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DEVELOPMENT AND OPTIMIZATION OF NUTRACEUTICAL FORMULATION CONTAINING CITICOLINE AND PIRACETAM

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ABSTRACT

Development, Optimization and Evaluation of Citicoline and Piracetam from their Formulation. The objective of present investigations were to optimize different concentration of HPMC as coating for taste masking. Citicoline, Piracetam and HPMC, distilled water and methanol. Formulation was prepared by wet granulation technique and evaluated for drug content, infrared spectroscopy, scanning electron microscopy and in vitro dissolution study. The purpose of this study was to develop and optimize taste masking granule formulation for Piracetam using HPMC as a coating material. Initially trials were done to optimize the concentration of HPMC on to granules or its uniformity of size and Assay, varying the concentration of HPMC as coating material. The cumulative drug release percentages at 15, 30, and 35 min were the target responses and were restricted to 50%, 68%, and 98% respectively. For formulation, the results suggests that considerable taste masking of Piracetam was carried out by using 200 mg of HPMC and weight reduction was achieved as compared to marketed formulation. Formulation of Citicoline and Piracetam were successfully developed in this work.

KEYWORDS: Citicoline, Piracetam, Taste Masking, Wet Granulation.

INTRODUCTION

In the present scenario, a variety of pharmaceutical research has been come in to focus to develop new dosage forms for effective therapy with increased safety. Considering value of life, most of these innovators have been focused on patient compliance.[1]

Palatableness of oral dosage form admits a key factor for achieving compliance especially in pediatric, geriatric, bedridden, nauseous or non-compliant patients.[2] Who find difficulty in swallowing or chewing solid dosage forms due to diseased state or is willingly reject to take solid dosage forms due to concern of choking. Hence, a taste masking granule containing a tablet seems a suitable alternative for them.[3] More than 50% of pharmaceutical products are orally administered for several reasons and bitter and unpleasant taste of drug is one of the important formulation problems that is encountered with such oral products.[4]

In the development of orally dosage forms and product development taste is most important factor.[5] Taste masking of oral pharmaceuticals play a significant role to improve patient compliance therefore taste masking technologies offer wide scope for innovation and invention in the development of patient friendly in fixed dose administration.

Negligible perception of unpleasant taste of the drug two major strategies are commonly utilized, are reduction of drug solubility in saliva where balance between reduced solubility and bioavailability must be achieved, and secondly is to alter the ability of the drug to interact with taste receptor.[6]

Taste smell, texture and after taste are important factors in the development of dosage form, these are important factor in product preference. Good flavor and texture are significantly affect sell of product. Undesirable taste is one of the important formulation problem encountered with most the drugs, the methods most commonly involved for achieving taste masking include various chemical and physical method that prevent the drug substance from interaction with taste buds. The simplest method involves use of flavor enhancer. Where these methods fail more complex methodologies are adopted.[7,8]

Citicoline is an intermediate in the biosynthesis and generation of CDP-choline it blood-brain barrier and reaches the central nervous and cognitive enhancing, neuroprotective. Citicoline also act as a precursor for synthesis of phospholipids are essential constitutients of cell membrane i.e. phosphotidylcholine, phosphotidylserine, phosphotidylethenolamine.[9,10]

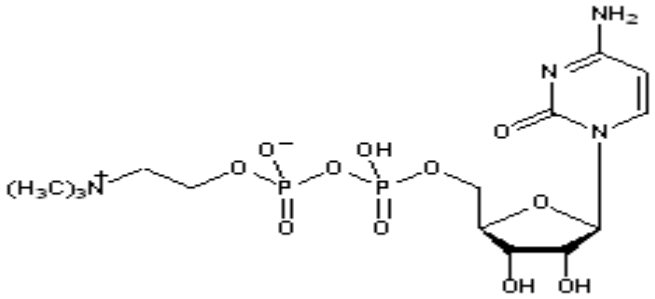


Fig. 1: Chemical structure of Citicoline.

Piracetam is a derivative of GABA (gamma amino butyric acid) refred as a 2- oxopyrrolidine acetamide. Piracetam increase the flow between the right and left hemisphere of brain, this can be useful for the treatment of stroke, vertigo, dyslexia, alcoholism. Piracetam stimulates the CNS with physical manifestation of similar to acetylcholine esterase inhibitors which deactivates the neurotransmitter. Piracetam may exert its global effect on brain.[11-12]

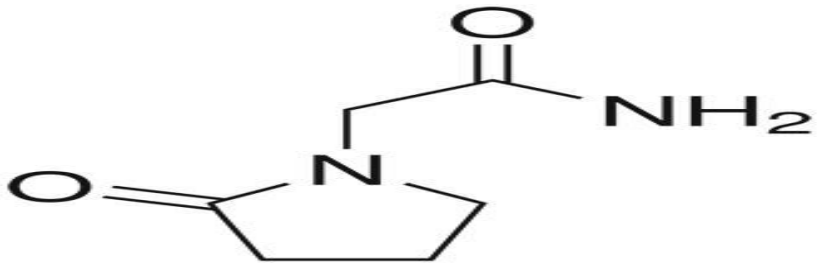


Fig. 2: Chemical structure of Piracetam.

MATERIAL AND METHOD

Instrument: A Shimadzu model 1700 (Japan) double beam UV/Visible spectrophotometer with spectral Width of 2 nm, wavelength accuracy of 0.5 nm and a pair of 10 mm matched quartz cell was used to measure absorbance of all the solutions.

Reagents and Chemicals: Citicoline and Piracetam pure drug were obtained as gift samples from the SRS pharmaceuticals Pvt. Ltd., Mumbai, India. The marked tablet formulation strocit plus manufactured by Intas Pharmaceuticals, Sikkim, were procured from local market. All other reagents were of analytical grade for Spectrophotometric method.

Formulation Trials: Initial formulation trials were done on optimization of taste masking granules (F1-F4) and then trials are done on the coating solution composition for extending the drug release.

***Precompression parameters*[13]**

Following precompression parameters such as bulk density, tapped density**,** hausner's Ratio Compressibility index and flow properties by angle of repose were studied by using standard procedure.

Compatibility Studies

FTIR technique has been used to study the physical and chemical interaction between drug and excipient.

DSC Study

Drug excipient compatibility study were carried out by Shimadzu DSC-60 in dry N_2 atmosphere (flow rate 50 ml/min) and temperature scanning rate was 10^0C/min up to 300^0C. About 2 mg of each sample were weighed using closed aluminum pans. The DSC thermogram of drug and intermediate step and final formulation were studies.

X-ray diffraction study

The X-ray diffractometer used for the present study was form Philips analytical. The target material of instrument was copper and nickel was used as the filter and a voltage of 35 kv and current of 30 ma was used the diffraction was done at room temperature of 300^0c.

Preparation of taste masking granule of Piracetam

Taste masking granules of Piracetam for F1-F4 batches were prepared as per batch formula by wet granulation method. Piracetam was accurately weighed and transfer in mortar and pestle. HPMC dissolved in 10 ml of water was added to form a coherent mass then the coherent mass was passed thorough sieve no 20 to form granules. The wet granules were dried at 50^0c for 15 minutes.

Preparation of tablet formulation

Citicoline was mixed with prepared taste masking granules of Piracatam and this mixture was compressed in to tablet using a standard capsule shape machine. The composition of tablet formulation for F1-F4 batches listed in **Table 1.**

***Evaluation of tablet formulation*[14,15]**

Prepared tablet formulations was evaluated for weight variation test, Hardness, Thickness, Friability test and Disintegration time by using standard procedures.

Drug content

Drug content for F1-F4 formulations was determined by developed and validated inhouse absorption ratio method for simultaneous estimation of Citicoline and Piracetam from tablet assay method. Absorption ratio method was used for measuring the absorbance after suitable dilution using a Schimadzu 1700.

***In Vitro Dissolution Studies*[16]**

The release rate of Citicoline and Piracetam from tablets was determined using the USP XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl at 37 + 0.5^0C at 75 rpm a sample (5 ml) of the solution was withdrawn from the dissolution apparatus for 40 minute, and samples were replaced with fresh dissolution medium. The sample diluted to a suitable concentration with distilled water. Absorbance of this solution was measured using Schimadzu UV-Vis double beam spectrophotometer at λ_{max} of 213 nm for Citicoline and 228 nm for Piracetam cumulative percentage drug release was calculated using the equation obtained from absorbance ratio method.

Stability study

The stability studies of optimized batch were carried out at room temperature for a period of three months. The effects of temperature and time on the physical characteristics of the tablet were evaluated. The samples were observed periodically for any change in the disintegration time and Cumulative drug release.

RESULT AND DISCUSSION

Compatibility Studies

FTIR technique has been used to study the physical and chemical interaction between drug and excipient, in the present study it was observed that there was no chemical interaction between Citicoline, Piracetam and the polymer used. From the result of IR it was found that the peaks for functional groups of pure drug i.e.–NH, -CN, were appeared in IR spectrum of formulation also which indicates that drug shows compatibility with each other. Comparative IR spectral data is shown in Fig. 3 and interpretation of IR spectrum for tablet formulation is given in Table 1.

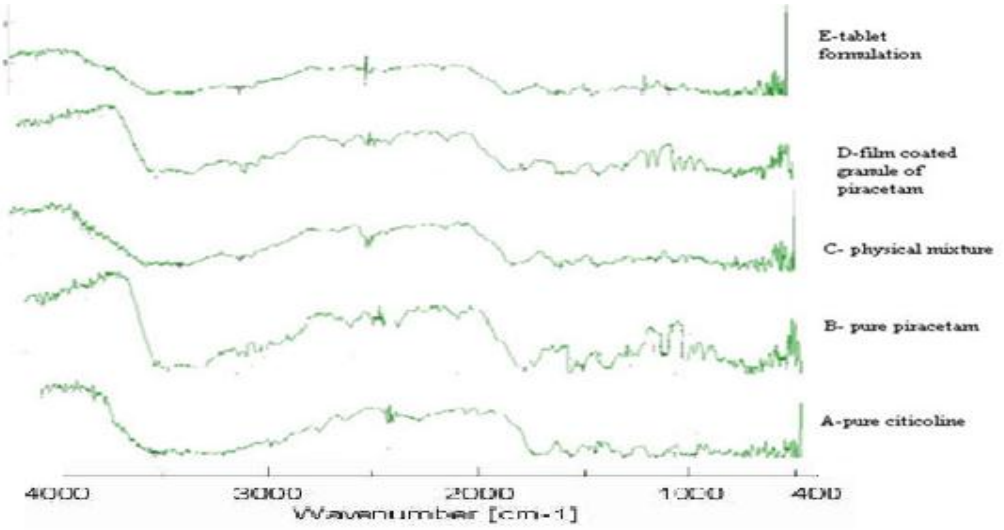


Fig. 3: Comparative IR spectral data A) Pure Citicoline, B) Pure Piracetam, C) Physical Mixture D) film coated granules of Piracetam, E) Tablet formulation.

Table. 1: Interpretation of IR spectrum for tablet formulation.

Sr. No.	Wave No (cm^{-1})	Assigned Functional Group	Sr. No.	Wave No (cm^{-1})	Assigned Functional Group
1	3397.43	–NH	5	2970.1	C-H stretching
2	1395.28	C-N	6	1684.2	C=O saturated acyclic
3	1644.97	C=N	7	1710	C=O saturated acyclic
4	3316.4	Aliphatic primary amine	8	3338	Aliphatic primary amine

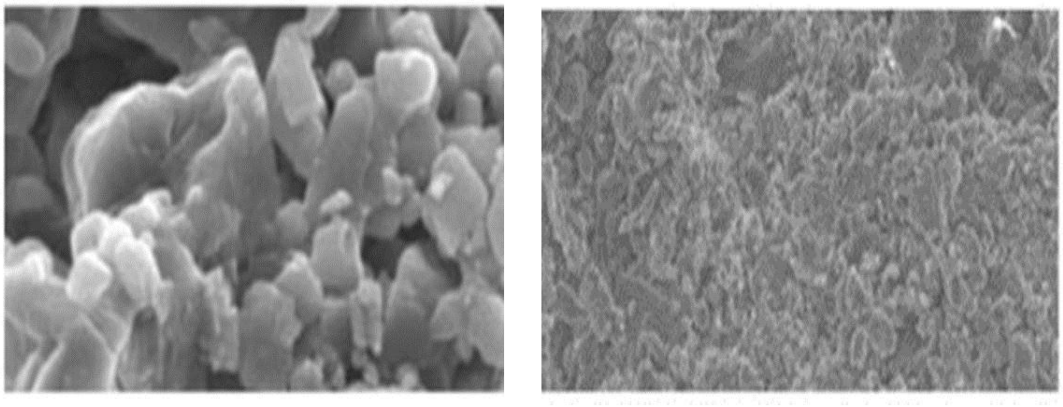
Formula for preparation of tablet formulation

Different polymers were tired after that hydrophilic polymer HPMC was selected. Formula for trial batches F1-F4 of tablet formulation is shown in Table 2.

Table. 2: Tablet formula for different batches.

Sr. No.	Ingredients	F1	F2	F3	F4
		Mg/tab			
1	Citicoline	500	500	500	500
2	Piracetam	800	800	800	800
3	HPMC	50	100	150	200
	Total weight	**1350**	**1400**	**1450**	**1500**

SEM Study: Prepared taste masking granules of Piracetam was evaluated for coating of HPMC by SEM study. It was observed that polymer coating achieved on Piracetam drug particle, which can be clearly indicating in SEM study. SEM for Piracetam pure drug and coated granule of Piracetam is shown in Fig. 4.



A - Piracetam B- Coated granules of Piracetam

Fig. 4: SEM images for A) Piracetam pure drug and B) coated granule of Piracetam.

DSC Study.

From the results of DSC it was found that at the endothermic peak at 109°c and exothermic peak at 273°c in DSC of Citicoline and endothermic at 150^0c in Piracetam coated granules of Piracetam. Same peaks were appeared in thermal analysis of formulation which reveals that there is no interaction with excipient and hence they are compatible with each other. Comparative DSC spectral data is shown in Fig. 5.

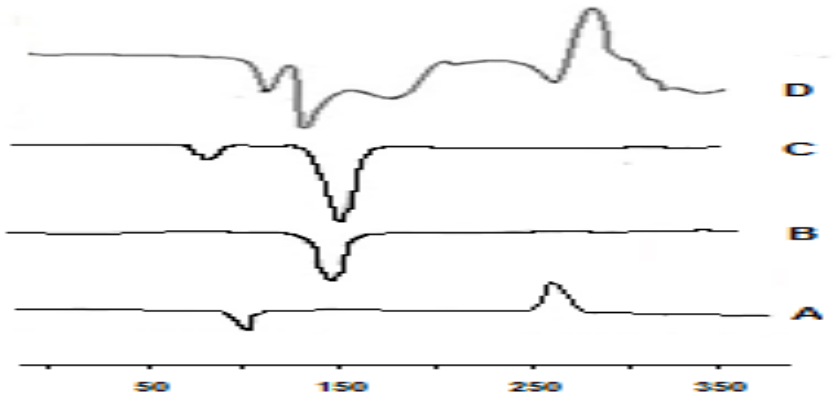


Fig. 5: Comparative DSC spectral data A) Pure Citicoline, B) Pure Piracetam, C) film coated granules of Piracetam, D) Tablet formulation.

Table. 3: Interpretation of DSC spectra.

Parameter	Citicoline	Piracetam	Coated Granule	Tablet Formulation
Peak(^{0} c)	Endothermic peak at 109 Exothermic peak at 273	Endothermic peak at 150	Endothermic peak at 109 for Citicoline,154 for Piracetam	Exothermic peak at 245 and endothermic peak at 98 for coated tablet. Endothermic peak at 120 for Piracetam

X-ray diffraction study: The result of XRD It was found that sharp and intense peak at diffraction angle 22.22, 20.50, 22.366, 21.33.For citicoline, piracetam, coated granule, tablet formulation so it indicates that diffraction peak for the drug and formulation were similar this indicates that no chemical interaction was found in drug and excipient. Comparative XRD spectral data is shown in Fig. 6 and interpretation given in Table 4.

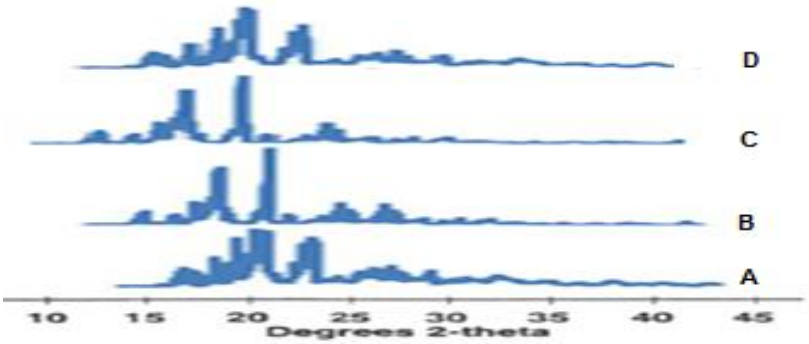


Fig. 6: Comparative XRD spectral data A) Pure Citicoline, B) Pure Piracetam, C) film coated granules of Piracetam, D) Tablet formulation.

Table. 4: Interpretation of XRD spectra.

Sample	2Θ	Intensity(cms)
Citicoline	22.22	260
Piracetam	20.50	258
Coated Granules	22.366	255
Tablet Formulation	21.33	250

Precompression parameters

Precompression composite was evaluated for precompression parameters suitability. From obtained results it is found that precompression composite passes tests for relative parameter. Result for Precompression parameters is given in Table 5.

Table. 5: Precompression parameters.

Batch No.	Angle of Repose(^{0}c)	Compressibility Index (%)	Hausner's Ratio (%)	Bulk density	Tap Density
F1	21.79±0.62	16.30±0.40	1.1±0.08	1.1±0.13	1.2±0.12
F2	20.46±0.32	22.18±0.38	2.1±0.03	2.0±0.26	1.3±0.01
F3	22.31±0.07	14.18±0.07	1.3±0.01	1.9±0.11	1.4±0.03
F4	19.57 ±0.45	16.17±0.71	1.0±0.03	1.2±0.05	1.1±0.01

Evaluation of tablet formulation

Final tablet formulation was evaluated for various tablet parameters. Results indicate passing of respective parameters. Result for evaluation of Tablet parameters is given in Table 6.

Table. 6: Evaluation of Tablet.

Batch No.	Weight Variation (%)	Thickness (mm)	Friability (%)	Hardness Kg/cm^2	Disintegration time (mins)
F1	1.316±0.03	7.36±0.01	0.62±0.04	3.6±0.152	18.05±0.577
F2	1.317±0.04	7.38±0.05	0.68±0.08	3.8±0.452	21.57 ±0.57
F3	1.318±0.02	7.31±0.02	0.57±0.04	3.5±0.102	19.33±0.45
F4	1.316±0.01	7.27±0.03	0.52±0.09	3.4±0.129	20.33±0.48

Drug Content: Results obtained for drug content for F1-F4 formulations is given in Table 7.

Table. 7: Drug content.

Batch	Drug Content (%)	
	Citicoline	**Piracetam**
F1	98. 35±0.020	99.69±0.112
F2	98.31±0.018	97.62±0.015
F3	97.21±0.028	98.64±0.020
F4	98.34±0.033	99.03±0.024

In Vitro Dissolution Studies: The in vitro drug release for prepared F4 batch was found to be 97.27% and 99.53% in 40 minutes and for marketed formulation (Strocit plus) was found to be 97.51% and 97.75%f in 30 minutes for Citicoline and Piracetam respectively. Comparative cumulative percentage drug release for Citicoline and Piracetam of formulation F1, F2.F3.F4 and marketed tablet formulation is shown in Fig. 7 and 8, respectively.

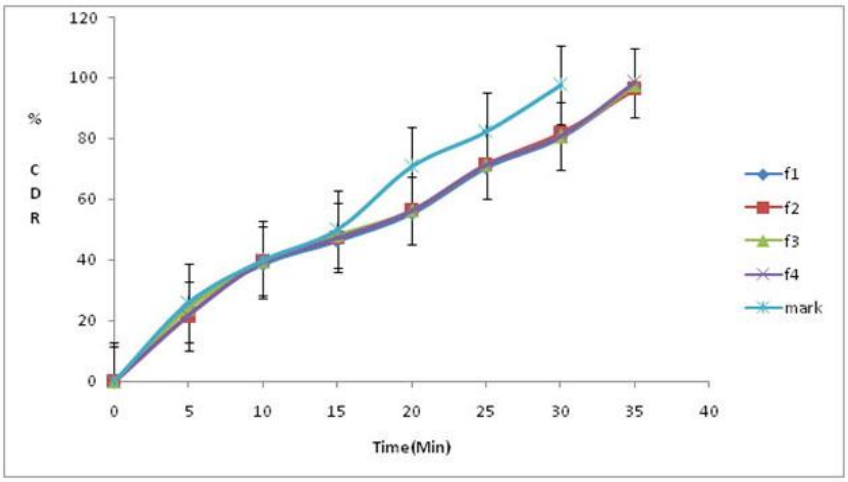


Fig. 7: Comparison of cumulative percentage drug release for Citicoline of formulation F1, F2.F3.F4 and marketed tablet formulation.

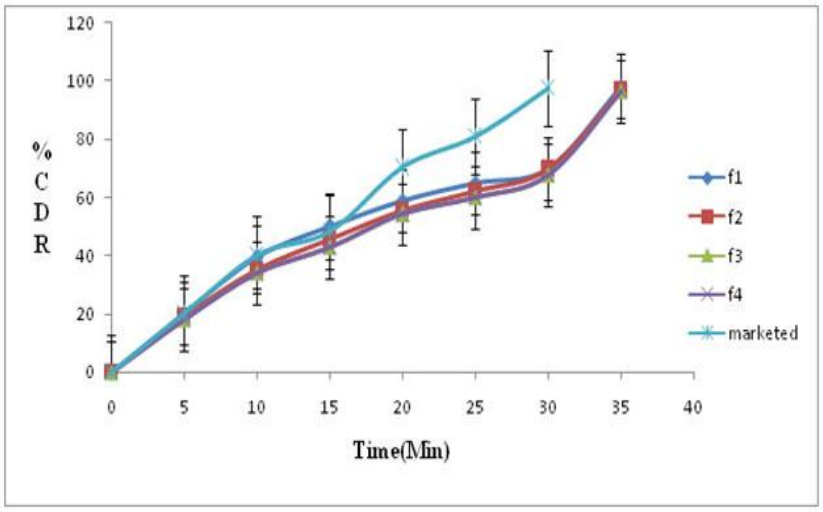


Fig. 8: Comparison of percentage cumulative drug release for Piracetam of formulation F1, F2.F3.F4, with Marketed Tablet.

Batch		% Drug release	
		Citicoline	Piracetam
F1	At 40 mins	98.35±0.20	99.69±0.12
F2		98.31±0.18	97.62±0.15
F3		97.43±0.28	98.64±0.20
F4		97.27±0.31	97.53±0.26
Marketed Formulation (Strocit Plus)	At 30 mins	97.51±0.37	97.75±0.40

Stability study

Three month stability studies were carried out on optimized formulation batch F4, drug content was estimated from developed assay method. It is observed that there is no significant difference in the drug content before and after stability studies. F4 formulation was found stable at room temperatures for a period of 3 months.

Table. 6: Stability study of optimized F4 formulation.

Drug content (%)	Initial	After 15 days	After 1 month	After 2 month	After 3 month
Citicoline	98.22±0.9	98.45±0.87	98.23±0.85	98.90±0.65	97.2±0.34
Piracetam	97.43±0.56	97.3±0.973	98.32±0.43	98.25±0.61	98.56±0.55

CONCLUSION

Through the research output of extensive experimental work it is being concluded that taste masking granules of Piracetam was achieved with low cost wet granulation. Direct compression of coated granule of Piracetam with a Citicoline has reduced the weight of tablet as compared to weight of marketed tablet. The prepared formulation is superior over the

marketed available formulation, for selected combination in term of weight reduction and easy processing for formulation. In this research work different polymers were tried and form that hydrophilic polymer HPMC was selected. The formulated tablets of all trials were evaluated for pre-compression and post-compression characteristics all the values were found to be satisfactory. IR, XRD and DSC studies clearly indicate that there was no drug-excipient interaction. In-vitro drug release studies were carried out as per USP type II apparatus in standard dissolution medium for optimized formulation F4 which showed similar drug release characteristics as that of marked formulation. The cumulative percentage release of optimized batch was 97.2 and 99.5% for Citicoline and Piracetam at 40 min respectively. Stability study showed that optimized formulation is stable for conducted study period. Development of taste masking granule of Piracetam is beneficial in treatment of Alzheimer disease specially associated with geriatric patients to enhance palatability. Increase in drug release time is beneficial to reduce frequency of administration and improve patient compliance.

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