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Original Article

DEVELOPMENT OF ORALLY DISINTEGRATING TABLETS OF MEMANTINE HYDROCHLORIDE- A REMEDY FOR ALZHEIMER'S DISEASE

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ABSTRACT

Objective: The study is directed towards the development of an orally disintegrating drug delivery system of memantine hydrochloride which can be commercially exploited for the well-being of society for the treatment of Alzheimer's disease, which is a most common form of dementia.

Methods: Orally disintegrating immediate-release tablets of memantine hydrochloride were prepared and optimized for disintegration time and *in vitro* drug release. The top spray granulation method was used for the preparation of granules. Subsequently, these granules were compressed to tablets. The levels of diluent, disintegrant and taste-masking agents were optimized using the design of experiments. The resulting tablets were evaluated for disintegration time and *in vitro* drug release. The optimized formulation was subjected to accelerated stability study for 3 mo.

Results: The optimized orally disintegrating tablet formulation exhibited a disintegration time of 2-3 min and complete drug release i.e. more than 85 % drug release within 10 min while performing *in vitro* drug release study. This is a prerequisite for faster action in the case of patients suffering from Alzheimer's disease. Accelerated stability studies indicated good physical and chemical stability of the optimized formulation.

Conclusion: Developed orally disintegrating tablet formulation of memantine hydrochloride could release the drug faster compared to conventional immediate-release tablets which is useful in paediatric, geriatric and psychiatric patients.

Keywords: Memantine, Orally-disintegrating, Tablets, Super-disintegrants, Alzheimer's disease, Top-spray

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INTRODUCTION

Dementia is a syndrome in which there is the disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment [1, 2]. Alzheimer's disease is the most common form of dementia, which is the major cause of disability in later life and accounts for 11.9 % of the years lived with disability due to a non-communicable disease [3, 4]. In the early stages of the disease, people most often notice memory problems that can be severe enough to interfere with their ability for routine tasks and work [5, 6]. In this disease, the change in forgetfulness is more dramatic than normal which commonly gets increased with age. More importantly, this difficulty is persistent, progressive, and severe and there is usually a noticeable, rapid decline in cognitive skills [7, 8].

Alzheimer's disease is further classified into two types, one is a familial type that is passed from one generation to another through a dominant gene, is very rare and is seen in only 5-10 % of cases. About 90 % of cases are the sporadic type, which can be developed even if nobody in the family has had the disease [9, 10]. In the United States, it is the fourth leading cause of death and the most common cause of dementia. The total number of people with dementia worldwide is projected to nearly double every 20 y, 65.7 million in 2030 and 115.4 million in 2050 [11-13]. The total number of new cases each year worldwide is nearly 7.7 million, implying one new case every 4 seconds. The fastest growth is taking place in China, India, and their south Asian and western Pacific neighbours. It is projected that by 2050, people aged 60 and over will account for 22 % of the world's population with 80 % living in Asia, Latin America or Africa [14].

Memantine hydrochloride is a low-moderate affinity, uncompetitive n-methyl-d-aspartate (NMDA) receptor antagonist with strong voltage dependency and rapid blocking/unblocking kinetics [15, 16]. These pharmacological features appear to allow memantine to block the sustained activation of the receptor by glutamate that may occur under pathological conditions, and to rapidly leave the NMDA receptor channel during normal physiological activation.

Current approach is intended to develop an orally disintegrating drug delivery system of memantine hydrochloride which is gaining importance in the field of pharmaceutical technology as these systems are beneficial for many patients particularly from paediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules and also in patients travelling with little or no access to water, leading to non-compliance and ineffective therapy [17, 18].

MATERIALS AND METHODS

Chemicals and reagents

Memantine hydrochloride was obtained as a gift sample from Cadila Healthcare Ltd, Mumbai, India; microcrystalline cellulose, mannitol, croscarmellose sodium, silica colloidal anhydrous and magnesium stearate procured from Signet chemicals ltd, Eudragit EPO as a gift sample from Evonik GmbH, India. All these suppliers were based in Mumbai, India.

Methods

Analytical development

The analytical development was carried out by a high-performance liquid chromatography (HPLC) method using HPLC system (Shimadzu LC2010C, UV Detector) equipped with a column (Zorbax SB C18, 4.6 × 50 mm, 3.5 µm).

Preparation of orally disintegrating tablets of memantine hydrochloride

Initial developmental trials to formulate the orally disintegrating tablets of memantine hydrochloride were taken to select excipients and their primary levels. The taste and flavour enhancers were used with wet granulation technique to mask the bitterness of the drug.

Based on the observations and results of these trials, actual optimization batches were planned (table 1a and 1b).

Manufacturing process

Memantine hydrochloride, microcrystalline cellulose, mannitol were sifted through # 40 sieve and transferred to the bowl of top spray granulator. Eudragit EPO ready mix clear was dispersed in purified

water and used to spray on the blend by top spray granulation method and subsequently dried. The dried granules were milled using a suitable screen and blended with sifted extra granular materials viz. croscarmellose sodium, silica colloidal anhydrous, tartaric acid, neotame, acesulfame potassium and tutti-frutti flavour. The blend was lubricated with magnesium stearate in the blender. The lubricated blend was transferred to the hopper of the compression machine and tablets were compressed at the hardness of 2-4 kg/cm^2 using 8 mm circular, flat-faced bevelled edge, plain punches using Cadmach single rotary compression machine.

Table 1a: Composition of optimization trials (F1-F7)

Ingredients	F1	F2	F3	F4	F5	F6	F7
	mg/tablet						
Memantine hydrochloride	5.000	5.000	5.000	5.000	5.000	5.000	5.000
Microcrystalline cellulose	85.650	103.650	83.650	59.650	103.650	63.650	67.650
Mannitol	40.000	20.000	40.000	60.000	20.000	60.000	60.000
Eudragit EPO Ready mix Clear	2.000	4.000	4.000	6.000	2.000	4.000	2.000
Purified water	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Croscarmellose sodium	4.000	4.000	4.000	6.000	6.000	4.000	2.000
Silica colloidal anhydrous	1.450	1.450	1.450	1.450	1.450	1.450	1.450
Tartaric acid	3.500	3.500	3.500	3.500	3.500	3.500	3.500
Tutti-frutti flavour	4.500	4.500	4.500	4.500	4.500	4.500	4.500
Neotame	1.500	1.500	1.500	1.500	1.500	1.500	1.500
Acesulfame potassium	0.900	0.900	0.900	0.900	0.900	0.900	0.900
Magnesium stearate	1.500	1.500	1.500	1.500	1.500	1.500	1.500

Table 1b: Composition of optimization trials (F8-F15)

Ingredients	F8	F9	F10	F11	F12	F13	F14	F15
	mg/tablet							
Memantine hydrochloride	5.000	5.000	5.000	5.000	5.000	5.000	5.000	5.000
Microcrystalline cellulose	103.650	81.650	63.650	81.650	99.650	107.650	63.650	85.650
Mannitol	20.000	40.000	60.000	40.000	20.000	20.000	60.000	40.000
Eudragit EPO Ready mix Clear	6.000	6.000	2.000	4.000	6.000	2.000	6.000	4.000
Purified water	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Croscarmellose sodium	2.000	4.000	6.000	6.000	6.000	2.000	2.000	2.000
Silica colloidal anhydrous	1.450	1.450	1.450	1.450	1.450	1.450	1.450	1.450
Tartaric acid	3.500	3.500	3.500	3.500	3.500	3.500	3.500	3.500
Tutti-frutti flavour	4.500	4.500	4.500	4.500	4.500	4.500	4.500	4.500
Neotame	1.500	1.500	1.500	1.500	1.500	1.500	1.500	1.500
Acesulfame potassium	0.900	0.900	0.900	0.900	0.900	0.900	0.900	0.900
Magnesium stearate	1.500	1.500	1.500	1.500	1.500	1.500	1.500	1.500

Evaluation of blend

The lubricated blend was evaluated for flow characteristics: bulk density (BD), tapped density (TD), compressibility index (CI), Hausner's ratio (HR) and angle of repose. The flow characteristics were determined by using approximately 25 g weighed amount of blend in 100 ml measuring cylinder.

Evaluation of tablets

The formulations were evaluated for hardness, weight variation, thickness, friability, disintegration time, disintegration time in the oral cavity, *in vitro* dispersion time, wetting time and water absorption ratio, assay, content uniformity and *in vitro* dissolution study.

Tablet hardness

Hardness is the crushing strength of a tablet which determines the ease of handling and the rigors of the transportation. For each formulation, 10 tablets were used for the study.

Weight variation test

The weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average. The table given below shows the weight variation tolerance for uncoated tablets.

Thickness

The thickness of the tablets was measured using digital vernier caliper.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause the tablet to chip, cap or break. Roche friabilator was used for this purpose. This device subjects the tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. The pre-weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dedusted and re-weighed.

Disintegration time

One tablet was placed in each of six tubes of the disintegration test apparatus. Disintegration test was carried out at 37±2 °C according to United States Pharmacopoeia (USP) 22nd edition. The time required for the complete passage of tablet fragments through the sieve (#10) was considered as the disintegration time of the tablet.

Disintegration time in oral cavity

The disintegration time in the oral cavity of 6 human volunteers was measured by placing the tablet on the tongue until no lumps remain. It is expressed in seconds [17].

***In vitro* dispersion time**

In vitro dispersion, time was measured by dropping tablets in 100 ml of water and stirring until completely dispersed. A smooth dispersion is produced which passes through a screen with a nominal mesh aperture of 710 µm.

Wetting time and water absorption test

Wetting time is closely related to the inner structure of tablets and to the hydrophilicity of the excipients. According to the following equation proposed by Washburn E. W., the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powder. It is obvious that pore

size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus, wetting time is an important step in the disintegration process to take place.

A piece of tissue paper folded twice was placed in a small petri dish (internal diameter = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37 ℃ [17].

The same procedure was repeated for determining the water absorption ratio. The wetted tablet was then weighed. Water absorption ratio, R, was determined according to the following equation:

$$R = \{(W_a - W_b) \setminus W_a\} \times 100$$

Where W_a = Weight of tablet before study.

W_b = Weight of tablet after study.

Assay

30 tablets were randomly selected from each batch. Out of 30 tablets, 10 tablets were crushed into fine powder. Powder equivalent to label claim was weighed accurately, dissolved in the media and analyzed for assay.

Uniformity of dosage units (By content uniformity)

One tablet was taken in 100 ml volumetric flask, which was shaken with 15 ml of methanol and sonicated for 10 min. 15 ml of 0.2 N sodium hydroxide solution was added and sonicated for 15 min with vigorous shaking. 10 ml of internal standard solution was added and shaken for 15 min and then allowed to separate 2 layers for about 15 min. The top toluene layer was separated by using pasture pipette and dried over anhydrous sodium sulphate. The initial 2-3 ml was discarded and remaining solution was used for analysis.

***In vitro* dissolution studies**

The *in vitro* dissolution study was carried out using 900 ml of 0.01 N HCl at 37±0.5 °C temperature at 50 rpm using USP Type 2 (paddle) dissolution test apparatus. Samples were withdrawn at 1, 2, 4, 6, 8, and 10 min time intervals.

Reproducibility of optimized composition trial and accelerated stability studies

Reproducible batch was prepared similar to the composition of optimized batch in order to evaluate the reproducibility and the stability profile of the formulation. The tablets were packed in blisters and subjected to accelerated storage conditions of 40 °C/75 % RH. Samples were evaluated at the time intervals of 1, 2 and 3 mo [17].

Statistical analysis

One way analysis of variance (ANOVA) was employed to assess difference between the assay values of initial and that of stability samples using Sigma stat software (Sigma stat 2.03, SPSS). Similar statistical test was applied to find the difference in the *in vitro* drug release at each time point among stability samples. The observed p values using ANOVA were considered for determining the statistical significance for the assay and *in vitro* drug release at each time point among stability samples.

RESULTS AND DISCUSSION

Calibration curve

The linearity for memantine hydrochloride was demonstrated over the range of 50 % to 150 % of the label claim. The plot was found to be linear with a correlation coefficient of 0.99996 and y-intercept of 1.4 % with respect to 100 % linearity level response.

Formulation development

Evaluation of tablets

Most of the earlier work by various authors involved development of the orally disintegrating tablets of memantine hydrochloride by OVAT (One variable at a time) approach [17]. In this study, 15 trials were performed with respect to the design of experiments and observed parameters for the same have given in table 2, 3 and 4. The tablets were compressed at the target weight. The weight variation range was observed at target weight±5 %, which falls within the acceptable weight variation range of±7.5 % as per USP. Hence, all formulations complied with the weight variation test indicating the minimal impact of formulation compositions. The hardness of all formulations was observed in the range of 2.5–4.0 kg/cm^2. Generally, an increase in the concentration of polymer contributes to higher hardness values; however, it is not an absolute indicator of strength [17]. The hardness of all formulations was kept constant within the above-mentioned range by adjusting the compression force in order to compare the disintegration time of the formulations prepared using different compositions. The friability of none of the formulations exceeded 0.517 %. The friability data indicate that the tablets were mechanically stable and could handle the rigors of transportation and handling. The thickness of all formulations was observed between 2.60–2.88 mm indicating fairly acceptable tabletting.

Disintegration time is a very important parameter of fast disintegrating tablets. The internal structure of a tablet, pore size distribution, water penetration into tablet and swelling of disintegrant are key aspects to determine the mechanism of disintegration. The disintegration time of formulation was satisfying because it disintegrated in the range of 1 to 4 min. The trial, F10 demonstrated the best disintegrating time, i.e. 61±2.08 s (table 3) which depicts the impact of high concentration of mannitol and croscarmellose sodium. But the lubricated blend of this batch was found to have poor flow characteristics, as the mannitol concentration used in this trial was very high. The mannitol has poor flow and binding properties. Trial F1, having a lower concentration of binder, was not able to yield sufficient hardness, whereas, lower drug content in trial F2 could be attributed to the segregation as a result of vast differences in ratio of diluents (microcrystalline cellulose: mannitol). The trials F6, F7, F12 and F13 exhibited poor flow characteristics. The trial F5 also showed a lower disintegration time of 64±2.13 s, but found to comprise of the lower assay value. Trials F4, F7, F8, F9, F12, F13, F14 and F15 were found to have less than 90 % dissolution in 10 min. Trial F10 and F11 depicted lower disintegration time and complete drug release but at the cost of higher concentration of mannitol and croscarmellose sodium, which was not worthwhile. The percentage drug content (assay) of formulation F1–F15 was found to be 92.0±2.59 % w/w to 99.8±0.23 % w/w (table 2, 3 and 4) which is within the acceptable limits as per individual monograph of selected drugs. *In vitro* dispersion time was measured by the time taken to undergo uniform dispersion as per the British Pharmacopoeia. The rapid dispersion was observed in the trial F10 indicating better disintegrating properties of croscarmellose sodium. It also revealed the effect of mannitol and microcrystalline cellulose combination along with aqueous solvent on the tablet characteristics. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue. Some individuals have the tendency to chew or crush the tablet after keeping in the oral cavity. This is the reason that the disintegration time in the oral cavity and the wetting values do not coincide. It was observed that the pore size get smaller due to an increase in compression force, and hence, wetting time increases due to decrease in porosity. A linear relationship exists between wetting time and disintegration time. Even though, wetting time is considered very valuable parameters to assess the disintegration time. The wetting time of formulation F1–F15 was found in the range of 109.1±0.85 s to 289.1±1.15 s. This may be due to the ability of swelling and water absorption capacity [18]. The water absorption ratio is closely related to the inner structure of tablets. The water absorption ratio values of formulation F1–F15 were found to be 51.1±0.9 to 136.2±1.2. The wide range of these values attributed to the difference in the concentrations of mannitol and croscarmellose sodium in each trial. Croscarmellose sodium is a very effective super disintegrant as it allows water penetration into tablets through the hydrophilic, fibrous particles and the subsequent development of a strong disintegration force. It avoids lump formation on disintegration.

***In vitro* dissolution study**

The dissolution study on formulation F1–F15 showed the dissolution ranging 74±2.27 % to 100±1.09 % in 10 min (table 2-4 and fig. 1). High dissolution resulted due to faster breakdown and rapid dispersion of the tablet. It may be due to rapid diffusion or the porous nature of the tablet. The dissolution graphs shown in fig. 1 depict the same. Based on the data, it can be concluded that the addition of super disintegrant improved the dissolution profile of the water-soluble drug besides expediting the disintegration time.

Table 2: Physico-chemical characteristics of formulation F1 to F5

Parameters	F1	F2	F3	F4	F5
Bulk density (g/ml)	0.467	0.498	0.477	0.389	0.396
Tapped density (g/ml)	0.556	0.612	0.538	0.497	0.492
Compressibility Index (%)	16.007	18.627	11.338	21.730	19.512
Hausner's ratio	1.191	1.229	1.128	1.278	1.242
Angle of repose	27.9	31.2	26.8	29.5	31.2
Weight variation (mg)	150±4	150±3	150±1	150±2	150±2
Thickness (mm)	2.75±0.06	2.75±0.08	2.70±0.08	2.75±0.04	2.80±0.08
Friability (%)	0.419	0.208	0.234	0.312	0.419
Hardness (kg/cm^2)	2.8±0.4	3.4±0.2	3.6±0.4	2.7±0.3	3.5±0.4
Disintegration time (s)	93±3.05	118±2.32	104±1.04	140±3.21	64±2.13
Dispersion time (s)	113±2.17	138±1.01	126±2.95	157±1.89	99±1.29
Content uniformity (%)	97.2±1.2	91.4±2.9	98.8±2.1	95.0±1.37	92.6±3.20
Water absorption ratio	58±0.8	69.6±1.2	63.5±1.1	79.2±1.2	53.1±1.9
Assay (% w/w)	97.3±1.12	95.4±2.87	98.9±0.93	97.1±1.27	93.2±2.23
Wetting time (s)	127.1±1.12	152.6±1.55	139.6±1.18	180.0±1.09	110.0±3.1
Dissolution (%)	99±1.03	94±2.23	91±1.51	84±2.05	97±0.98

Values are represented as mean±standard deviation, n = 3 for assay, n = 6 for dissolution and n = 10 for all physical parameters.

Table 3: Physico-chemical characteristics of formulation F6 to F10

Parameters	F6	F7	F8	F9	F10
Bulk density (g/ml)	0.315	0.322	0.378	0.477	0.398
Tapped density (g/ml)	0.466	0.451	0.488	0.543	0.478
Compressibility Index (%)	32.403	28.603	22.541	12.155	16.736
Hausner's ratio	1.479	1.401	1.291	1.138	1.201
Angle of repose	26.3	28.4	34.3	28.5	26.6
Weight variation (mg)	150±2	150±1	150±5	150±3	150±4
Thickness (mm)	2.65±0.04	2.68±0.04	2.80±0.05	2.70±0.06	2.68±0.07
Friability (%)	0.277	0.293	0.437	0.119	0.258
Hardness (kg/cm^2)	2.7±0.2	2.8±0.3	3.0±0.5	3.3±0.4	3.0±0.3
Disintegration time (s)	118±1.48	118±3.65	228±2.11	205±1.10	61±2.08
Dispersion time (s)	138±2.15	152±0.95	252±2.17	238±2.11	98±1.10
Content uniformity (%)	98.3±1.70	91.1±1.90	96.2±3.20	99.5±2.10	98.7±1.50
Water absorption ratio	64.3±1.4	70.1±1.0	132.3±1.8	132.0±1.4	51.1±0.9
Assay (% w/w)	97.6±1.08	92.0±2.59	95.5±1.99	99.8±0.23	98.9±0.67
Wetting time (s)	148.1±1.15	162.5±2.10	263.1±1.12	258.1±1.75	109.1±0.85
Dissolution (%)	96±1.12	87±1.23	78±1.17	80±2.21	100±1.09

Values are represented as mean±standard deviation, n = 3 for assay, n = 6 for dissolution and n = 10 for all physical parameters.

Table 4: Physico-chemical characteristics of formulation F11 to F15

Parameters	F11	F12	F13	F14	F15
Bulk density (g/ml)	0.481	0.337	0.331	0.357	0.469
Tapped density (g/ml)	0.539	0.499	0.517	0.504	0.537
Compressibility Index (%)	10.761	32.465	35.977	29.167	12.663
Hausner's ratio	1.121	1.481	1.562	1.412	1.145
Angle of repose	26.1	29.1	32.8	30.7	26.9
Weight variation (mg)	150±1	150±2	150±5	150±2	150±3
Thickness (mm)	2.70±0.06	2.65±0.05	2.78±0.05	2.68±0.06	2.70±0.06
Friability (%)	0.311	0.517	0.473	0.336	0.112
Hardness (kg/cm^2)	3.4±0.3	3.2±0.3	3.5±0.5	2.8±0.3	3.4±0.3
Disintegration time (s)	84±1.27	125±0.31	112±1.12	235±2.36	195±1.47
Dispersion time (s)	108±1.46	145±2.05	139±3.17	267±3.19	218±2.15
Content uniformity (%)	98.3±1.70	94.5±4.20	93.6±1.90	98.3±1.70	98.3±1.70
Water absorption ratio	54.3±1.1	72.1±1.9	70.0±1.5	136.2±1.2	109.1±1.8
Assay (% w/w)	97.6±1.12	96.1±2.10	94.3±3.12	98.8±0.78	99.0±0.44
Wetting time (s)	119.3±1.37	161.3±1.07	148.9±1.01	289.1±1.15	228.6±1.30
Dissolution (%)	98±3.01	86±1.09	89±1.61	74±2.27	85±1.17

Values are represented as mean±standard deviation, n = 3 for assay, n = 6 for dissolution and n = 10 for all physical parameters.

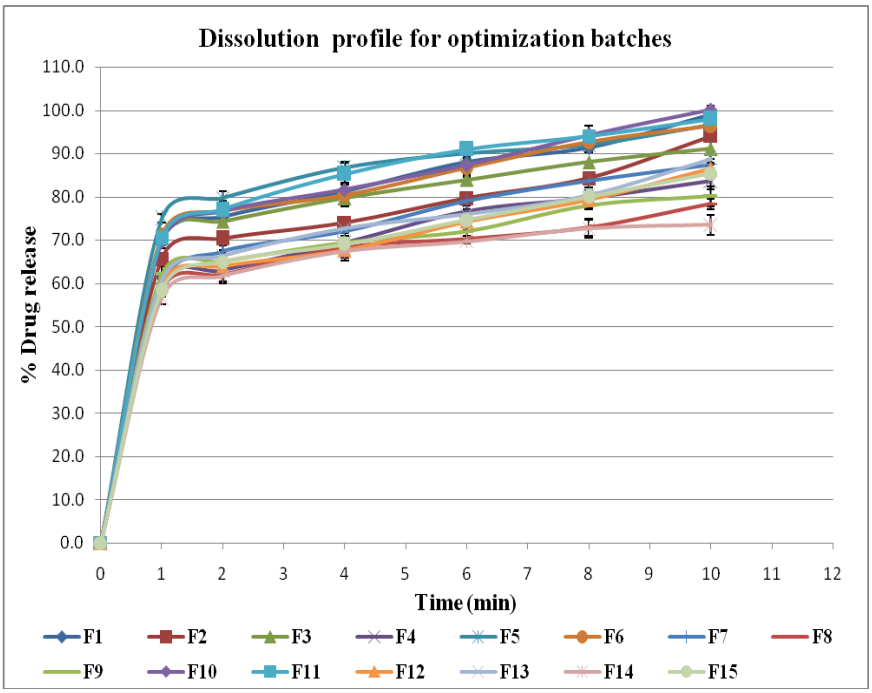

Fig. 1: Dissolution profile for optimization batches (mean±SD, n = 3)

Reproducibility of optimized composition trial and accelerated stability studies

The reproducibility was evaluated for batch F3 with respect to assay and dissolution profile. Stability samples when evaluated at various time intervals, showed no significant difference in appearance, hardness or other physical traits as compared to initial samples (table 5). The statistical analysis of assay values of stability samples indicated no significant difference. *In vitro* release profile of samples when compared with that of initial using ANOVA, exhibited no significant difference. Thus, indicating overall good stability of the formulation at accelerated conditions.

Table 5: Evaluation of stability sample

Test	Specification	Initial	1 mo	2 mo	3 mo
Description	White to off-white coloured round, biconvex tablets	White to off-white coloured round, biconvex tablets	White to off-white coloured round, biconvex tablets	White to off-white coloured round, biconvex tablets	White to off-white coloured round, biconvex tablets
Average weight	150 mg±3 %	complies	complies	Complies	Complies
Hardness	3–7 kg/cm^2	3.5–6 kg/cm^2	3.5–5 kg/cm^2	3–5 kg/cm^2	3–4.5 kg/cm^2
Disintegration time	30–180 s	115 s	110 s	110 s	100 s
Assay	90-110 %	99.9±0.5 %	99.1±0.8 %	98.7±1.2 %	98.1±2.0 %
Drug release	NLT 85 %	92.8 %	92.1 %	91.6 %	91.0 %

Values of assay and drug release are represented as mean±standard deviation, n = 3, n = 6 respectively.

CONCLUSION

Memantine hydrochloride mouth dissolving tablet formulation was manufactured by the top spray granulation method and subsequent compression to tablets. Various compositions with different excipients and their levels were used, among them, F3 was found to be the best formulation which showed satisfactory results for the tests conducted. Based on the evaluation parameters like friability, dispersion test, wetting time disintegration time in the oral cavity and *in vitro* dissolution study, F3 was found to be optimized formulation with a disintegration time of 104±1.04 s and release of the drug was 91±1.51 % within 10 min indicating a better *in vitro* drug release when compared to other formulations.

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AUTHORS CONTRIBUTIONS

All authors have equally participated and contributed to the conceptualization of idea and have read and approved this version of the article. However, the first author has played role in the inception and execution of concept and manuscript preparation and the second author reviewed and provided technical support.

CONFLICT OF INTERESTS

The authors of this scientific publication report no conflict of interest in this work.

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