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Formulation and development of orodispersible tablet of Memantine HCl by sublimation approach

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ABSTRACT

The present study aimed to formulate orodispersible tablets of memantine hydrochloride to increase its bioavailability. Orodispersible tablets were prepared by direct compression technique using sublimation approach. The prepared powder mixtures were subjected to both pre and post compression evaluation parameters including; micromeritics properties, tablet hardness, friability, wetting time, disintegration time and in vitro drug release. The results of micromeritics studies revealed that all formulations were of acceptable to good flowability. Tablet hardness and friability indicated good mechanical strength. The F9 formulation which is having high concentration of camphor was given promising results for tablet disintegration, wetting time and gives faster dissolution rate. This increase in the dissolution rate may be due to the presence of crospovidone which is used as a superdisintegrant. This work is helped in understanding the effect of formulation processing variables especially the subliming agent on the drug release profile.

Key words: Orodispersible tablets; Memantine HCl; Direct compression; Alzheimer's disease.

INTRODUCTION

Oral drug delivery remains the preferred route for administration of various drug to produce systemic effects of drugs. Solid oral dosage forms represents the preferred class of product, as tablet represents a unit dosage form in which one usual dose of the drug has been accurately placed. It avoids, errors in the total dose to be taken when the drug is self- administered by the patient. Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased, as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that dysphagia[1] (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting and motion sickness complications[2].

ODTs with good taste and flavour increase the acceptabilily of bitter drugs by various groups of population. Thus, these conventional dosage forms result in high prevalence of noncompliance and unsuccessful therapy with respect to swallowing specially in the case of geriatric, pediatric or any mentally retarded persons. Since the absorption is taking place directly from the mouth, so, bioavailability of the drug increases. Drugs present in orodispersible tablets are also not suffering from first pass metabolism [3]. Memantine hydrochloride is a NMDA receptor antagonist specially used for Alzheimer's disease, this commonly occurring for elderly people. ODTs gets dissolved quickly due to the existence of superdisintegrants, resulting in speedy absorption of drug which in twist provides rapid onset of action. The dissolution rate and bioavailability of a poorly soluble drug from solid dosage form depend much on formulation additives and formulation characteristics. On the basis of these considerations, in the present study it

was proposed to formulate an oral delivery system, in the form of orodispersible tablet of memantine hydrochloride to increase its bioavailability [4].

Orodispersible tablets were prepared by direct compression technique using sublimation approach. The prepared tablets were subjected to both pre and post compression parameters evaluation, including; Carr's index, angle of repose, Hausner's ratio, hardness, friability, wetting time, disintegration time and dissolution rate.

MATERIALS AND METHODS

Memantine hydrochloride was a gift sample from Hetero pharmaceuticals Pvt Ltd., (Hyderabad, India). Camphor, sodium starch glycolate, croscarmellose sodium, crospovidone and mannitol were purchased from Sigma alrich, india. Lactose, aspartame, magnesium stearate talc were purchased from S.D fine chemicals. All the other chemicals used were of analytical reagent grade.

Development of Orodispersible tablet of Memantine HCl

The Memantine hydrochloride orodispersible tablets were prepared by direct compression method employing various excipients as mentioned in the Table 1. Memantine hydrochloride, camphor, superdisintegrant (Sodium starch glycolate, Croscarmellose sodium, Crospovidone) in various proportions, lactose, microcrystalline cellulose, aspartame, magnesium stearate, talc were passed through #40 mesh and mixed well. The magnesium stearate was individually passed through #60 mesh. The blend was lubricated with magnesium stearate. The tablets were compressed using a 10 station tablet compression machine using 8mm round shaped punches.

Table 1: Formulation of Memantine hydrochloride orodispersible tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Memantine HCl	05	05	05	05	05	05	05	05	05
Camphor	05	10	15	05	10	15	05	10	15
Sodium starch glycolate	02	04	06	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	02	04	06	-	-	-
Crospovidone	-	-	-	-	-	-	02	04	06
Lactose	60	60	60	60	60	60	60	60	60
Mannitol	24	17	10	24	17	10	24	17	10
Aspartame	02	02	02	02	02	02	02	02	02
Magnesium stearate	01	01	01	01	01	01	01	01	01
Talc	01	01	01	01	01	01	01	01	01
Total	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Ingredients weight mentioned in mg

CHARACTERIZATION OF BLEND

Micromeritic Properties [5,6,7,8]

Prior to compression, the blend was evaluated for their micromeritic properties such as bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose.

Bulk density and Tapped density [5,6,7]

A known amount of granules from each formula, previously lightly shaken to break any agglomerates formed was introduced into a graduated measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own height onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued, until no further change in the volume was noted. BD and TD were calculated using the following formulas.

BD = Weight of the powder/volume of the packing

TD = Weight of the powder/tapped volume of the packing

Compressibility index [5,6,7]

The compressibility index of the granules was determined by Carr's compressibility index which was calculated by using the following formula:

Carr's index (%) = [(TD-BD) ×100]/TD

Hausner's factor [5,6,7]
Hausner found that the ratio DF/DO was related to inter particle friction and, as such, could be used to predict powder flow properties. It is calculated by using the following formula:

Hausner's factor = TD/BD

Where,
TD is Tapped bulk density and BD is loose bulk density.

Angle of repose [5,6,7]
The flow properties are critical for an efficient tableting operation. A good flow property of the powder or granulation is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. In some cases, dry powder has to be pregranulated to improve their flow properties. During the pre-formulation, the flow ability of the drug and granulation should be studied especially when the anticipated dose of the drug is large. When a heap of powder is allowed to stand with only the gravitational force acting on it, the angle between the free surface of the static heap and the horizontal plane can achieve a certain maximum value for a given powder. This angle is defined as the static angle of repose and is a common way of explaining flow characteristics of powder granulation. In most pharmaceutical powders and granules, the angle of repose values range from 25-40° and lower values indicating better flow characteristics.

The angle of repose is defined as the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

Tan = h/r

Where,
h and r are the height and radius of the powder cone

EVALUATION OF TABLETS
The formulated tablets were evaluated for the following physicochemical parameters.

Thickness [5,6,7,8]
The thickness of tablet can vary without any change in weight. This is generally due to the differences of density of granules, pressure applied for compression and the speed of compression. It was measured by vernier caliper.

Hardness [5,6,7,8]
Tablets require certain amount of strength to have a resistance from breakage, while transportation and handling before use. It was measured by Monsanto Hardness Tester. The test was performed on six tablets and the average was calculated.

Friability test [5,6,7,8]
The friability of the tablet was determined by using friabilator. It is expressed in percentage (%).Twenty tablets were initially weighed (W_1) and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 minutes in which tablets are subjected to combined effect of shock and abrasion in a plastic chamber dropping the tablets at a height of 6 inch in each revolution. The tablets were de dusted and weighed again (W_2). The friability(%) was calculated.

% friability = (W_1 - W_2 / W_1) × 100

Where,
W_1 = weight of tablets before test
W2 = weight of tablets after test

Weight variation test [5,6,7,8]
Twenty tablets were selected randomly and weighed individually. Average weight of tablets was calculated and compared with that of the individual tablets. For the tablet to be accepted, the weight of not more than two tablets deviate from the average weight by not more than 7.5%.

Disintegration time [9,10]
The disintegration time was performed by using an USP disintegration test apparatus with distilled water at 37±0.5°C. The disintegration time was taken to be the time when no granules of any tablets were left on the mesh of the apparatus. The time reported to obtain complete disintegration of six tablets were recorded. The mean disintegration time and standard deviations were calculated.

Wetting time [5,6,7,8]
Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. The water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

It is obvious that pores 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 is the important step for is integration process to take place. A piece of tissue paper folded double was placed in a petri dish (internal diameter is 6.5 cm) containing 6mL of water. The 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 ^{0}C. Wetting-time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

Content uniformity test [5,6,7,8]
Twenty tablets from each batch were powdered and weighed accurately. The drug content was determined using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations. Weighed quantity of powder samples were diluted suitably and analyzed for cumulative drug release by using UV.

Dissolution Studies [11]
The release rate of formulated memantine HCl was determined using USP dissolution testing apparatus II (Electro Lab, India). The dissolution test was performed by using 900 ml phosphate buffer of pH 6.8 as a dissolution medium at 37±0.5°C temperature and speed 50 rpm. Sample of 10ml was withdrawn at regular interval of minutes and replaced with fresh medium to maintain sink condition and the percentage of drug release was determined by using UV spectrophotometer at 282 nm.

Stability studies as per the ICH guidelines [12]
Stability studies performed on final batch as per ICH guidelines for 60 days at 40°C±2°C/75% RH±5%. Samples were withdrawn at 0, 3 and 6 months intervals and evaluated for their physical property, disintegration time and *in vitro* drug release.

RESULTS AND DISCUSSION

Evaluation of granules
A granule is an aggregation of component particles that is held together by the presence of bonds of finite strength. Direct compression method was, therefore, used in the present study. Physical properties of granules such as specific surface area, shape, hardness, surface characteristics and size can significantly affect the rate of dissolution of drugs contained in a heterogeneous formulation. The granules of all drug formulations were evaluated for angle of repose, loose bulk density (BD), tapped density (TD), compressibility index (CI) and Hausner's ratio. The results were obtained are shown in table 2. The powder was too cohesive to flow through the funnel, where as the angle of repose values for granules were ranged from 33°09' to 39°14'respectively. The Hausner's ratio values of the prepared memantine granules were ranged from 1.15 to 1.24. The latter was thought to indicate good flow properties of the prepared granules.

The percentage compressibility, an indirect method of measuring powder flow ability from bulk densities developed by Carr. The percentage compressibility of memantine was found to be in the range of 13.11 to 19.40. This result was in good agreement with the results of angle of repose, supporting the idea that granulation improved both flow

ability and compressibility. Finally, the disintegrates level and disintegrates type did not affect the physical properties of the granules markedly. These results were found to be considered satisfactory. The batches formulated with mannitol was used for ensuring the better flow of the granules with the various disintegrant used with various concentration. This can be attributed to the inherent quality of mannitol having better compressibility. From all the formulation the camphor at various concentrations were added in order to decrease the disintegrating time and wetting time. This data also reveals that an increase in the ratio of diluents to drug contributes for the better compressibility index of the granules for memantine formulations.

Table 2: Flow properties of powder blend

S.No	Angle of Repose (θ)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's Ratio	Carr's Index
F1	39.14±0.022	0.52±0.34	0.63±0.004	1.21±0.03	17.46±2.41
F2	37.64±0.051	0.54±0.56	0.67±0.02	1.24±0.06	19.4±1.19
F3	36.07±0.034	0.52±0.56	0.62±0.06	1.19±0.02	16.12±1.56
F4	38.28±0.087	0.5±0.45	0.61±0.008	1.22±0.02	18.03±1.92
F5	37.79±0.031	0.51±0.72	0.62±0.03	1.21±0.04	17.74±2.04
F6	36.34±0.023	0.51±0.04	0.61±0.045	1.196±0.09	16.39±2.41
F7	38.02±0.045	0.49±0.22	0.6±0.021	1.22±0.02	18.33±0.91
F8	34.83±0.067	0.51±0.24	0.6±0.024	1.1760.03	15±1.02
F9	33.09±0.056	0.53±0.27	0.61±0.047	1.15±0.02	13.11±0.67

Evaluation of memantine orodispersible tablets

The oral disintegrating tablets of memantine hydrochloride were prepared by employing disintegrant at various concentrations by direct compression method using sublimation approach. The physical properties of different batches of developed oral disintegrating tablets are given in table 3 for memantine respectively. These properties were studied by determining average weight, thickness, drug content, hardness, friability, disintegration time and wetting time of the prepared tablets. The average percentage of deviation of 20 tablets of each formula is less than 3%, hence all the formulations passes the test for uniformity of weight as per official requirements. The thickness of the prepared memantine tablets was ranged from 1.2 - 1.8 mm. It was also observed that increasing the disintegrant concentration resulted in no alteration in the thickness of the tablets formulation significantly. These results might indicate that the disintegrant does not alter the binding property of the formulations. Good uniformity in drug content is found among the different batches of tablets as all the values are within 96.3% to 99.2% of the labeled claim. In general, increase in the concentration of polymer contributes to higher hardness values. The hardness is, however, not an absolute indicator of strength. Hardness of the prepared tablets fell in the range of 2.4 - 3.7 kg/cm^2. The friability of the prepared tablets fell into the range of 0.25 to 0.61%. The European Pharmacopoeia states that loss up to 1% is acceptable. Therefore, these results were considered satisfactory. There was no marked difference in the friability observed with the tablets prepared using different disintegrant concentrations. These findings were in good agreement with the results of thickness measurement, supporting the idea that the used disintegrant does not alter the binding properties. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the specifications for weight variation, drug content, hardness and friability.

Table 3: Physical characteristics of formulated tablets

S.No	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm)	1.20± 0.26	1.2± 0.23	1.3± 0.70	1.6± 0.38	1.6± 0.21	1.7± 0.24	1.7± 0.53	1.6± 0.38	1.8± 0.21
Hardness (kg/cm^2)	2.5± 0.19	2.4± 0.23	2.7± 0.19	3.3± 0.27	3.2± 0.18	3.4± 0.29	3.4± 0.13	3.6± 0.11	3.7± 0.16
Friability (%)	0.54± 0.32	0.61 ±0.41	0.41 ±0.23	0.39 ±0.67	0.33± 0.56	0.31± 0.61	0.3± 0.24	0.28± 0.21	0.25± 0.27
Disintegration Time (sec)	38± 1.3	29± 1.5	24± 1.3	32± 1.4	27± 1.7	25± 1.3	20± 1.4	16± 1.2	11± 1.3
Wetting Time (sec)	40± 0.9	32± 0.7	28± 1.3	35± 1.7	30± 0.9	37± 1.2	22± 0.6	17± 0.9	15± 0.6
Weight Variation (mg)	102± 0.45	99± 0.32	99± 0.63	103± 0.49	101± 0.13	102± 0.34	98± 0.42	99± 0.45	101± 0.13
Drug content (%)	96.3	97.5	98.7	97.9	98.5	98.3	96.9	98.1	99.2

***In vitro* release studies of developed memantine hydrochloride orodispersible tablets**

A suitable *in vitro* dissolution method serves as a valuable quality control tool to assess batch to batch release performance and to assure the physiological availability of the drug. The *in vitro* dissolution test is also used to

guide formulation development and to monitor manufacturing processes. As a regulatory test, it is used to approve minor changes in formulation, changes in the site of manufacturing and also to assess the scale up of the bio-batch to the production batch. All the batches have shown that as the disintegrant concentration increases. The drug release rates for memantine orodispersible tablets are shown in table 4 and figure 1. However, the drug releases from these tablets were found to increase with increase in the concentration of disintegrant used in the formulation. Thus, it can be concluded that *in vitro* release of drugs is a direct function of its solubility in the dissolution medium.

Table 4: Dissolution parameters of formulated tablets

Time	% Drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2 min	24.3	28.7	32.5	35.2	38.5	38.9	39.3	39.5	40.4
4 min	34.7	46.7	57.4	49.4	50.2	60.7	74.1	76.1	78.4
6 min	45.3	54.3	65.2	64.7	66	67	79.6	80.8	82.2
8 min	52.6	64.4	68	69.9	68.7	76.8	81.4	82.3	83.5
10 min	59	69.3	71.9	73.2	77.3	78.3	83.5	91	92.1
12 min	65.8	72.5	74.3	79.5	79.5	82.4	90	92.5	93
14 min	71.2	74.9	79.8	83.1	84.2	86.9	91.2	93.3	95.1
16 min	74.9	78	82.4	88.6	89.6	91.1	92.3	95.4	96.7
18 min	77.5	82.2	86.1	90	91	92.8	93.8	96.7	97.9
20 min	83.4	85.6	89.5	91.5	92.9	94.4	95.9	97.2	99.7

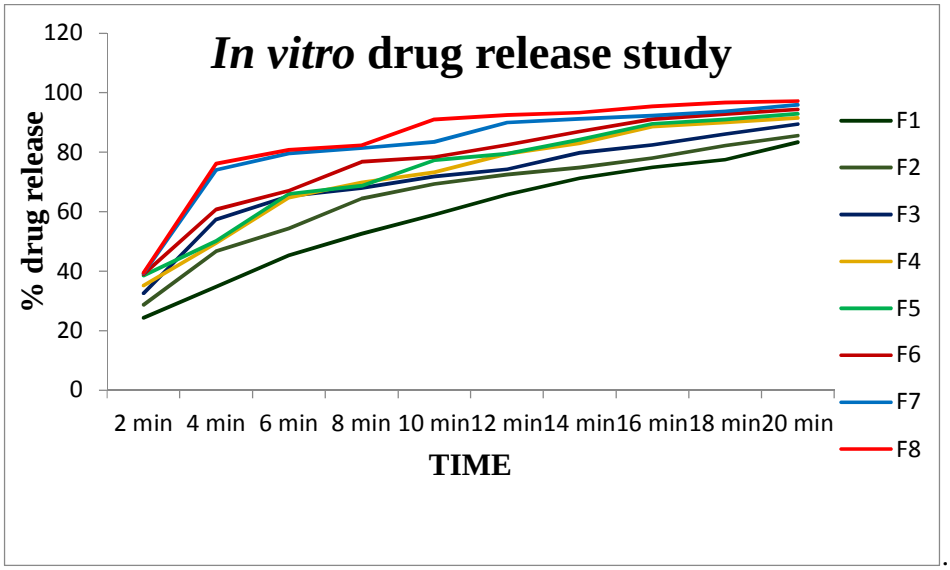

Figure 1: *In vitro* drug release

STABILITY STUDIES

No significant change was observed for the formulated orodispersible tablets of memantine with respect to its physicochemical parameters as evident by table 5. Based on these observations, it was concluded that the developed formulations of memantine tablets were physically and chemically stable and retain their pharmaceutical properties at various temperature and humidity conditions for a period of six months.

Table 5: Stability studies

Test	Stability Results (40 ± 2° C / 75 ± 5%RH)		
	Initial	3rd Month	6th Month
Hardness	3.7	3.5	3.3
Drug Content (%)	99.9	99.3	98.4
Disintegration	11	13	14

CONCLUSION

Orodispersible tablets of memantine hydrochloride could be considered useful oral delivery systems to increase the drug bioavailability. Memantine hydrochloride is bitter drug; Simple flavour and taste enhancers with direct compression technique were sufficient to mask the bitterness of this drug. Compressed tablet process would be an effective, low cost and simple alternative approach compared with the use of more expensive process like lyophilization and adjuvant in the formulation of orodispersible tablets. Low dose, low bitter drugs were successfully prepared by simple direct compression method with taste and flavour enhancers. Among the different formulations, F9 by using sublimed agent and high concentration of crospovidone was found as best formulation from evaluation studies.

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