Available online on 15.04.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

Development and characterization of controlled release bilayered tablets of Citicoline sodium

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ABSTRACT

Objectives: The aim of present investigation was formulation development and evaluation of bi-layer tablets of citicoline sodium. **Materials and Methods:** An aqueous granulation process was adopted to formulate citicoline sodium (CTS) bilayer tablets. Wet granulation method has been utilized for the formulation of bilayer CTS tablet. Citicoline sodium, microcrystalline cellulose (pH 101 & 102), HPMC K4, K15, K-100, PVP K-30, Magnesium stearate, cross-carmellose sodium, sodium starch glycolate and red oxide were used for preparation. Pre-formulation studies of citicoline sodium and drug excipient compatibility study was carried to optimize the formulation variables. Two layers, immediate release (IR layer) and sustained release (SR) has been developed and evaluated for the various parameters e.g. micromeritic properties, percentage yield, particle size, hardness, thickness, weight variation, percent friability and percent assay, *In-vitro* dissolution and *In-vitro* release studies. **Result and Discussion:** Pre-formulation study of citicoline sodium denotes that evaluated parameters confirm the suitability and compliance of drug with polymers. Drug excipient compatibility study through the DSC confirmed that polymer, excipient and drug were compatible with each other and no incompatibility issue found during the preparation of formulation. FT-IR study is also executed to confirm the drug-excipient incompatibility. In all physical mixtures of drug and polymer, there was neither masking of single characteristic peak nor existence of additional peak in drug spectra; this has proven that drug and polymers are compatible with each other. Hardness 10-11 kg/cm^2, thickness 7.3-7.4 mm, percent weight variation 1.2%, friability 0.1-0.3%, assay was 99-101% denotes the successful development of CTS tablets. **Conclusion:** These all parameters denote that the formulation has optimized, evaluated and were in the standard range. Hence, this optimized bilayer tablet formulation could be a potential formulation to promote sustained release, promote delivery of drugs from a single dosage form to improve patient compliance and give better disease management.

Keywords: Citicoline sodium, bi-layer tablet, DSC, immediate release, sustain release.

Article Info: Received 17 Feb 2019; Review Completed 23 March 2019; Accepted 25 March 2019; Available online 15 April 2019

Cite this article as:

Rayakwar N, Dangi YS, Development and characterization of controlled release bilayered tablets of Citicoline sodium, Journal of Drug Delivery and Therapeutics. 2019; 9(2-s):125-131 http://dx.doi.org/10.22270/jddt.v9i2-s.2471

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INTRODUCTION

Conventional oral dosage form has many disadvantages includes high frequency of dosing, drug dependency and side effects. Usually conventional dosage form produces wide range fluctuation in drug concentration in blood stream and tissues with consequent undesirable toxicity and poor efficiency. The factor such as repetitive dosing and unpredictable absorption led to the concept of controlled and sustained drug delivery systems. Sustained-release and controlled dosage forms are designed to release drug at a pre-determined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects[1].

The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance[2]. In this era the interest is increased in development of controlled releases formulation with aim to reduce frequency of dosing/dose, improve the patient compliances, minimized dose dependent side effects and prolong the circulation period of the drugs.

Now a day multilayer tablet dosage form shows great acceptability. Multilayer tablet are bi-layer, tri-layer and four layer tablets[3]. Mainly bi-layer tablet is the new era for the successful development of controlled release formulation. Bi-layer tablet is single dosage form with combination of two or more active pharmaceutical ingredients (API) which promoting patient convenience compliance and reduce the dose frequency[4]. Bi-layered tablet is suitable for sequential release of two drugs in combination and separate by two compatible substances and bilayer tablet has advantageous in which one layer is immediate release as initial dose and second layer is maintenance dose[5]. In the case of bi-layered tablets drug release can be rendered almost unidirectional if

the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity[6].

Citicoline sodium is also known as cytidine Diphosphate-choline (cdp-choline) and cytidine 5'diphosphocholine[7]. Citicoline is often called a "brain nutrient" because it increases levels of several important neuro-transmitters including acetylcholine, dopamine and Noradrenalin. It helps to maintain the integrity of neuronal cell membranes and increases energy production in the frontal cortex. In the US, Citicoline is marketed as a dietary supplement[8]. 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. As an exogenous source of choline for acetylcholine production, Citicoline thus spares membrane phospholipids (in particular, phosphatidyl choline) and prevents neuronal cell death. It is also used in Alzheimer disease and Parkinson's disease.

Various techniques for bi-layer tablet are nowadays in marketed includes OROS® push pull technology system consist of mainly two or three layer. L-OROS™ technology used for the solubility problem in that case Alza developed L-OROS system, where a lipid soft gel product contain drug in dissolved state and coated with first a barrier membrane, second with osmotic push layer and third with semi-permeable membrane and drilled with an exit orifice[9]. DUROS technology consists an outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a mini syringe and release minute quantity of concentrated form in continues and consistent over an months or year.

EnSotrol technology[10] and Elan drug technologies is the dual release drug delivery system (DUREDAS™ Technology), which provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tab letting process can provide an immediate release granulate and a modified-release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers. These techniques encourage the formulation development of the citicoline sodium bi-layered sustained released formulation.

The aim of the present paper is the formulation development of sustained released bi-layer tablets of citicoline sodium and characterized for their sustained release credential.

MATERIALS AND METHODS

Citicoline Sodium was procured from Euticals spa, Italy. Microcrystalline Cellulose (pH 101 & 102) was obtained from N.B. Enterprise, Gujarat, India. HPMC K4M, HPMC K15 M, HPMC K-100 M were procured from color con Asia Private Ltd, Mumbai, India, PVP K-30 was purchased from Shital Chemicals Ltd, Gujarat, India. Magnesium Stearate was procured from Sunshine Organics Pvt. Ltd, Gujarat, India, Cross carmellose sodium and sodium starch glycolate were purchased from SD Fine Chemicals Ltd., Mumbai, India and Red oxide was purchased from Hindustan Mineral Products Company Ltd. Mumbai. All the chemical were analytical grade.

Calibration curve for API

The calibration curve of CTS has been prepared by dissolving the CTS in distilled water[11].

Preparation of standard solution

Weight accurately about 1000 mg of Citicoline sodium (working standard) in a 100 ml volumetric flask, add sufficient water, sonicate to dissolve and make up the volume with water and mix. Dilute 1 ml of this solution to 100 ml with water and filter the solution through what-man filter paper no. 42. Make the dilution of concentration of 10, 15, 20, 25, 30, 35, 40, 45 and 50µg/ml.

Sample preparation for assay

Weight accurately 1000 mg of Citicoline sodium by mixing content of 20 crushed tablets, taken into a 500 ml volumetric flask and add 300 ml of distilled water, sonicate to dissolve and make the volume up to 500 ml with water and mix. Centrifuge the solution for 5 min and filter the solution through what-man filter paper No. 42. Further dilute 1 ml of the filtrate to 100 ml with water. Absorbance were taken at 272 nm on UV spectrophotometer (1800, Shimdzu UV).

Preparation of tablets

Citicoline sodium (CTS) tablet was prepared by the granulation process. Two layers, Immediate release (IR) and sustained release (SR) layer has been prepared for the formulation of the bi-layer tablets.

Manufacturing process for immediate release layer

In the preparation of the IR layers, firstly citicoline sodium passed through the 20# mesh security sieve (S.S.). Avicel PH 102, PVP K 30 and Ac-di-sol passes through 40#, and Red oxide of iron shifted through 100#. Mix the material in rapid mixer granulator for 10 min at slow speed and after proper mixing purified water was added slowly to the dry mix and then granulates the materials; add additional quantity of purified water, if required. Granulate for 6-8 min with impeller and chopper at slow speed and for 2 min at fast speed.

Dry the granules in the fluid bed dryer 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 ranges 55°C 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., knives forward at slow speed of cad mill and again pass through 16#. Sift Magnesium stearate through 40# and mixed with dried granules in Cage blender for 10 min at 13±2 RPM speed. Different batches of the IR layer has been formulated and evaluated by the various parameters.

Manufacturing process for sustain release (SR) layer

Same procedure adopted for the SR layer as discuss in IR layer preparation, only HPMC K100M, was used in the place of PVP K 30 and Ac-di-sol. Different batches of the SR layer has been formulated and evaluated by the various parameters.

Preparation method of bilayer tablet

Compress the IR and SR Layers

In that first SR layer compress by the tablet compression machine using an optimum size 21.5×10.5 mm shape punch and adjust the die fill weight 1210±5.0%. Compression was operates using up to optimum hardness up to 4 kg/cm^2 and then after IR layer granules was put inside the die and commence the regular compression. Twenty tablets were evaluated for the various parameters. Weight variation was checked for in-process evaluation by using electronic balance. Eight batches has been prepared (A1 –A8) and

evaluated for different parameters. Tablet hardness was evaluated by using hardness tester (Monsanto tester). Friability determined by the Roche friabilator for 5 min at a speed of 25 rpm/min. The thickness and diameter of the tablets were measured by vernier caliper scale[12].

Apparatus used for the manufacturing, in-process evaluation and preliminary testing and evaluation of the finished product (bilayer tablets), includes digital balance, electronic weighing balance (Shimadzu, Tokyo, Japan), UV-Visible spectrophotometer (Shimadzu 1700), sonicator (Bransone Ultrasonic), Digital pH meter (Thermo Orion), Hot air oven, Bulk/tapped density apparatus (Expo Hi-Tech), Rotary compression machine (Cadmac), Thickness tester, Monsanto Hardness Tester, Friabilator (Electro lab), disintegration test apparatus and dissolution test apparatus (Electro lab), FTIR-8400 S and Humidity chamber, Environment test chamber (Expo Hi-Tech).

Evaluation of bi-layer tablets

Tablet thickness and size

Vernier caliper was used for measurement of thickness and diameter. These parameters are important for uniformity of tablet size[13].

Weight variation test

To study weight variation 20 tablets of the formulation were weighed using a electronic weighing balance (Shimadzu, Tokyo, Japan) and the test was performed according to the official method. As per I.P. weight variation should not more than 5 percent[14].

Uniformity of weight

Twenty tablets were selected at random and the average weight was calculated. Weight Variation was calculated and was compared with I. P. standards[15].

Drug content

Twenty tablets were weighed individually, and the drug was extracted in water. The range of content uniformity is 90-110 percent[16].

Hardness

Hardness denotes as an important indicator for tablet strength, for shipping or breakage under conditions of storage, transportation and handling before usage. The resistance of tablets hardness measured with hardness tester i.e. mainly by Monsanto Hardness tester.

The unit for hardness is kg/cm^2. The hardness of 20 tablets was determined using the Monsanto hardness tester and the average values were calculated[17]. 4 kg/cm^2 is considered to be minimum for a satisfactory tablet[16].

Thickness

The thickness of the tables was determined by using vernier calipers. 20 tablets were used and average values were calculated. This procedure has repeated in triplicate.

Friability

Friability is an indicator for tablet strength. The friability of the tablets was measured in a Roche friabilator. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm and dropping the tablets through a distance of six inches height with each revolution[15]. In after 4 min, the tablets were weighed and percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. This procedure has repeated in triplicate.

% loss= [(Initial wt. of tablets – Final wt. of tablets)/Initial wt. of tablets] ×100.

Disintegration test

The disintegration test was carried out by use of disintegration test apparatus. Six tablets were subjected for analyzed in the apparatus and calculate the disintegration time and average value was calculated.

***In-vitro* drug release study**

In-vitro drug release study was performed by using dissolution apparatus. These studies are carried out using USP dissolution test apparatus I at 100 rpm, 37±0.5°C, and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hrs (average gastric emptying time is 2 hrs) in simulated gastric or intestinal fluids are used. Experiment continued for another 10 hours with pH 6.8 phosphate buffer (900ml) as the dissolution medium. 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium at different time intervals. The samples withdrawn were analyzed by using UV spectrophotometer[15,18].

Characterization of bilayer tablet

1. Particle size distribution

There are number of methods for measuring particle size. Mostly sieving method used for measuring particle size distribution.

Pre Compression parameter

Physical Properties of Tablets

Pre compression parameter of bilayer tablets were evaluated for bulk density, tapped density, Hausner's ratio, angle of repose and Carr's index. This Define the Physical properties of the formulation.

Bulk density[19]

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined by transferring the accurate weighed amount of sample in 50 ml measuring cylinder, the granules without any agglomerates and measured the volume of packing and tapped 50 times on a plane surface and tapped volume of packing recorded and LBD and TBD calculated by following formula.

$$\text{LBD} = \frac{\text{Mass of powder}}{\text{Volume of packing}} \qquad \text{TBD} = \frac{\text{Mass of powder}}{\text{Tapped volume of packing}}$$

Hausner's ratio

Hausner's ratio is computed by applying the next equation

Hausner's ratio= Tapped density/ Bulk density

Percentage compressibility index[20]

Percentage compressibility of powder mix was determined by Carr's Compressibility Index calculated by following formula.

% Carr's Index= (TBD-LBD) ×100/TBD;

Where, TBD= Tapped bulk density; LBD= Loose bulk density.

Angle of repose

The frictional forces in loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a mass of powder or granules and the horizontal plane. Angle of repose is calculated by applying the next equation;

$\tan \theta = h/r$; $\theta = \tan^{-1}(h/r)$, where θ=angle of repose; h=height; r=radius.

RESULT AND DISCUSSION

Pre-formulation study of drug citicoline sodium (CTS) was performed and result indicates that CTS was freely soluble in water, 0.1N HCl, acetate buffer (pH 4.5) and soluble in phosphate buffer (pH 6.8 and pH 7.5). Standard curve of citicoline sodium was depicted in Figure 1. Regression value was 0.999. Drug excipient compatibility study also carried by the Differential scanning colorimetric spectroscopy and indicates that the drug and excipient were compatible with each other. For the DSC Study the peak of the CTS was found at 197°C and in the formulation, there was no significant change in endothermic peak is observed when it was mixed with the other excipient (Figure 2, 2A-2E) and FT-IR spectra also indicates that no extra peak has been generated that reflects that drug and all other excipient were compatible with each other. In all physical mixtures of drug and polymer, there was neither masking of single characteristic peak nor existence of additional peak in drug spectra, so we can prove that drug and polymers are compatible with each other.

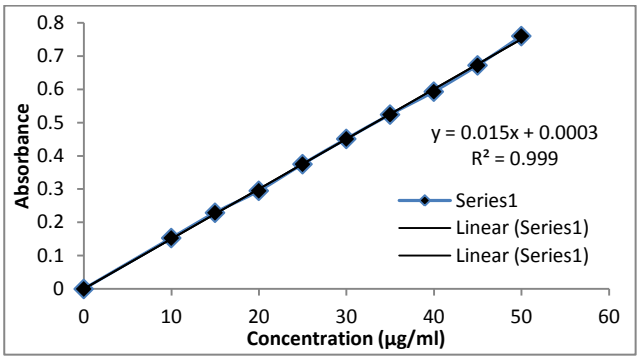

Figure 1: Standard curve of citicoline sodium

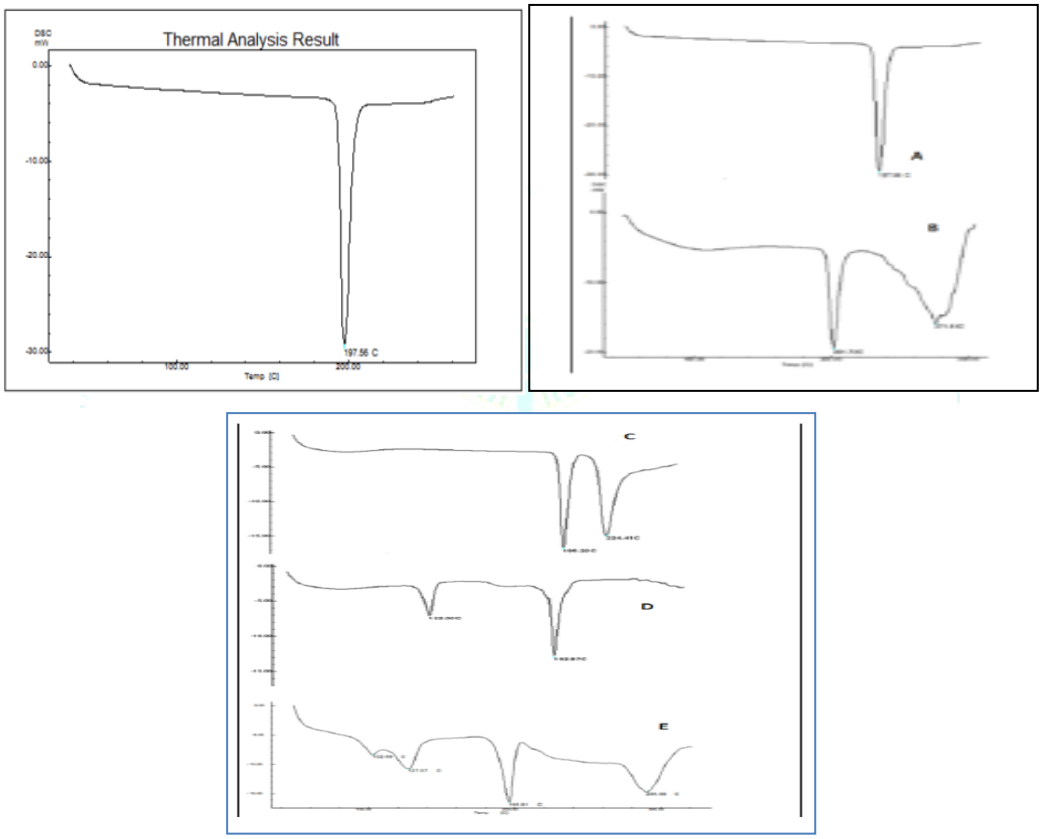

Figure 2: DSC thermogram of Citicoline sodium (CTS); (A) DSC thermo gram of CTS, (B) DSC thermo gram of CTS with HPMC K 100 M; (C) Citicoline sodium with MCC, (D) Citicoline sodium with magnesium stearate, (E) Citicoline sodium with all excipient.

Table 1: Pre-formulation study of optimized batch of IR layer

Properties	IR 1	IR 2	IR 3	IR 4	IR 5	IR 6	IR 7	IR 8
Bulk density (gm/ml)	0.46± 0.12	0.51± 0.11	0.42± 0.13	0.49± 0.10	0.42± 0.11	0.41± 0.13	0.41± 0.12	0.40± 0.15
Tapped density (gm/ml)	0.46± 0.13	0.52± 0.14	0.43± 0.12	0.52± 0.11	0.44± 0.10	0.41± 0.12	0.42± 0.14	0.48± 0.15
Carr's Index	9.2± 0.25	9.5± 0.31	9.6± 0.26	8.9± 0.31	9.3± 0.24	8.9± 0.21	9.2± 0.18	9.3± 0.28
Hausner's ratio	1.1± 0.26	1.11± 0.27	1.01± 0.19	1.12± 0.28	1.11± 0.25	1.12± 0.31	1.12± 0.24	1.11± 0.18
Angle of repose	32.45± 0.78	31.2± 0.85	32.41± 0.87	28.43± 0.78	30.28± 0.78	31.21± 0.78	28.44± 0.78	28.0± 0.78
Disintegration time (min.) n=6	3.58± 0.10	2.87± 0.18	1.52 ±0.12	0.89± 0.10	4.23± 0.10	3.78± 0.14	2.89± 0.12	1.23± 0.10

*n=6, mean ± SD

Table 2: Pre-formulation study of optimized batch of SR layer

Properties	IR 1	IR 2	IR 3	IR 4	IR 5	IR 6	IR 7	IR 8
Bulk density (gm/ml)	0.438± 0.012	0.425± 0.009	0.416 ±0.007	0.416± 0.009	0.408± 0.010	0.408± 0.010	0.400± 0.011	0392± 0.012
Tapped density (gm/ml)	0.500± 0.013	0.488± 0.014	0.476± 0.009	0.476± 0.008	0.476± 0.011	0.465± 0.012	0.454± 0.009	0.454± 0.010
Carr's Index	12.40± 0.018	12.40±0.0 18	12.60±0.0 15	10.71±0.0 16	12.60±0. 018	12.26±0.01 6	12.25±0.01 2	11.89±0.01 0
Hausner's ratio	1.141± 0.018	1.148± 0.017	1.144± 0.015	1.120± 0.016	1.144± 0.019	1.40± 0.016	1.139± 0.018	1.138± 0.009
Angle of repose	32.45± 0.68	29.47± 0.58	28.44± 0.65	32.37± 0.66	30.25± 0.64	28.00± 0.58	28.44± 0.59	28.0± 0.56
Disintegratio n time min.) n=6	1.68± 0.12	2.37± 0.16	2.02± 0.14	2.45± 0.10	3.32 ± 0.10	3.78± 0.14	2.89± 0.12	1.23± 0.10

*n=6, mean ± SD

Table 3: Value of Hardness, thickness, percent friability, weight variation and percent assay batches IR1-IR8 (mean±SD, n=6)

Batch No.	Hardness	Thickness	Weight variation	Percent Friability	Percent assay
IR1	11±0.25	7.3±0.18	1544±15.20	0.25±0.005	99.4±2.12
IR 2	10.5±0.23	7.4±0.17	1540±10.14	0.14±0.004	99.5±2.15
IR 3	10.5±0.19	7.3±0.17	1542±16.24	0.23±0.005	100.6±2.36
IR 4	10.5±0.21	7.3±0.12	1541±20.25	0.18±0.003	101.4±1.98
IR 5	11.0±0.20	7.3±0.15	1542±20.20	0.25±0.002	100.4±1.78
IR 6	10.5±0.25	7.3±0.13	1540±19.36	0.25±0.005	99.2±2.14
IR 7	11.0±0.24	7.3±0.16	1542±14.20	0.33±0.005	100.5±2.12
IR 8	11.0±0.19	7.3±0.18	1545±18.20	0.21±0.007	99.8±3.12

*n=6, mean ± SD

Pre-formulation study of optimized batch of IR layer was enclosed in Table 1. The IR4 batch has shown fast disintegration time as compare with other batches. So it has confirmed that the concentration the Ac-Di-sol and MCC, was affect the release of drug content form IR layer and optimized for better disintegration. Preformulation of the IR4 tablet has showed the good flow property among all other batch of the IR layer tablets. Table 5 showed the different dissolution efficiency of the IR layer, in which the maximum dissolution efficiency of IR4 is 32.15, compared with the other batch of tablets and also shown highest drug release 98.18% at 20 min which was selected further for the optimization of the bi-layer tablets. These parameters were optimized by different trial of the bi-layer tablets. Evaluation of IR layer batches IR1-IR8 batches was shown in Table 3.

Table 4: Value of Hardness, Thickness, percent friability, percent assay and Weight variation of Batches SR1-SR8 (mean ± SD, n=6)

Batch No.	Hardness	Thickness	Weight variation	Percent Friability	Percent assay
SR1	10.0±0.01	7.4±0.14	1212±20.15	0.20±0.006	99.2±2.5
SR 2	10.5±0.02	7.3±0.12	1211±15.23	0.23±0.004	98.8±3.1
SR 3	11.0±0.02	7.3±0.13	1212±18.58	0.16±0.006	99.7±2.9
SR 4	11.0±0.01	7.4±0.12	1210±19.85	0.22±0.007	101.2±3.2
SR 5	10.5±0.01	7.4±0.15	1213±21.25	0.37±0.005	99.4±2.8
SR 6	10.0±0.02	7.4±0.12	1209±18.98	0.21±0.006	99.2±2.7
SR 7	11.0±0.01	7.3±0.11	1210±19.84	0.30±0.007	100.7±2.5
SR 8	11.0±0.01	7.3±0.12	1212±11.85	0.24±0.007	99.8±3.2

*n=6, mean ± SD

The SR1-SR8 batches were prepared by using different concentration of Avicel PH102, HPMC K4M, HPMC K15M and HPMC K100 by using water as a solvent for the granulation. In all batches (SR1-SR8), SR8 batch has good flow property and compressibility. Pre-formulation study of optimized batch of SR layer was enclosed in Table 2. In the SR1-SR3 HPMC K4M was used and SR4-SR6 HPMC K15M was used but the drug release was not found as per in-house specification. In preparation of SR7-SR8 layers HPMC K100M was used promote the drug release profile as per the in-house limitation. Evaluation of SR layer batches SR1-SR8 batches was shown in Table 4.

Table 5: Pre-formulation study of batch A1-A8 (bilayer tablet)

Properties	IR 1	IR 2	IR 3	IR 4	IR 5	IR 6	IR 7	IR 8
Bulk density (gm/ml)	0.392± 0.008	0.392± 0.009	0.392 ±0.008	0.385± 0.010	0.385± 0.011	0.377± 0.008	0.377± 0.010	0.377± 0.009
Tapped density (gm/ml)	0.465± 0.013	0.468± 0.014	0.454± 0.009	0.456± 0.008	0.476± 0.011	0.444± 0.008	0.454± 0.013	0.434± 0.011
Carr's Index	15.70± 0.35	13.66± 0.45	13.66± 0.41	15.20± 0.38	15.20± 0.41	15.09± 0.39	15.09± 0.51	15.70± 0.45
Hausner's ratio	1.186± 0.024	1.158± 0.023	1.158± 0.019	1.179± 0.024	1.177± 0.019	1.179± 0.032	1.177± 0.042	1.151± 0.035
Angle of repose	23.1± 0.68	24.76± 0.75	27.13± 0.65	27.10± 0.58	26.90± 0.72	27.50± 0.69	28.12± 0.73	28.0± 0.64

n=6, mean ± SD

In-vitro dissolution profile of IR layer IR1-IR8 batches was shown in Figure 3. The comparative dissolution profile shown in table 26, Release profile of SR8 follows dissolution profile percent limit as per in-house limitation. From the above all trial batches, SR8 was optimized and it was used for the further study for the development of the bi-layer tablets.

In-vitro release profile of SR layer depicted in Figure 4. Bilayer tablets have been prepared by wet compression method A1-A8. The comparative dissolution profile of A1-A8 was shown in Table 7.

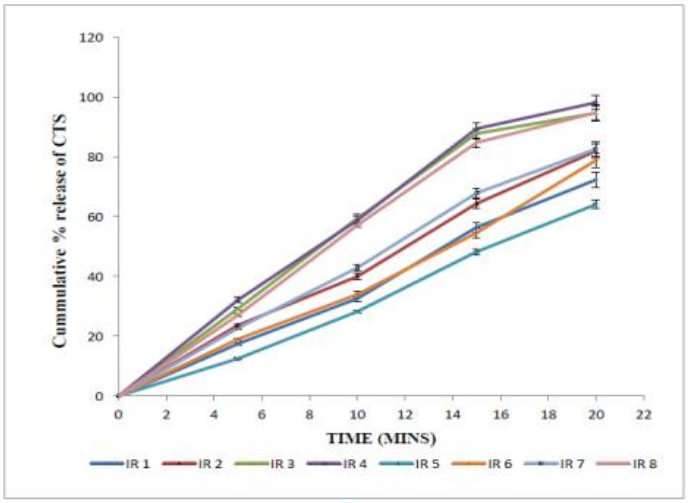

Figure 3: Drug dissolution profile of various developed formulations (IR1-IR8).

Table 6: Value of Hardness, Thickness, Diameter and Weight variation of batches A1-A8

Batch No.	Hardness*	Thickness*	Weight variation*	Percent Friability*	Percent assay*
A1	11±0.25	7.3±0.18	1544±15.20	0.25±0.005	99.4±2.12
A2	10.5±0.23	7.4±0.17	1540±10.14	0.14±0.004	99.5±2.15
A3	10.5±0.19	7.3±0.17	1542±16.24	0.23±0.005	100.6±2.36
A4	10.5±0.21	7.3±0.12	1541±20.25	0.18±0.003	101.4±1.98
A5	11.0±0.20	7.3±0.15	1542±20.20	0.25±0.002	100.4±1.78
A6	10.5±0.25	7.3±0.13	1540±19.36	0.25±0.005	99.2±2.14
A7	11.0±0.24	7.3±0.16	1542±14.20	0.33±0.005	100.5±2.12
A8	11.0±0.19	7.3±0.18	1545±18.20	0.21±0.007	99.8±3.12

*n=6, mean ± SD

Batch A2 gave maximum release compare to A3-A8 batches (A1 batch gave maximum release but it was >85 % at 8 hrs), and it also gave the same release profile as per in-house dissolution profile. Optimized batch A2 has passed all the specified range of parameter.

Table 7: In-vitro dissolution profile of batches A1-A8 (bilayer tablet)

Time (hrs.)	Percent drug release							
	A1	A2	A3	A4	A5	A6	A7	A8
0.25	22.8 ±0.52	22.4 ±0.53	21.8 ±0.60	21.6 ±0.52	21.5 ±0.52	21.6 ±0.52	21.8 ±0.52	22.4 ±0.52
1	39.8 ±0.52	32.4±1.92	29.5 ±0.81	36.1 ±0.65	35.7 ±0.59	36.1 ±0.53	36.1 ±0.78	38.3 ±0.72
4	64.5±1.8	63.2 ±1.92	60.4 ±1.75	61.4 ±1.73	61.2 ±0.52	60.3 ±0.52	60.2 ±1.73	56.9 ±1.68
8	85.7±1.8	83.2±1.3	80.7±1.6	79.8±2.8	79.3±2.6	78.7±1.6	78.3±2.5	77.9±1.6
12	98.4 ±2.31	97.5 ±2.12	95.6 ±2.11	94.7 ±2.15	93.8 ±2.17	93.4 ±2.28	92.8 ±2.25	91.2 ±2.11

n=6, mean ± SD

Pre-formulation study of batch A1-A8 batches of bilayer tablet was shown in Table 5 and which was the optimized for the further study because less than the above value then the tablet layer become separated during the friability study. Evaluation of bilayer tablets batches A1-A8 was depicted in Table 6.

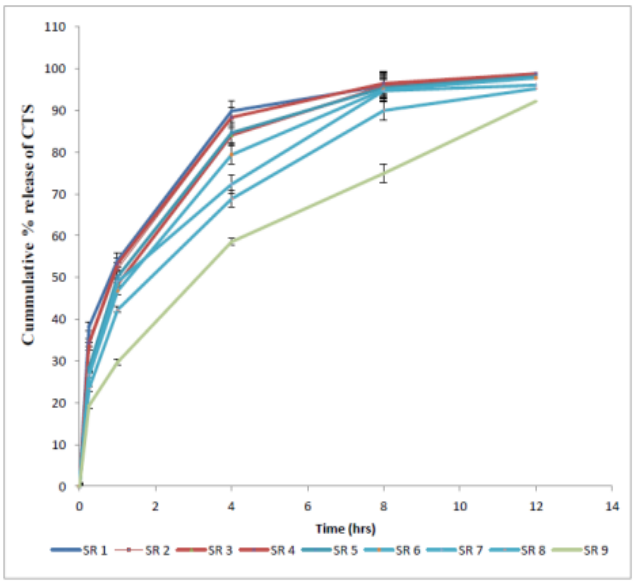

Figure 4: Drug dissolution profile of various developed formulations (SR1-SR8)

DISCUSSION

The aim of present investigation was the formulation development, evaluation and stability study of bilayer tablets of Citicoline sodium (CTS tablet). Optimized formulation design has been developed by using trail batches of CTS tablets. The amount of HPMC K100M and Ac-di-Sol were selected as factor for optimization. The DSC study depicted that no change in drug melting peak after the formulation with all other excipient. IR spectrum also concluded that no significant change in the peak of the citicoline sodium, which shown no interaction between drug and other excipient.

Dissolution study of tablet has shown that the tablet by using the Ac-Di-Sol as a disintegrating agent shown better immediate release of drug as compare with the Sodium starch glycolate and could be retarded for 12 hrs; when release of citicoline achieved highest is kept at optimum level. So role of HPMC K 100 M polymer concentration is very important for IR formulation. Optimization formulation was further evaluated for the physical parameters and Micromeritic properties.

In Case of SR layer incorporation of Citicoline (cerebral vasodilator agent) with inert HPMC K100 and Ac-Di-Sol (super disintegrating agent). HPMC and other polymer in different concentration were 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. Hence, this optimized bi-layer tablet could be a potential formulation for delivery of drugs from a single dosage form which could improve patient compliance and give better disease management.

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