4M	150	200	250	---	---	---	---	---	---
HPMC K15M	---	---	---	150	200	250	---	---	---
HPMC K100M	---	---	---	---	---	---	150	200	250
MCC	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
MS	15	15	15	15	15	15	15	15	15

All the quantities are in mg. CTS - Citicoline sodium, MS - Mg. Stearate, MCC – Micro crystalline cellulose (pH 102), HPMC – Hydroxy propyl methyl cellulose and q.s. – Quantity sufficient. The total tablet weight was 1210 mg.

Table 5. Optimization batch of IR layer.

Ingre-dients	IR1 (mg)	IR2 (mg)	IR3 (mg)	IR4 (mg)	IR5 (mg)	IR6 (mg)	IR7 (mg)	IR8 (mg)
CTS	223	223	223	223	223	223	223	223
MCC	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
ADS	8	8	8	8	8	8	8	8
SSG	---	---	---	---	---	---	---	---
ROI	2	2	2	2	2	2	2	2
PVP K30	2	2	2	2	2	2	2	2
MS	3	3	3	3	3	3	3	3

CTS - Citicoline sodium, MS - Mg. Stearate, MCC – Micro crystalline cellulose (pH 101), ADS - Ac-di-sol, PVP – Polyvinyl Pyrrolidine and q.s. – Quantity sufficient. The total tablet weight was 280 mg.

Table 6. Formulation Optimization batches of SR layer.

Ingre-dients	A1	A2	A3	A4	A5	A6	A7	A8
CTS	894	894	894	894	894	894	894	894
HPMC K100M	230	240	250	260	270	280	290	300
MCC	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
MS	15	15	15	15	15	15	15	15
TW	1260	1260	1260	1260	1260	1260	1260	1260
TWBT	1540	1540	1540	1540	1540	1540	1540	1540

All the quantities are in mg. CTS - Citicoline sodium, MS - Mg. Stearate, MCC – Micro crystalline cellulose (pH 102), HPMC – Hydroxy propyl methyl cellulose and q.s. – Quantity sufficient. TWBT - Total weight of bilayer Tablet and TW - Total weight.

RESULTS AND DISCUSSION:

DSC Study:

For the DSC Study revealed that in the formulation, there was no any significant change in endothermic peak is observed when it was mixed with the other Excipients. Therefore it was stated that the all excipient used in the present study are compatible with CTS (Fig 2 and 3).

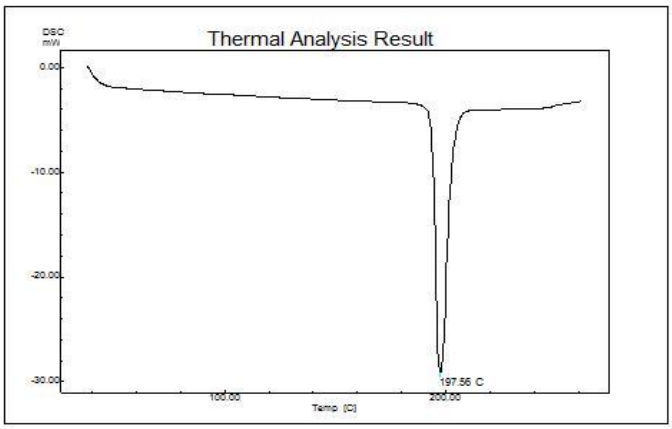

Fig 2. DSC thermo gram of CTS.

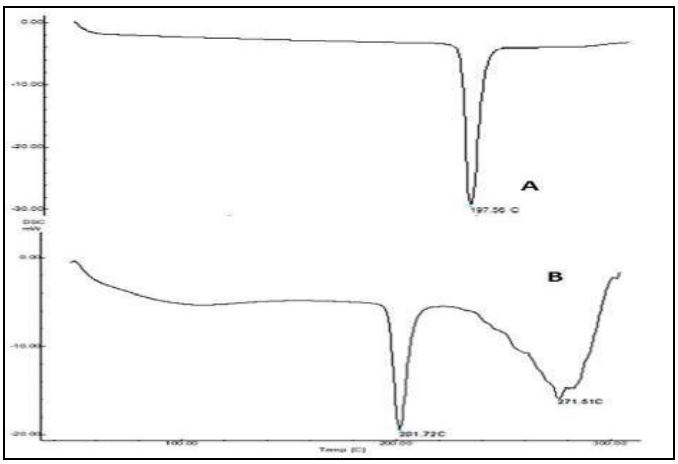

Fig 3. A. DSC thermo gram of CTS, B. DSC thermo gram of CTS with HPMC K 100 M.

FT-IR study:

The Citicoline tablet showed the characteristic peaks as shown in Fig 5 match with the characteristic peak of Citicoline working standard Fig 4. In all physical mixtures of drug and polymer, there was neither masking of single characteristic peak nor existence of additional peak in drug spectra.

The Physicochemical study of CTS:

Optimized batch A2 has passed all the specified range of parameter. A2 batch gave weight variation in the range of 1540 ± 40 mg. It had also sufficient hardness 10 to 11 kg/cm^2 to stand mechanical shock, which was the optimized for the further study because less than the

above value then the tablet layer become separated during the friability study. Drug content and friability of batch A2 was found 99.5 ± 5 % and 0.14 ± 0.007 % respectively, which was desirable for our formulation. Therefore A2 batch is considered optimized batch for the SR layer.

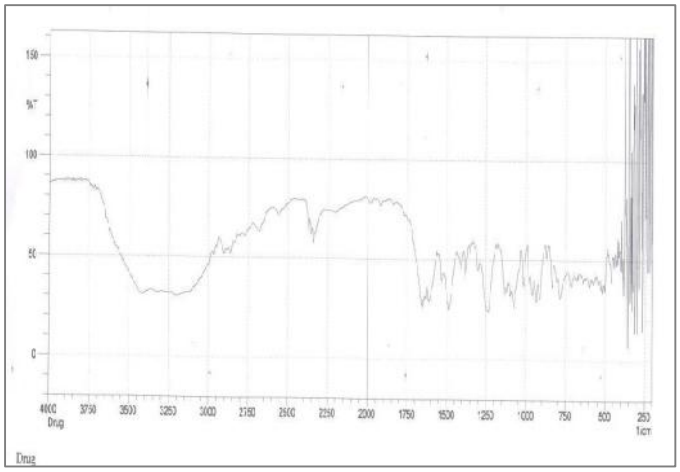

Fig 4. IR spectrum of Citicoline standard.

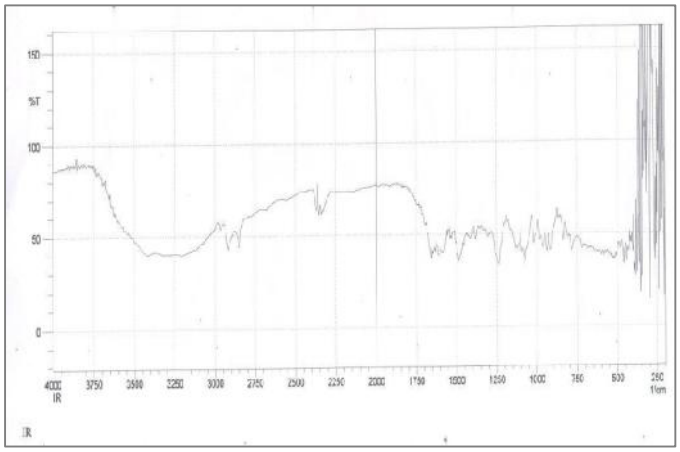

Fig 5. IR spectrum of Citicoline tablet.

Dissolution Study:

The comparative dissolution profile of A1 to A8 shown in Table 7. Batch A2 gave maximum release compare to A3 to A8 batches (A1 batch gave maximum release but it was >85 % at 8 h), and it also gave the same release profile as per in-house dissolution profile. The dissolution profile of the best batch A2 was fitted to zero-order, first-order, Higuchi and korsmeyer models to ascertain the kinetic modeling of drug release. It may be concluded that the drug release from Citicoline tablet is best explained by korsmeyer-peppas model because R^2 value of Higuchi model has 0.9883. The values of n in korsmeyer- peppas equation are 0.393 which is less than 0.50.

CONCLUSION:

In the present work, the incorporation of Citicoline, an cerebral vasodilator agent was performed in inert HPMC Ac-Di-Sol. Where Ac-Di-Sol is used as super disintegrating agent and HPMC and 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 DSC and FTIR. Thus by HPMC K 100 M with MCC (pH 101) in solvent result in formation of thick gel which give diffusion path for drug and give control release profile. Hydroxy Propyl Methyl Cellulose proved useful as a rate controlling polymer to produce a controlled release formulation of Citicoline using the diffusion-dissolution controlled mechanism. The prepared optimized bi-layer tablet formulation of Citicoline was stable. Hence, this optimized bi-layer tablet dosage form could be a potential formulation for delivery of drugs from a single dosage form which could improve patient compliance and give better disease management.

Table 7. Dissolution profile of batches A2 and A2 batch after 1 month stability study prepared by wet compression method.

Time (h)	CPR of A2 Initial	CPR of A2 after 1 month
0	0	0
0.25	22.4±0.78	21.5±0.82
1	32.4±0.85	31.81±0.79
4	63.2±1.22	61.50±1.18
8	83.2±2.14	81.09±2.10
12	97.5±2.25	98.5±2.21

Date are presented as mean ± standard deviations (n = 3).

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