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FORMULATION AND EVALUATION OF PALATABLE MOUTH DISSOLVING TABLETS CONTAINING TACRINE HYDROCHLORIDE: A USER FREIENDLY ORAL SOLID DOSAGE FORM FOR PATIENTS SUFFERING FROM ALZHEIMER'S DISEASE

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ABSTRACT

The objective of the current investigation was to formulate and evaluate the palatable mouth dissolving tablets (MDTs) of Tacrine hydrochloride that rapidly disintegrate into the mouth and redress the difficulty faced by geriatric patients suffering from Alzheimer's disease in swallowing the conventional tablets. Besides, MDTs can also enhance the bio availability of Tacrine that undergoes extensive first pass metabolism on oral administration. MDTs of Tacrine hydrochloride were prepared by direct compression technique. Stevioside was incorporated as a novel sweetener to mask the unpleasant taste of drug. The developed MDTs were evaluated for weight variation, hardness, friability, drug content, wetting time, *in vitro* dispersion and *in vitro* dissolution. All the formulations demonstrated acceptable weight variation with disintegration time less than 30 seconds and rapid *in vitro* dissolution. The current investigation is an attempt to develop and provide a user friendly, oral solid dosage form to geriatric patients suffering from Alzheimer's disease.

Keywords: *Mouth Dissolving Tablets, Tacrine hydrochloride, Superdisintegrant, Direct Compression.*

INTRODUCTION

Oral route is the most preferred and popular means of drug administration. However, patients, belonging to geriatric segment of the population experience difficulty in swallowing tablets and hard gelatine capsules that consequently results in non-compliance and ineffective therapy. [1] Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecules by formulating it as a convenient dosage form for administration so as to achieve better patient compliance. One of such approaches led to development of mouth dissolving tablets [2, 3 and 4]. Advantages of this drug delivery system comprise of: convenience in administration of dosage form even in absence of water, accurate dosing as compared to liquids, easy portability, quick onset of action followed by rapid drug action and many more. Mouth dissolving tablets (MDTs) are prepared by various techniques, viz. direct compression, lyophilization and moulding. Being simple and cost effective, direct compression technique is considered to be an attractive substitute to conventional granulation technologies. [5] Superdisintegrants are added to a drug formulation to facilitate the fast disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants. [6] Tacrine was the first acetylcholinestearse inhibitor that was approved for the treatment of Alzheimer disease. It is chemically 9-amino-1,2,3,4-tetrahydroacridine. Tacrine hydrochloride is white in colour. It has a slightly bitter taste and is water soluble. The pH of 1.5% (w/v) Tacrine solution is 4.5–6.0 and has a pKa value of 9.85. [7, 8] Although the precise mechanism of action of Tacrine is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic functions. Tacrine primarily leads to the reversible inhibition of cholinesterase, butyrylcholinesterase more than acetyl cholinesterase. [9] This inhibition is thought to increase the level of acetylcholine available in the brain. Tacrine may also block potassium channels, increasing the duration of the action potential and augmenting acetylcholine release from cholinergic neurons. [9, 10] Orally, Tacrine is readily absorbed. However, the absolute bioavailability is about 17% only; poor oral bio availability of the drug may be probably attributed to very high first-pass metabolism.[11] Clinical trial results have demonstrated that administration of Tacrine HCl (5 or 10 mg, once daily) significantly improves memory and cognitive function in patients with Alzheimer's disease. Tacrine is currently available in market in the form of tablet and capsule. However, geriatric patients suffering from Alzheimer's disease find it difficult to swallow down the tablets which in turn results into non adherence of patients to therapy that culminates into poor patient compliance and ultimately, therapeutic failure.

The objective of the current investigation was to formulate and evaluate the palatable mouth dissolving tablets that rapidly disintegrate into the mouth and largely alleviate the difficulty of swallowing the tablet faced by old patients suffering from Alzheimer's disease. Besides, it was also hypothesized that mouth dissolving tablets of Tacrine would also enhance the bio availability of Tacrine that undergoes extensive first pass metabolism on oral administration. Sweeteners are incorporated to improve the palatability of an oral dosage form, however, the disadvantages associated with sweeteners such as after bitter taste with saccharin, carcinogenicity in case of aspartame, dental caries and similar problems with sugar based sweeteners constrain their utility. [12] In the current work, we have used a novel sweetener stevioside obtained from herbal source and having sweetness index much higher than sugar. Its ability to sweeten is rated between 70 to 400 times that of white sugar. Stevioside in form of Stevia leaf powder was incorporated as an organoleptic additive to mask the bitter taste of the drug. It tastes 300 times sweeter than sugar, but has low calorific and glycaemic indices. Stevioside cannot be digested by gastro intestinal enzymes, is not absorbed in the body and hence, does not interfere with glucose metabolism. [13]

1. MATERIALS AND METHODS

1.1 Materials

Tacrine HCl was obtained from Sigma-Aldrich, Bangalore. Crospovidone, Sodium starch glycolate (SSG) and Croscarmellose sodium were obtained from Talent healthcare, Haridwar. Stevia leaf powder was obtained

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from Maruti trading company, Ahmedabad whereas Micro crystalline cellulose, Magnesium stearate and Mannitol were obtained from S.D. Fine chemicals Limited, Mumbai. All other chemicals and reagents were of analytical grade and were used as procured, without further purification.

1.2 Methods

Formulation of mouth dissolving tablets of Tacrine HCl

Selection of suitable superdisintegrant followed by optimization of its concentration is the key step to formulate a mouth dissolving tablet. Tablets were prepared by direct compression technique. Tacrine hydrochloride was accurately weighed and blended with other excipients. (Table 1) All the ingredients were passed through sieve # 22. MDTs were prepared by compressing the drug-excipient blend to compression using 8 mm flat punches on eight station rotary tablet compression machine. (Rimek II, Karnavati Engg. Ltd, Ahmedabad). The pre blend was characterized and subsequently optimized for its physico chemical properties in terms of flowability, angle of repose, bulk density and related derived properties prior to subjecting the same to compression for formulating tablets.(data not shown)

Table 1: Composition of Tacrine HCl MDTs prepared by direct compression method

Ingredients	A1	A2	A3	A4	A5	A6
Tacrine HCl	10	10	10	10	10	10
Crospovidone	5	7.5	-	-	-	-
Croscarmellose sodium	-	-	5	7.5	-	
Sodium starch glycolate	-	-	-	-	5	7.5
Avicel pH 102	100	100	100	100	100	100
Mannitol	28	25.5	28	25.5	28	25.5
Magnesium stereate	2	2	2	2	2	2
Stevia leaf powder	5	5	5	5	5	5

2.1 CHARACTERIZATION AND OPTIMIZATION OF FORMULATED MOUTH DISSOLVING TABLETS (MDTS) OF TACRINE HYDRFOCHLORIDE

The MDTs of Tacrine formulated by direct compression technique were subjected to physico chemical characterization in terms of weight variation, hardness, friability, *in vitro* disintegration etc. as per the compendial specifications.

2.1.1 Weight Variation

Weight variation test was carried out for the prepared Tacrine MDTs as per the procedure mentioned in Indian Pharmacopoeia [14]. 20 tablets were selected randomly from the lot and weighed individually to check for weight variation. [15, 16, 17]

2.1.2 Hardness

Hardness or tablet crushing strength (fc) is the force required to break a tablet in a diametric compression. Hardness of the prepared tablets was measured using Monsanto tablet hardness tester.

2.1.3 Friability

The friability of a sample of 20 tablets was measured using Roche friabilator (Electroquip, Mumbai, India). Twenty tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated. Friability below 1% was considered acceptable.

2.1.4 Determination of in vitro Disintegration Time

The disintegration time of the tablet was measured in water (37±2°C) using disintegration test apparatus with disk. The time taken for the complete disintegration of the tablet with no palpable mass in the apparatus was measured in seconds. Three tablets from each batch (formulation) were tested for computing the disintegration time.

2.1.5 Assessment of Drug-Excipient Interaction by Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies were performed on drug, excipients and the optimized formulation using Shimadzu Corporation, (Tokyo, Japan) Model-1601 PC. The samples were analyzed between wave numbers 4000cm-1 and 400 cm-1. Approximately 10 mg of the sample was analyzed using FTIR spectrophotometer.

2.1.6 Wetting Time and Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small petri dish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was taken and weighed.

Water absorption ratio (R) was determined using following equation.

$R=10 X (w_a-w_b)/w_b$ .....Equ. No. (1)

Where,

w_b is weight of tablet before water absorption

w_a is weight of tablet after water absorption.

2.1.7 Thickness

10 tablets were taken from each formulation were taken at random and their thickness was measured using digital Vernier caliper.

2.1.8 *In vitro* Dissolution and Drug Release Study

MDTs of Tacrine hydrochloride were optimized on the basis of characterization of physico chemical parameters of prepared tablets. Dissolution profile of the MDTs of Tacrine Hydrochloride (optimized as per the procedure discussed above) was studied by using USP type II apparatus. Optimized MDTs were added to dissolution medium (distilled water) stirred at 50 rpm. Temperature of dissolution medium was maintained at 37±0.5°c. Aliquots of dissolution medium containing dissolved drug were withdrawn at specific time interval and replaced by an equal volume of fresh dissolution medium. Aliquots were analyzed spectrophotometrically at 240 nm.

3. RESULTS AND DISCUSSION

The formulated Tacrine hydrochloride MDTs were subjected to physico chemical characterization in terms of weight variation, hardness, friability, dimensional analysis of formulated tablets, thickness, *in vitro* disintegration time, wetting time and drug content. Results are summarized in Table 2. The unacceptable and slightly bitter taste of Tacrine was effectively masked with MDTs formulated using Stevia leaf powder as a sweetener. (data not shown). The palatability of the drug significantly improved after incorporation of Stevia leaf powder as a sweetener. The tablets exhibited average weight of 150 mg with less than 5% weight variation. Hence, all the formulated MDTs were found to pass the weight variation test. Hardness of the prepared MDTs was observed to be in range of 3.1-3.5 kg/cm2?. Percentage friability was observed to be less than 0.60% for the formulated MDTs. On the basis of the findings of hardness and friability test, it could be inferred that all formulations possessed good physical strength and could withstand the probable mechanical shocks that are likely to be encountered during handling, shipping and transportation. The average diameter of the formulated Tacrine MDTs was in range of 8.1-8.8 mm, thickness in range of 2-2.05 mm. The average *in vitro* disintegration time was observed to be in the range of 43-75 sec. Content of Tacrine HCl from all the formulations was found to be in the range of 92% to 98.75%. The wetting time was determined for all the prepared Tacrine MDTs (Table 2) in order to get the insight into the disintegration time as well as mechanism underlying the disintegration of formulated tablets. Wetting time is a parameter that indicates the ease with which the tablet disintegrates in the buccal cavity. Wetting is related to the inner structure of the tablets and hydrophobicity of the components. It was observed that wetting time of optimized tablets (Batch A2) was in the range of 17-18 seconds indicating quick disintegration of the tablet. The wetting time observed in case of A2 formulation (formulated using 7.5% CrosPovidone as super disintegrant) was 17.30 seconds which was significantly lesser than the same observed in case of tablets formulated using equal amount of CrosCarmellose (47.78 sec) and Sodium Starch glycolate (62.42 sec in) as super disintegrants. The quick wetting of MDTs (as observed with 7.5% CrosPovidone) was accompanied by relatively rapid disintegration of tablets when assessed using simulated salivary fluid (pH=6.8) It was observed that incorporation of Crospovidone as a super disintegrating agent resulted in least disintegration time (24 seconds) for MDTs and exhibited nearly 98% drug release within 14 minutes.

An ideal disintegration time for mouth dissolving tablets (MDTs) should be preferentially below 60 seconds so as to serve the purpose of rapid disintegration. The rapid disintegration observed with optimized MDTs (Batch A2) may be attributed to the rapid uptake of water from the biological medium followed by swelling and burst effect that leads to increased rate and extent of drug release, which can ultimately result in enhanced bio availability. The *in vitro* disintegration of MDTs prepared using 7.5% CrosPovidone (Batch A2) was quite rapid with disintegration time of 24 seconds whereas the slow disintegration was observed with MDTs prepared using sodium starch glycolate – SSG (disintegration time: 75 seconds). The results clearly indicated relatively slower and delayed disintegration in case of MDTs prepared using SSG. The mechanism underlying the rapid disintegration as observed in case of Crosprovidone and CrossCarmellose is predominantly by wicking through capillary action and formation of fibrous structure with little or almost negligible gelling unlike SSG that shows remarkable gelling. Gel formation (as observed in case of MDTs prepared using SSG) consequently, results in delayed and retarded disintegration of MDTs. CrosPovidone shows relatively higher uptake of biological fluids and thus, facilitates instantaneous disintegration of MDTs as compared to the same observed with CrossCarmellose and SSG. The results of *in vitro* disintegration test are in congruence with findings of Sharma et al. [18]

Table 2: Physico Chemical Characterization of Tacrine HCl Mouth Dissolving Tablet (MDT)

Batch No.	Weight variation (mg) €*	Hardness (Kg/cm^2)*	Friability (%)†	*In-vitro* Disinte-gration Time (Sec) *	Diameter (mm) †	Thickness (mm) †	Drug content (%)*	Wetting time (in sec) †
A1	151.2 ± 0.38	3.10 ± 0.11	0.598 ± 0.02	43 ±1.37	08.15 ±0.02	2.05 ±0.05	96.66 ± 0.12	34.17 ± 0.85
A2	150.3 ± 0.07	3.30 ± 0.02	0.532 ± 0.004	24±0.72	08.08 ±0.04	2.03 ±0.02	98.75 ± 0.34	17.30 ± 0.42
A3	148.7 ± 0.73	3.50 ± 0.06	0.466 ±0.02	74±1.24	08.80 ±0.02	2.02 ±0.06	92.08 ± 0.58	60.12 ± 0.64
A4	149.6 ± 0.33	3.40 ± 0.01	0.466 ±0.02	57±0.92	08.50 ±0.01	2.05 ±0.05	93.75 ± 0.28	47.78 ± 0.41
A5	150.8 ± 0.20	3.50 ± 0.06	0.530 ±0.004	87±1.10	08.70 ±0.08	2.04 ±0.04	93.33 ± 0.67	68.78± 0.88
A6	151.5 ± 0.16	3.40 ± 0.01	0.597 ±0.02	75±0.83	08.20 ±0.04	2.03 ±0.03	95.41 ± 0.21	62.42 ± 0.67

€ All values are mean ± SD, (n = 20), * All values are mean ± SD, (n = 6),
† All values are mean ± SD, (n = 3)

The formulated MDTs optimized on basis of findings of physico chemical characterization as well as *in vitro* disintegration test were then subjected to *in vitro* dissolution studies in order to assess the *in vitro* drug release profile of optimized MDTs. *In vitro* dissolution studies of the optimized MDTs were performed using USP dissolution apparatus Type II. Results are summarized in Fig. 1, 2 and 3. Incorporation of super disintegrants at level of 7.5% resulted in 98.75%, 93% and 91% drug release in 14 minutes time interval with Crospovidone, Croscarmellose and SSG respectively. Thus, on the basis of collective findings of *in vitro* disintegration test, wetting time determination and *in vitro* drug release studies, it was observed that MDTs formulated using 7.5% Cros Povidone (Formulation code A2) exhibited optimum disintegration and drug release profile and hence, Crospovidone (when incorporated at proportion of 7.5% w/w) can be considered to be the ideal super disintegrating agent and hence, batch A2 was selected as an optimized batch.

FTIR spectra of the drug, excipients and the optimized formulation were recorded in range of 4000 cm^{-1} to - 400 cm^{-1}. (Fig. 4 and Fig. 5) The IR spectrum of Tacrine hydrochloride exhibited distinctive peaks at 3336.25 cm^{-1} due to N-H stretching, 2938.98 cm^{-1} C-H stretching, 1265.07 cm^{-1} N-H stretching, 1461.78 cm^{-1} aromatic ring present. The IR spectrum of tablet exhibited distinctive peaks at 3370.96 cm^{-1} N-H stretching, 2965.98 cm^{-1} C-H stretching, 1280.50 cm^{-1} C-N stretching, 1542.77 cm^{-1} aromatic ring present, 686.53 cm^{-1} cis-RCH=CHR, 2719.14 cm^{-1} Aldehyde C-H, 2132.88 cm^{-1} C ≡ C stretching. As indicated in Fig. 4 and 5, there was no significant shifting of drug peaks in physical mixture testifying that there was no significant drug-excipient interaction in the optimized formulation.

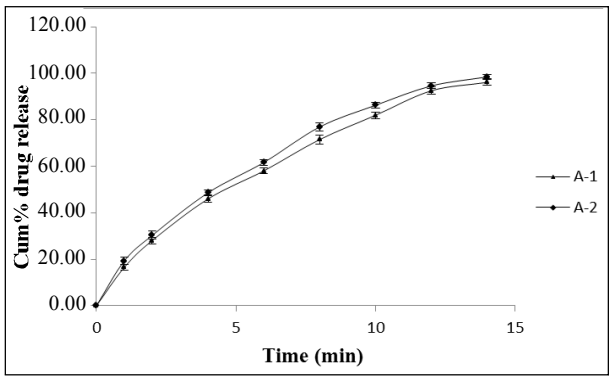

Figure 1: *In vitro* dissolution studies of A-1 and A-2 formulation

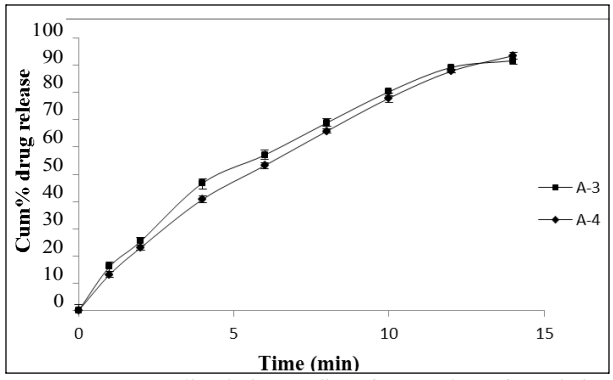

Figure 2: *In vitro* dissolution studies of A-3 and A-4 formulation

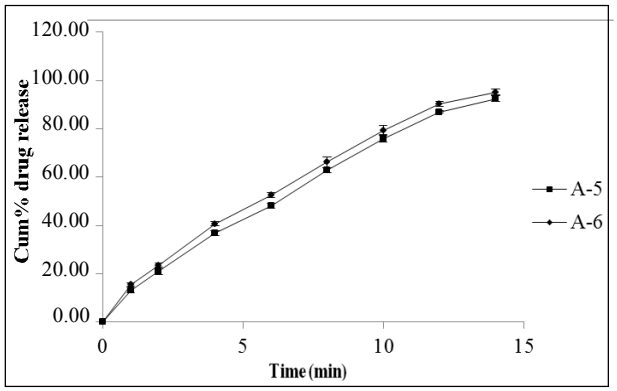

Figure 3: *In vitro* dissolution studies of A-5 and A-6 formulation

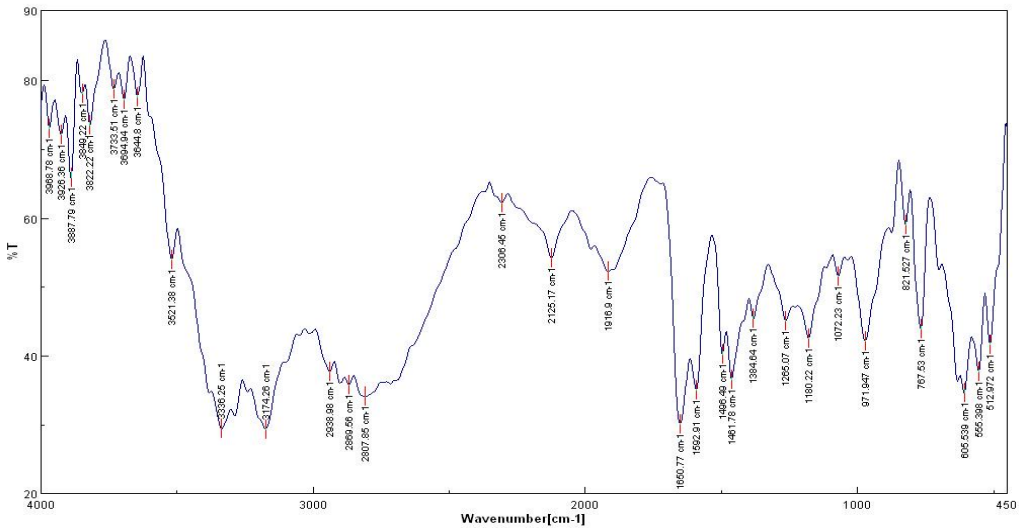

Figure 4: FTIR spectrum of Tacrine hydrochloride (pure drug)

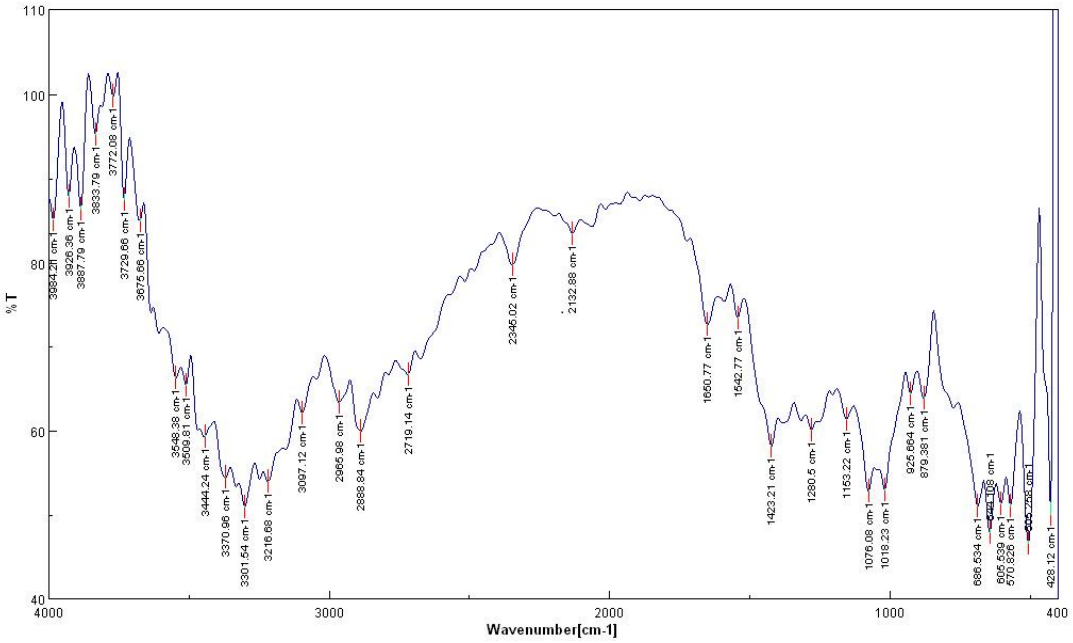

Figure 5: FTIR spectrum of Tacrine Tablet

5. CONCLUSION

The optimized mouth dissolving tablets of Tacrine hydrochloride demonstrated acceptable hardness, friability, mechanical strength and weight uniformity. On the basis of findings of physico chemical characterization as well as *in vitro* disintegration and drug release studies, formula A2 was selected as the optimized formulation. The formulation A2 (prepared using 7.5% w/w CrosPovidone as super disintegrant) exhibited hardness of 3.3 kg/cm^2, friability of 0.54% indicating appreciable mechanical strength of the prepared tablets. *In vitro* disintegration time and *in vitro* drug release for A2 formulation were observed to be 24 sec (less than one minute) and 98.75% (> 98%) in 14 minutes respectively indicating the fast disintegration of the MDTs followed by rapid drug release. The quick disintegration of MDTs followed by rapid drug release is expected to accomplish the quicker onset of drug action. Results of FTIR spectroscopic studies clearly indicated the absence of any significant drug-excipient interaction. From the results, one can conclude that MDTs prepared by direct compression were observed to be mechanically strong, were capable of releasing the drug quickly in buccal cavity and hence, can serve as potential tool in alleviating the swallowing related problems encountered in consumption of oral solid dosage forms by geriatric patients. Besides, MDTs can significantly reduce the first pass metabolism of Tacrine that is usually observed on its oral administration and hence, issue of lower oral bio availability of Tacrine can also be redressed by formulating the latter as MDT. In nutshell, the findings of the present investigation demonstrated potential of MDTs in promoting rapid drug absorption, improved bioavailability with effective therapy in general and patient compliance at large.

6. DECLARATION

The authors declare no conflict of interest.

7. ACKNOWLEDGEMENT

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