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Formulation and Evaluation of fixed dose combination of Nootropic drugs

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ABSTRACT

Cognitive functions are the critical brain functions responsible for the effective learning and understanding in the humans. They are responsible for various functions like attention, memory, reasoning and in turn helps to improve knowledge. Cognitive impairment is majorly seen in elderly as the brain is prone to neuro degradation. It may also occur in young adults due to poor diet or exercise. Improving cognition is of utmost importance and can be done by the use of cognition enhancers like Nootropics. This class of drugs is said to act by various mechanisms, which in turn leads to the betterment of the neurotransmission in the brain. They may act on acetylcholine, Gamma Butyric Acid, on the beta amyloid receptor or on NMDA. This research emphasis on the enhancement of cognition along with treating various neurodegenerative diseases like dementia, Alzheimer's or Parkinson's. Nootropic drugs are chosen for this formulation as they exhibit a rationale in combination with each other since they follow distinctive route of mechanism to treat the diseases. They also show action by preventing the worsening of the disease and by curing the disease. As compared to other combination of nootropic, in this combination, the side effects are reduced of one in presence of the other and show a much higher bioavailability. They cross the blood brain barrier and central nervous system half-life is longer as compared to the systemic half-life owing to their efficacy and superiority over other nootropics when it comes to treating cognition Fixed dose combination of these nootropic drugs is desired and the dose can't be varied as they no longer show their effect if not used in the exact dose required. The dosage of this varied drug depends on the severity of the disease and patient condition. The research has helped to achieve the reduction in the total tablet mass from 1500 mg to 1420 mg with the use of few excipients. This made it easier for patients to swallow the tablet easily due to an oval shape of the tablet formulation.

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INTRODUCTION

Development and evaluation of fixed dose combination of nootropic drugs

Cognitive Function encompasses reasoning, memory, attention and language and lead directly to the attainment of information and thus knowledge (Baddeley, 2003). Nevertheless, if cognitive performance is directly linked to these functions, other endogenous factors like mood and physical health can impact it tremendously classification of Cognitive functions in the Figure 1.

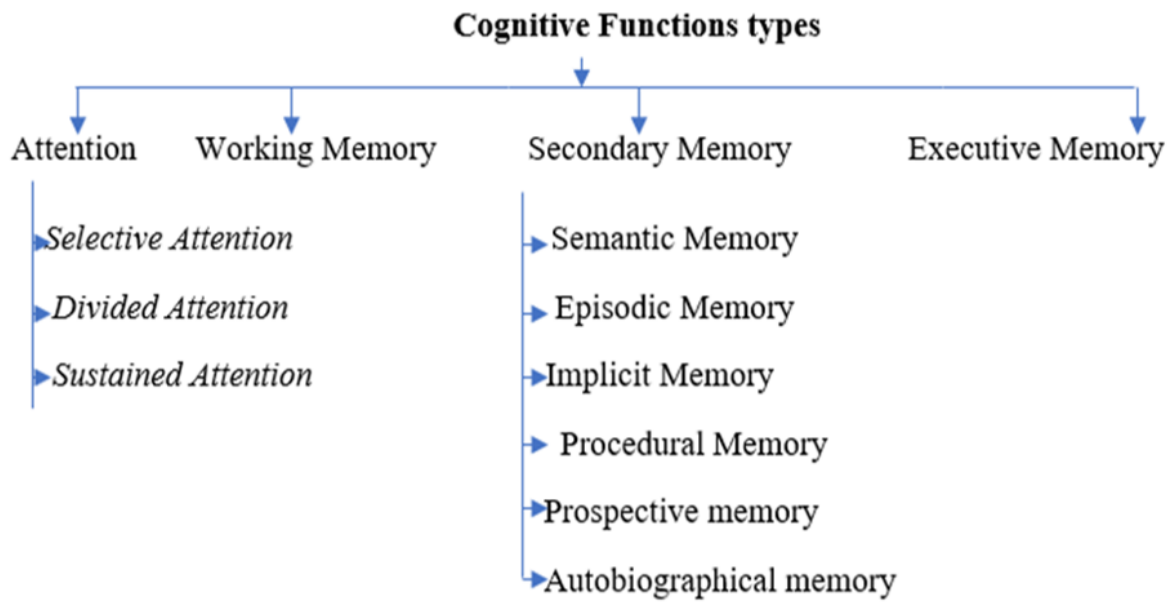

Figure 1: Types of Cognitive functions

Maintenance of Healthy cognitive function

Though cognitive decline is a natural process, certain activities can help maintain cognitive functioning of the brain.

Mental Activity

If brain is not solicitated adequately, it would become dormant and cognitive decline would occur due to lack of intellectual stimulation. Training the brain to put to use with mental activity like playing Chess or video games can improve cognition.

Physical Activity

As the body does some exercise, the blood circulation increases the brain achieves more oxygen leading to improvement in brain functioning (Mandolesi *et al.*, 2018).

Balanced Diet

Diet affects cerebral health. Thus, a balanced diet is essential for the body and brain to function well. Diet that includes a good quantity of food containing Vitamin B and Vitamin C helps improve the cognitive functions (Solfrizzi *et al.*, 2003).

Decline of Cognitive Functions

Cognitive functions can be impaired or declined by age. This may lead to many cognitive diseases like dementia, Alzheimer's, Parkinson's etc. Alzheimer's disease is the leading cause of death in the world. Thus, it is highly important to maintain the normal cognitive functioning of the brain and delay brain aging

Treatment of impaired cognitive functions

Brain supplements and Cognition enhancers are used to treat and improve cognitive functions are mentioned in Table 1. (Suliman *et al.*, 2016; Malhotra *et al.*, 2018; Joshi, 2013).

Solid oral Immediate release dosage form

Solid oral dosage is preferable route of drug administration. Oral drug is convenient for systemic effect as well as Therapeutic effects. Oral dose is cost effective and easy for patient to take medication without any profession administrator. Immediate-release preparations These preparations are primarily intended to achieve fast onset of action for drugs such as analgesics, Antipyretics and coronary vasodilators. The release the drug once it is ingested orally. There is no delay in onset of action (Nyol and Gupta, 2013).

Nootropics

Class of drugs aimed directly at promoting the efficiency of the essential brain integrative activity mechanisms. The most important features of nootropic are facilitation of learning, memory Consolidation. Their ability to increase or enhance resistance to learning impairments and several experimental types of brain hypoxia, and cerebral drug intoxications. They are also devoid of the usual psychotropic effects in that they cause neither stimulation nor sedation and in general have no locomotor effect.

MATERIALS AND METHODS

Citicoline

Piracetam

Maize starch

Table 1: Brain supplements and Cognition enhancer

Brain supplements		
S. No	Drugs	Function
1.	Ginkgo (Ginkgo biloba')	Improves blood flow to the brain, anti-inflammatory and has potent antioxidants protect brain cells from free radical damage.
2.	Bacopa (Bacopa monnieri)	Improves memory, treat epilepsy and reduce anxiety
3.	American Ginseng (Panax quinquefolius)	Comparing with Panax ginseng , American ginseng is considered superior excels as a cognitive enhancer. Quickly shows result for improve short-term memory.
	Cognition enhancers	
S. No	**Drugs**	**Functions and uses**
1.	Amino Acid cognition enhancers	
	a. Tyrosine	Acts as both a stress hormone and neurotransmitter.
	b. Tryptophan	Tryptophan is the precursor of serotonin (the "happiness brain chemical") and the sleep hormone melatonin.
	c. Taurine	Taurine behaves much like the calming neurotransmitter GABA (gamma-aminobutyric acid) and, once in the brain, activates GABA receptors.
	d. L-Theanine	L-theanine is one of the most unique natural brain enhancers around. It's found mainly in tea and increases levels of the neurotransmitter's serotonin, dopamine, and GABA.
2.	Nootropics	
	a. Adderall and Ritalin	Adderall and Ritalin are prescription stimulants for treating ADHD that increasing focus and energy.
	b. Modafinil	This is only medically approved uses are for narcolepsy, shift work sleep disorder, and obstructive sleep apnea.
	c. Racetams	Racetam class of drugs show their effect on GABA. Its mechanism is not fully known. Theories include that they work by enhancing brain cell membrane fluidity improving the function of the neurotransmitter acetylcholine.
	d. Choline Based Nootropic Drugs	Choline is an essential nutrient for brain development, healthy brain cells, and neurotransmitter formation. It is a precursor of Ach.

Piracetam

croscarmellose Sodium

Sodium Starch Glycolate

Microcrystalline Cellulose PH 101

Magnesium state

Colloidal Silicon Dioxide

PVP K 30

Preformulation Studies

The physicochemical properties of the drugs play an important role in the design of appropriate drug delivery systems. It would be possible to vary the formulation parameters according to the pre-formulation characteristics of the drug and other formulation excipients. An insight into such parameters allows the formulator to select various additives and formulation conditions for the successful, and effective drug delivery to the biological system. Critical information provided during the pre-formulation can enhance the rapid and successful introduction of new therapeutic entities for humans. Hence, pre-formulation studies are essential for proper designing of drug delivery systems.

Micromeritics of the drug

This provides us with a knowledge about the physical and chemical properties of the API like its particle size, low property and compressibility. It helps in determining the bioavailability, stability and consistency of the material. The following are various tests performed to determine the characteristics of the drug. The results of which are given in Table 8, (IP, 2018).

Bulk density, Tap density, Compressibility index

It is important to improve the effectiveness of the roller compaction process and granules produced for milling. A tool to determine the void volume and predicting material segregation. Bulk volume was measured by taking weighed quantity powder mix in measuring cylinder, Bulk volume is noted (Vb), and weight of the blend (M) was determined. The measuring cylinder containing known mass of powder blend was tapped for a fixed time and the tapped volume (Vt) occupied in the cylinder and the weight of the blend (M) was measured. From that bulk density, tapped density, Hausner's bulk ratio and Carr's index were calculated as follows,

$$Bulk\ Density(BD) = \left(\frac{M}{V_b}\right) \times 100$$

$$Tapped\ Density(T8) = \left(\frac{M}{V_t}\right) \times 100$$

$$Compressibility\ Index\ or\ Carr's\ Index\ = \left(\frac{TD-BD}{TD}\right) \times 100$$

$$Hausner's\ Ratio\ = \frac{TD}{BD}$$

M- Mass of the blend taken

Vb- Bulk Volume

Vt- Tapped Volume

Angle of repose

It determines how efficiently the blend would move from the Hopper to the die cavity in compression process. This ultimately leads to a prediction whether the blend would sit to the walls of the Hopper after processing. It is defined as the maximum angle that can be obtained between the free standing of a powder heap and the horizontal plane which is given by the equation.

$$\theta\ = \tan^{-1}\left(\frac{h}{r}\right)$$

where, θ - Angle of repose

h- Height of the powder heap from the horizontal base

r-Radius of the base of the heap

Sieve analysis

It determines the particle size of the blend and ensures that a good ratio is established between the granules and the fines of the blend. Sieves are arranged according to the increasing mesh no. from 20,40,60,80 and 100. A measured quantity of blend is introduced into the top most sieve i.e. sieve no. 20. The sifter is allowed to be shaken on its own for 5 minutes at 20 power. The segregated granules and fines are weighed and calculated as,

%Blend retained on sieve =

$$\left(\frac{Weight\ of\ blend\ retaines\ on\ that\ sieve}{Total\ weight\ of\ blend}\right) \times 100$$

Solubility of the drug

Solubility is the amount of solvent needed to dissolve 1 part of solute. The solubility of and citicoline and Piracetam was tested in various buffer solutions and organic solvents according to British Pharmacopoeia(BP) and According to BCS Class. According to British Pharmacopoeia the amount of solute/drug needed to dissolve 100 mg of the solute determines the solubility of the solute in that particular solvent. Whereas, for the determination of BCS class, we consider the highest dose of the drug to be solubilised in

250 ml of solvent when taken in a volumetric flask at room temperature. The results of solubility according to BP and BCS class (BP, 2018). The results of solubility according to BP was performed and BCS is given inTable 9.

The physical and chemical interactions between drugs, and excipients can affect the chemical nature, the stability, bioavailability of the drugs, therapeutic efficacy and safety. This study was carried out by triturating every ingredient mix and placing the mixture in equal proportion in 3 vials which are labelled and charged to various stability conditions for 15 days.

The compatibility studies between Drug and excipients were examined for Physical, and chemical parameters, Visual observation was carried out for determining any physical changes. Chemical degradation was determined by calculating the amount of relative substances (impurities) in the combinations. The result for physical and chemical degradation is given in Table 10.

Linearity of the drugs using UV spectrophotometry

Preparation of Stock Solution

31.2mg of Citicoline was weighed and dissolved in 100ml demineralised water to produce the stock solution A. 31.2mg of Piracetam was weighed and dissolved in 100ml demineralised water to produce the slock solution B

Preparation of sample solution of various concentrations 2ml, 3ml, 4ml, 5ml, and 6ml solution was withdrawn from Stock Solution A and diluted with distilled water to 50ml in a volumetric flask of 50ml to produce concentrations of 12.48ppm, 18.72ppm, 24.96ppm, 31.2ppm and 37.44ppm.

Same was performed using stock solution B to produce various concentrations like 12.48ppm, 18.72ppm, 24.90ppm, 31.2ppm and 37.44ppm. The results are given in Tables 11 and 12 and Figures 2 and 3.

Formulation of immediate release dosage

The formulation is performed to find the best trial batch to optimise it. All trial batches are performed according to the results obtained by design of experiments, this would allow us to correlate the theoretical value with the one practically obtained.

Design of Experiment

Design of Experiment (DoE) was done using Design Expert Software; DoE Was performed using Box Benken method and trial batches were achieved. The responses for disintegration time and hardness was obtained.

Method of preparation

The solid oral dosage form was prepared using the following procedure Drug and Excipients processed using wet granulation technique. In this, the drug, superdisintegrants and diluent were added into the Rapid Mixer Granulator. Through the binder addition Window, the binding solution was added upon continuous mixing. Later the damp mass is sieved from sieve no. 20 to obtain uniform sized granules. Drying of granules was carried out using Fluidised Bed Dryer to achieve desired sized granules with acceptable flow properties. % Moisture content in the granules was a mean of end point determination. Superdisintegrants was added extra granularly for improved disintegration effect. Colloidal silicone dioxide and superdisintegrants was added into octagonal blender to carry out the pre lubrication stage of processing (Mohanachandran *et al.*, 2011). Lubrication was done using Magnesium Stearate, where it was added to the pre lubricated blend in the octagonal blender. Lubrication gave a desired flow to the granules (Rawat *et al.*, 2014). The blend was compressed into tablet by the tablet compression machine. Various IPQC tests like hardness, thickness, disintegration time were measured to obtain a desired tablet property. The tablets were coated in conventional coating pan using ready mix coating material and a selected colour to obtain a desired formulation appearance.

Trial batch for binder/binding agent was performed and mentioned in Table 2.

Various Trial Batches

The above batch was processed and compressed into tablets of total weight. Upon testing the tablet showed out hardness on much higher side. Thus, a new trial batch (F2) was taken where only water was used as the sole binding agent and Povidone is eliminated. Trial batch studies for the study of diluent is given in theTables 3 and 4.

Use of diluent in both the batches enhanced the total tablet weight and upon testing the tablet showed out of acceptance limit range outcome for hardness and disintegration time (DT). Thus, new batches were carried out to study the effect of superdisintegrant on the DT and hardness and by removing diluent to reduce the tablet weight.

Trial batch for super disintegrants was performed for all batch and mentioned in Table 5.

Optimization of working formula

Optimisation of the trial batch was done according to the results obtained for the evaluation parameter mentioned in the results. The formula for optimised batch for uncoated tablets and coated tablets

Table 2: Trial batch (F1) For the study of binder/binding agent

S.No	Materials used	Quality (mg)	Category
Dry mix			
1	Citicoline	522.5	API
2	Piracetam	800	API
3	Microcrystalline cellulose	52.5	Diluent
Binder			
4	Povidone (PVP K 30)	30	Binder
5	Distilled water	q. s	Solvent to make a binding solution
Prelubrication			
6	Croscarmellose Sodium	70	Superdisintegrant
7	Colloidal Silicon Dioxide	10	Prelubricating agent
Lubrication			
8	Magnesium Stearate	15	Lubricating Agent

Table 3: Trial batch (F2) using Microcrystalline cellulose

S.No	Material Used	Quantity (mg)
	Dry mix	
1	Citicoline	522.5
2	Piracetam	800
3	Microcrystalline cellulose	82.5
	Binder	
4	Water	q. s
	Pre lubrication	
5	Croscarmellose Sodium	70
6	Colloidal Silicon Dioxide	10
	Lubrication	
7	Magnesium Stearate	15

Table 4: Trial Batch (F3) using Maize starch

S.No	Material Used	Quantity (mg)
	Dry mix	
1	Citicoline	522.5
2	Piracetam	800
3	Maize starch	82.5
	Binder	
4	Water	q. s
	Prelubrication	
5	Croscarmellose Sodium	70
6	Colloidal Silicon Dioxide	10
	Lubrication	
7	Magnesium Stearate	15

Table 5: Trial batches for the study of super disintegrants

S.No	Materials	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)
			Dry mix				
1	Citicoline	522.5	522.5	522.5	522.5	522.5	522.5
2	Piracetam	800	800	800	800	800	800
3	Croscarmellose	0	35	0	35	35	0
4	Sodium	0	0	0	0	0	0
5	Crospovidone Sodium Starch Glycolate	0	0	35	0	0	70
			Binder				
6	Water	q. s	q. s	q. s	q. s	q. s	q. s
			PreLubrication				
7	Croscarmellose	0	35	0	0	0	35
8	Sodium	35	0	0	0	70	70
9	Crospovidone	0	0	35	35	0	0
10	Sodium Starch Glycolate Colloidal Silicon Dioxide	12.5	12.5	12.5	12.5	12.5	12.5
			Lubrication				
11	Magnesium stearate	15	15	15	15	15	15

Table 6: working formula of optimised batch for uncoated tablets

S. No	Materials	Quantity (mg)
	Dry Mix	
1	Citicoline	522.5
2	Piracetam	800
3	Croscarmellose Sodium	35
	Prelubrication	
4	Colloidal silicon dioxide	35
5	Croscarmellose sodium	12.5
	Lubrication	
6	Magnesium stearate	15

Table 7: Working formula for coating of tablets of the optimised batch

S.No	Materials	Quantity (%)
1	Ready-mix coating materials(HPMC,Polypropylene glycol, polyethylene glycol, SLS,Titanium dioxide)	10
2	Colour Sunset Yellow Supra	0.2
3	Purified Water	89.80

is given in Tables 6 and 7.

Evaluation parameters

The results of all the evaluation test is obtained

Weight variation

This test was performed according to IP 2018. The process suggested that, selected twenty tablets randomly and weight each tablet on an electric weighing balance. Average the total weigh of the tablets.

Hardness

The hardness of five individual tablet was tested using hardness test apparatus. Tablet was kept according to the longitudinal length and pressure was applied until a fracture is created. The result was noted in kilo poise (kp)

Thickness

The thickness of the tablet was measured using Vernier caliper. The result was measured in millimetre (mm).

Disintegration time

The test was performed according to IP. Randomly selected 6 tablets were added in the tubes of disintegration apparatus which is initially dipped in disintegration basket containing water as disintegrating solvent that has attained a temperature of 37°C±2°C. This basket was placed in the specialised water bath. The test was performed as the tubes moved vertical at 30±2 drops/minute and the time of disintegration of that tablet was noted in minutes.

Friability

It is performed in Roche Friabilator. As the tablet weights more than 650mg, the total tablet taken, weighed equivalent to or greater than 6.5gm. The equipment was set at 25rpm for 4 mins. Initial weight of the tablets was obtained. After the test was performed, the tablets were weighed again to check the reduction in weight. This test is performed to know the strength of the tablet when stress or shear is utilised. % friability is calculated a below and should not be more than 1 %.

%Friability =

$$\left[\frac{(Initial\ weight\ of\ tablet)-(Final\ weight\ of\ Tablet)}{Initial\ weight\ of\ tablet}\right] \times 100$$

Stability studies

Formulation was packed using ALU-ALU packing material. The integrity of the pack was tested using leak test where the pressure was set at 600 mm/Hg for 5 mins. The pack passed the leak test and hence it was chosen as packing material.

Evaluation was carried out at 40°C /75% RH as per ICH guidelines. Apart from initial analysis, the samples were evaluated for physio-chemical properties during stability studies at the mentioned stability conditions and intervals in the Table 11.The result for the stability lots is obtained in Table 16.

RESULTS AND DISCUSSION

The Micromeritics of Citicoline and Piracetam was performed and the results obtained are as below

Solubility Profile

Compatibility studies

Linearity of the drugs using UV spectrophotometry

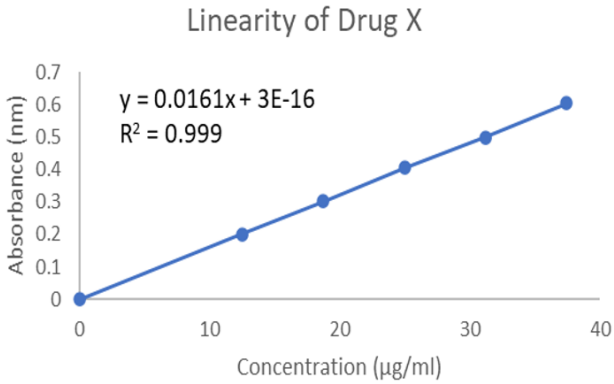

Figure 2: Regression equation and linearity plot of Citicoline that proves its analytical linearity

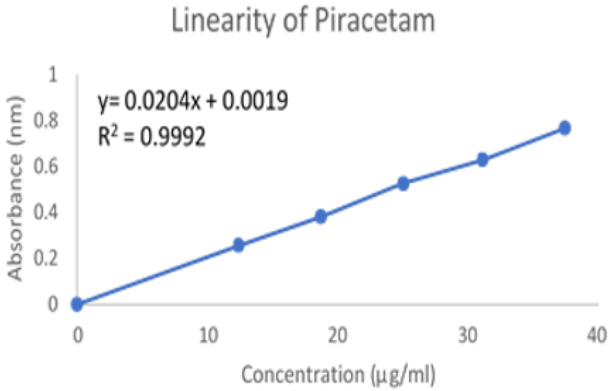

Figure 3: Regression equation and linearity plot of Piracetam that proves its analytical linearity

Micromeritics of all trial batches

Post compression evaluation of above trial batches

Stability Lots of Optimised Batch, its Evaluation and Process Parameters

F4 was considered as the optimised batch for stability studied. This batch was processed for stability trials (ST) as ST 1, ST 2 and ST 3. Tablets were

Table 8: Micromeritics of Drugs

Tests	Citicoline	Piracetam
Bulk Density	0.35gm/ml	0.74 gm/ml
Tapped Density	0,55 gm/ml	0.86 gm/ml
Carr's Index	36.36%	14.73%
Hausner's Ratio	1.57	1.17

Table 9: Determination of BCS classification of Citicoline and Piracetam

Solvents used	Volume used to dissolve highest dose i.e. 500mg Citicoline	Volume used to dissolve highest dose i.e. 800 mg Piracetam	Observation	Result
Demineralised water	250 ml	250 ml	Highly soluble	Hence the solubility of these drugs in various solvents determines that they fall in the BCS Class I
0.1N HCL	250 ml	250 ml	Highly soluble	
4.5 pH Acetate buffer	250 ml	250 ml	Highly soluble	
6.8 pH Phosphate buffer	250 ml	250 ml	Highly soluble	
7.5 pH Phosphate buffer	250 ml	250 ml	Highly soluble	

Table 10: Physical chemical parameters observed for the drugexcipient compatibility studies

Ingredient Mix	Ratio	Observation	60 °C		40°C 75% RH		RT	
			HUI	TUI	HUI	TUI	HUI	TUI
Citicoline + Piracetam	1:1	White to off White colour powder	BDL	BDL	BDL	BDL	BDL	BDL
Citicoline + Piracetam Maize starch	1:1:1	White to off White colour powder	BDL	BDL	BDL	BDL	BDL	BDL
Citicoline + Piracetam croscarmellose Sodium	1:1:1	White to off White colour powder	0.02	0.02	0.01	0.01	0.02	003
Citicoline+Piracetam+ Sodium Starch Glycolate	1:1:1	White to off White colour powder	0.05	0.05	0.05	0.05	0.02	0.04
Citicoline+Piracetam+ Microcrystalline Cellulose PH 101	1:1:1	White to off White colour powder	0.04	0.02	0.03	0.03	0.04	0.04
Citicoline+Piracetam+ Magnesium sterate	1:1:1	White to off White colour powder	0.04	0.01	0.02	0.02	0.02	0.02
Citicoline+Piracetam+ Colloidal Silicon Dioxide	1:1:1	White to off White colour powder	0.06	0.03	0.08	0.13	0.02	0.03
Citicoline+ Piracetam +PVP K 30	1:1:1	White to off White colour powder	0.02	0.01	0.03	0.04	0.01	0.01

Table 11: The linearity and regression equation of a Citicoline was obtained at λ max 271 nm

S.No	Concentration (μg/ml)	Absorbance at λmax 271 nm
1	0	0
2	12.48	0.2
3	18.72	0.302
4	24.96	0.405
5	31.2	0.499
6	37.44	0.604

Table 12: The linearity and regression equation an of Piracetam was obtained at λ max 210 nm

S.No	Concentration (μg/ml)	Absorbance at λmax 210nm
1	0	0
2	12.48	0.257
3	18.72	0.382
4	24.96	0.526
5	31.2	0.63
6	37.44	0.767

Table 13: Bulkdensity (BD), Tapped density (TD) and Carr's Index (CI) is observed for all the trial formulations of the lubricated blend

S.No	Evaluation Parameter	F1	F2	F3	F4	F5	F6	F7	F8
1	BD (gm/cc)	0.585	0.595	0.572	0.524	0.543	0.520	0.525	0.525
2	TD (gm/cc)	0.675	0.643	0.621	0.629	0.691	0.638	0.651	0.614
3	CI (%)	13.43	7.620	7.890	16.69	16.93	18.49	19.35	14.49

Table 14: Total weight, thickness, hardness, disintegration time and friability results of all the formulation batches are obtained

S.NO	Evaluation Parameter	F1	F2	F3	F4	F5	F6	F7	F8
1	Total weight(mg)	1500	1500	1385	1420	1420	1420	1455	1525
2	Thickness (mm)	7.90	7.90	7.82	7.85	7.85	7.85	7.87	7.88
3	Hardness (kp)	39	30.5	15	24	29	26	24.5	35
4	Disintegration	22	17	2	10	16	16	15	24
5	time(mins) Friability (%)	0.73	0.69	0.55	0.49	0.65	0.78	0.65	0.52

tested for post compression parameters and coating parameters after charged to temperature condition of 40°C/75%RH.

Relative substances study determined the percentage of unknown and known impurities in the formulation which is recorded as highest unknown impurities and total unknown impurities are mentioned in Table 17.

Micromeritics of Drugs

The flow property and compressibility of the drug is studied by examination its bulk density, tapped density, Carr's index and Hauser's ratio. Thus, results obtained in table 8, 13 and 15 states that Citicoline and Piracetam have good compressibility index of 36.36% and 14.73%. This proves that they are good combinations and retain a good flow property which makes them non adhering substances.

Solublity Profile

According to British pharmacopoeia method testing and for the determination of BCS class.

The drugs when tested for solubility with the procedure given in the British pharmacopoeia, stated

Table 15: Evaluation parameters of all the stability lots of batch size 2000 tablets

S. No	Parameters	ST 1	ST 2	ST 31
1	Micromeritics of Lubricated Blend			
a	Bulk Density (gm/cc)	0.579	0.636	0.651
c	Tapped density (gm/cc)	0.689	0.762	0.778
	Carr's Index (%)	15.87	16.45	16.25
d	Sieve Analysis			
	Below 40%	17.41	14.0	15.0
	Above 60%	51.89	52.82	54.86
2	Compression Parameter			
a	Description	White to off colour oval shaped, uncoated tablets, plain on both sides.		
b	Punch Dimension weight(mg)			
c	(Average=1420 mg)	22 × 10 mm oval shaped, plain on both sides.		
d	(SD=Average ±2%)	1419.0	1422.0	1418.0
e	Weight variation (mg)	1422 ±2%	1427 ±2%	1423 ±2%
f	Thickness (mm)	7.58-7.64	7.57-7.63	7.55-7.62
g	Hardness (kp)	19.00-27.00	20.0-23.0	24.0-28.0
h	(Acceptance =24-27 kp)	9 minutes 50 seconds	9 minutes 0.33	9 minutes 30 seconds
	Disintegration time (Not more than 15 minutes)	0.33		0.35
	Friability (%) at 100 rotations			
3	Coating Parameters			
a	Description	Orange coloured, oval shaped, film coated tablets, plain on both sides.		
b	Total weight (mg)			
c	Thickness (mm)	1455.0	1458.3	1456.2
d	Disintegration Time (minutes)	7.59-7.78	7.62-7.72	7.65-7.80
e	(Acceptance: Not More Than 30 minutes)	24.0-26.0	22.0-27.0	23.0-28.0
		10 minutes	9 minutes 37 seconds	9 minutes 45 seconds

Table 16: Assay and dissolution of the optimised batch and after 3 months it was kept for stability

Assay				
S.NO	Specifications	Assay of Citicoline	Assay of Piracetam	Acceptance
1	Optimised batch before charged to stability	97.12	98.33	90-110%
2	3 months after charged to stability			
A	At 30°C/65% RH	102.15	96.18	90-110%
B	At 40°C/75% RH	98.01	96.98	90-110%
		Dissolution		
SL NO.	Specifications	dissolution of Citicoline	dissolution of Piracetam	
1	Optimised batch before charged to stability			
A	At 45 minutes	94.57-97.03	96.22-97.83	
B	At 60 minutes	94.29-98.11	95.58-99.20	
2	3 months after charged to stability			
A	At 30°C/65% RH	102.28-105.80	98.42-101.09	
B	At 40°C/75% RH	102.58-104.27	99.57-100.11	

Table 17: Values of total unknown impurities and highest unknown impurities

Relative Substances			
S. No	Specification	Highest unknown impurities	Total unknown impurities
1	Optimised batch before charged to stability	0.027	0.033
2	3 months after charged to stability		
A	At 30°C/65 %RH	0.103	0.181
B	At 40°C/75%RH	0.106	0.191

that Citicoline and Piracetam are soluble in demineralised water, 0.1 N HCL, 4.5 pH Phosphate buffer and pH 7.5 Phosphate buffer. Piracetam is also freely soluble in Ethanol. Citicoline and Piracetam are said to be BCS class I drug, as they were soluble in all the buffer solution mentioned of varied pHrange (as they represent the various pH environment in the human alimentary route starting from mouth saliva to colon.)

Thus, the solubility of the drug, helps us to determine the solvent which can be used for analytical testing and other testing parameters to reduce the burden on the instruments and saves time.

Drug Excipient compatibility studies

Drug excipient compatibility studies resulted in insignificant colour change upon visual examination Table 10. Thus, there was no occurrence of any prominent physical changes. The value of all the impurity testing were within the acceptable limits as per each monography in IP. thus, no chemical degradation was observed over period of 15 days when charged to stability condition of 40°c/75% RH,60°C and RT. This test allowed us to finalise the excipients for further processing. The excipients selected are, crospovidone, sodium starch glycolate, colloidal silicon dioxide and magnesium stearate.

Linearity plot of Citicoline and Piracetam

Various concentration Tables 11 and 12 of Citicoline and Piracetam were used to determine the linearity of drug .Citicoline was tested at λ max of271 nm and Piracetam at 210 nm .The linearity graph obtained Figures 2 and 3stated that the R^2 value of Citicoline and Piracetam is 0.9999 and 0.9992 respectively (acceptance criteria R^2equivalent to 1).Thus, it is clear that the two drugs Citicoline and Piracetam are linear i.e. as there is an increase in concentration, the absorbance also increases linearity.

Design of experiment

Design of experiment (DoE) was performed. An experimental design was studied for the usage of superdisintegrants in various combination to optimise the best fit superdisintegeant to be used. Various tables and figures are shown in the previous section of results.

The best formulation is selected and the fourth formulation which contains only croscarmellose sodium in quantity of 70mg as compared to other super disintegration or when used in combination of other superdisintegration. The DT obtained is 10 minutes 16 sec and hardness are 24 kp of this formulation. Crospovidone and sodium starch glycolate is used in quantity of 0.5mg each. the desirability was 0.967 of the fourth response as compared 29 other responses. Thus, this design of formulation is a reliable with appreciable results.

Micromeritic study of granules

Bulk density, tapped density and carr's index was studied for the granules. The results obtained are mentioned in Tables 8, 13 and 15. The results stated that the granules have good compressibility and flow property. the compressibility and flow property. The compressibility index ranges from 4.885 to 19.35, bulk density ranges from 0.512gm/ml to 0.623gm/ml and the tapped density ranges from 0.614gm/ml to 0.695gm/ml.

Post compression evaluation of all trial batches

The optimised formulation was evaluated for various parameters of disintegration time, tablet weight, hardness, friability and thickness the results are shown in the Table 14 were interpreted as below

F1 formulation containing povidone (PVP K-30) as binder and microcrystalline cellulose as diluent, showed the hardness as 39 kp and disintegration time (DT) as 22 minutes. The tablet weight was found to be 1500 mg. hardness was said to be on a higher side and beyond the acceptance range (24-27kp), leading to hampering of the disintegration time. Thus, povidone (PVP K -30) was eliminated in the further formulations and demineralised water was used as the sole disintegration agent.

Formulation F2 contains maize starch as diluents. The tablets showed little change in hardness as com-

pared to F1. The DT obtained was above the acceptance limit (acceptance: not more than 15 mins).To reduce the tablet weight and to improve the hardness and DT we considered the assay of and citicoline and Piracetam as 100%, which lead to the removal of the diluents.

Formulation F3 to F8 were carried out using various combinations of super dis-integrategrants like croscarmellose sodium and sodium starch glycolate. Based on the box benken design obtained earlier, these formulations showed improved results for hardness disintegration time and reduction in tablet weight was achieved. Of these formulations, F4 was considered to have the most appreciable results of hardness as 24 kp (acceptance limit: 24-27), disintegration time as 10 minutes (NMT 15 minutes) and total tablet weight achieved was found to be 1420 mg.

Thus, F4 formulation containing croscarmelloses sodium in 35 mg+ 35 mg quantity (total 70 mg) proved to have the best results in design of experiments and when performed practically. It was optimised for further stability trials mentioned in Table 16.

Evaluation of stability lost and optimisation of process parameters

Formulation F4 was said to be optimised formulation. this formulation was optimised for larger batch size of 2000 tablets. These batches were then charged for stability. These batches were evaluated for micromeritics of granules, compression parameters and coating parameters. The results are observed in Table 15. Optimisation of these process parameters helped for the development of tablet batches of larger batch sizes.

Summary

The objective for development of this formulation was to develop an immediate release formulation with optimum disintegration time and hardness that is able to release the drug immediately upon administration in the stomach at acidic pH.

Compatibility study done at accelerated stability results that the and citicoline and Piracetam are stable and compatible with all excipients. Povidone acted as a binder that enhanced the hardness and disintegration time to such an extent that it was out of acceptance limit. Considering 100 percent assay of the drugs, microcrystalline cellulose and maize starch was eliminated.

Study was carried out using various combinations of super disintegrants like Croscarmellose sodium, crospovidone and sodium starch glycolate. Box Benken design resulted in 17 different trials containing combination of the above super disintegrants based on the hardness and disintegration time these trials were evaluated.

Batch containing Croscarmellose sodium in the concentration of 35 mg intragranular and 35 mg extra granularly, should the best possible results. The total tablet weight also reduced from 1500 mg to 1420 mg. this batch was later optimised and changed to stability at 40°C/75%RH, 30°C/60%RH and 25°/60%RH.

Evaluation test like hardness, thickness, disintegration time, weight variation and friability carried out for the stability batches showed appreciable results with acceptable range.

Analytical chromatograms of assay and dissolution of optimised batch before and after 3 months stability showed that the drug content ranges from 101-105% and 98-102% of and citicoline and Piracetam respectively. The drug release obtained at 60 minutes time interval was equivalent to 100% for both the drugs.

Relative substance testing was done for highest and total unknown Impurities. It was found to be within the acceptance limit.

CONCLUSIONS

Nootropic drugs when used in combination show a synergistic effect as the work by treating neuro degeneration using multiple mechanisms. The formulation used two nootropic drugs as Citicoline and Piracetam in a fixed dose combination. As the dose is fixed, the dosing frequency changes depending upon the severity of the condition. Croscarmellosesodium when used intragranular and extragranulary shows improved effect of disintegration as compared to crospovidone and sodium starch glycolate. Since, Croscarmellose sodium, works on the principle of wicking and swelling when used in tablet formulations.

Croscarmellose sodium when used in formulation F4 formulation showed a hardness as 24 kp when tested on hardness testing apparatus, disintegration time as 10 mins when tested on disintegration apparatus and total tablet weight as 1429 mg. F4 formulation was the best optimised formulation with a good reduction in tablet weight and size.Relative substance, dissolution and assay were the analytical parameters tested for these Formulations. Thus, a formulation with maximum possible reduction in tablet weight to achieve a swallowable shape of tablet and best possible disintegration time was developed to release the nootropic drugs for quicker absorption into the systemic circulation and

show an immediate action upon administration. The tablet shows improvement by reduction drug excipient interaction and reduces the burden of processing and storage.

Conflict of Interest

None.

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