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FORMULATION AND EVALUATION OF MEMANTINE ORAL DISSOLVING FILMS

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ABSTRACT

The invention discloses a memantine hydrochloride oral-dissolving film preparation. The preparation shields a stimulated flavor and is good in appearance. The memantine hydrochloride oral-dissolving film preparation comprises, by weight, 30-50% of memantine hydrochloride, preferentially, 30-40% of memantine hydrochloride, 35-55% of macromolecule film-forming materials, 3.0-15% of flavor corrective, 2-20% of plasticizers and 0-5% of other auxiliary materials. The other auxiliary materials comprise one or two of pigment and flavoring agents. Through increasing the content of the raw material chemicals, selecting the appropriate flavor corrective and the film forming materials and controlling the grain size of the raw material chemicals, the film preparation free of the stimulated flavor, smooth in surface, even in content of chemicals, high in disintegration speed and rapid in absorption is obtained; the film preparation is convenient to take and improves the compliance of a patient. The invention further provides a method of preparing the film preparation and an application of the film preparation in treating the Alzheimer disease.

Keywords: NMDR Agonist, Film Forming Materials and Flavouring Agents.

INTRODUCTION

Among the different routes of administration, the oral route of administration continues to be most preferred route due to various advantages including ease of administration, avoidance of pain, versatility and most importantly patient compliance. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity.

Recently, fast dissolving drug delivery system have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better compliance. These delivery systems either dissolve or disintegrate in mouth rapidly, without requiring any water to aid in swallowing. They also impart unique product differentiation, thus enabling use as line extensions for existing commercial products. This novel drug delivery system can also be beneficial for meeting the current needs of the industry are improved solubility/stability, biological half life and bioavailability enhancement of drugs.

The disadvantage of OS is that high dose cannot be incorporated into the strip.However, research has proven that the concentration level of active can be improvedup to 50% per dose weight.There remain a number of technical limitations with theuse of film strips. The volume of the dosage unit is clearly proportional to the size ofthe dose, which means these extremely thin dosage formsare best suited to lowerdose products. As an example of this, Labtec claim that the Rapid Film technologycan accommodate dose of up to 30 mg. This clearly limits the range of compatibledrugproducts. The other technical challenge with these dosage forms is achieving Dose Uniformity.

METHODOLOGY

Table 1: Ingredients and Manufactures

S. No.	Materials	Source
1.	Memantine	Pharmatrain, Hyderabad
2.	HPMC E15	S.D. Fine chemicals, Mumbai
3.	HPMC E5	S.D. Fine chemicals, Mumbai
4.	Propylene glycol	S.D. Fine chemicals, Mumbai
5.	Sorbitol	S.D. Fine chemicals, Mumbai
6.	Aspartame	S.D. Fine chemicals, Mumbai
7.	Tween 80	S.D. Fine chemicals, Mumbai
8.	citric acid	S.D. Fine chemicals, Mumbai
9.	Flavouring agent	S.D. Fine chemicals, Mumbai

Table 2: Equipment and Companies

S. No.	Name of the Equipment	Model
1	Electronic weighing balance	Scale-Tec
2	UV	Labindia Uv 3000+
3	FTIR	BRUKER
4	Melting point	Remi
5	Sonicator	Elma S 300H
6	Compression machine	Cmd(Cadmach)
7	Tablet hardness tester	Pfizer Hardness Tester, Mumbai
8	Verniercallipers	Cd-6”Cs
9	Friabilator	Roche Friabilator, Electrolab, Mumbai
10	Disintegration	Sisco
11	Dissolution apparatus	Electrolab TDT-08L

Table 3: Formulation of Memantine fast disintegrating films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Memantine	5	5	5	5	5	5	5	5	5
HPMC E15	15	30	45	-	-	-	7.5	15	22.5
HPMC E5	-	-	-	15	30	45	7.5	15	22.5
Propylene glycol	10	10	10	10	10	10	10	10	10
Sorbitol	54	39	24	54	39	24	54	39	24
Aspartame	5	5	5	5	5	5	5	5	5
Tween 80	5	5	5	5	5	5	5	5	5
Saliva stimulating agent (citric acid)	5	5	5	5	5	5	5	5	5
Flavouring agent	1	1	1	1	1	1	1	1	1
Total wt. (mg)	100	100	100	100	100	100	100	100	100

Formulation of Memantine Oral Disintegrating Films

Mouth dissolving film of Memantine was prepared by solvent casting technique. Solution ‘A’ was prepared by dissolving HPMC-E15 polymer in 5 ml of water.

Solution ‘B’ was prepared by dissolving Memantine, Aspartam, Sorbitol & citric acid in 5 ml of ethanol. The solutions ‘A’ and ‘B’ were mixed and stirred for 30min. and add Propylene glycol and tween 80 and flavouring agent and continue stirring for 10mins. The solutions were cast on to glass petri plate of 9 cm diameter and were dried in the oven at 70°C till a peel able film was formed. Then dried films were cut into rectangular shape pieces, with 4.0 cm2 (2.0 cm × 2.0 cm) total surface area. Desired quantity of Memantine was 10 mg (dose of drug) per 4.0 cm2 films.

Calculation

Diameter of the Petridish = 9 cm
Radius = Diameter/2 = 9/2 = 4.5 cm.
πr2 =3.14 X 4.5 X 4.5 = 63.59 cm2
Now, Dose is 5mg and cut the pieces in 2 cm X 2 cm = 4 cm2
4 cm2 contain 5 mg drug
So, 63.59 cm2 contain (?) Drug = 78.487 mg Drug

Evaluation of oral disintegrating films

1. Physical appearance
2. Weight uniformity
3. Thickness uniformity
4. Folding endurance
5. Surface pH
6. Drug content uniformity test
7. Invitro disintegration test
8. Invitro dissolution studies

1. Physical Appearance
This parameter was checked simply with visual inspection for physical appearance of films and evaluation of texture by feel or touch.

2. Weight uniformity of films
Three films of each formulation trial of 2cm*2cm size were taken and weighed individually in electronic balance and the average weights were calculated.

3. Thickness uniformity
All the eight batches were evaluated for thickness by using calibrated Vernier caliper with a least count of 0.01mm. The thickness was measured at three different spots of the films and the average was taken.

4. Folding endurance
The folding endurance was measured manually for the prepared films. The flexibility of films can be measured quantitatively in terms of folding endurance. A strip of film was cut (approximately 2*2cm) and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

5. Surface pH
Surface pH was found out by placing the film on the surface of 1ml of distilled water. The surface pH was noted by bringing pH paper near the surface of the films and allowing it to equilibrate for 1min. The change in the colour of pH paper was observed

6. Drug content uniformity test
Drug content uniformity of all nine batches was determined by UV-Spectrophotometric method. For this, each strip at three different places equivalent to 2mg of drug was cut and dissolved in 50ml of 6.8 Ph phosphate buffer solution with continuous stirring. This solution was filtered using Whattmann filter paper, and the filtrate was diluted to 100ml with the same buffer in a volumetric flask. This solution was analyzed by U.V.Spectrophotometer and the absorbance was recorded at 229nm. Drug content was calculated by using calibration curve of drug.

7. Invitro disintegration test
In vitro disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

8. Invitro dissolution studies
The in vitro dissolution test was performed in a Ph. Eur. 6.4 Ed. Paddle dissolution apparatus. The dissolution medium consisted of 900 mL 6.8pH phosphate buffer solution, maintained at 37±0.5°C and stirred at 50 rpm. One film was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and drug release was analyzed spectrophotometrically at 229nm. The volume withdrawn at each interval was replaced with freshly quantity of dissolution medium.
Cumulative percent drug release of Memantine was calculated and plotted against time.

9. In vitro Release Kinetics Studies
The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from IR was described by using zero order kinetics or first order kinetics.

A. Zero Order Release Kinetics
It defines a linear relationship between the fractions of drug released versus time.

$$Q=k_0t.$$

Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

B. First Order Release Kinetics
Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release pellets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

$$\text{Log } C = \text{Log } C_o - kt/2.303$$

Where C is the amount of drug dissolved at time t,
C_o is the amount of drug dissolved at t=0 and
k is the first order rate constant.
A graph of log cumulative of log % drug remaining Vs time yields a straight line. Will be linear if the release obeys the first order release kinetics.

RESULTSAND DISCUSSION
1. Construction of Standard calibration curve of Memantine in 6.8 phosphate buffer
The absorbance of the solution was measured at 229nm, using UV spectrometer with 7.4 phosphate buffer as blank. The values are shown in table. A graph of absorbance Vs Concentration was plotted which indicated in

compliance to Beer's law in the concentration range 2 to 10 µg/ml.

Table 4: Standard Calibration graph values of Memantine 6.8 phosphate buffer at λMax =229 nm

Concentration (µg/ml)	Absorbance
0	0
2	0.154
4	0.287
6	0.422
8	0.574
10	0.703

Standard plot of Memantine plotted by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown fig.

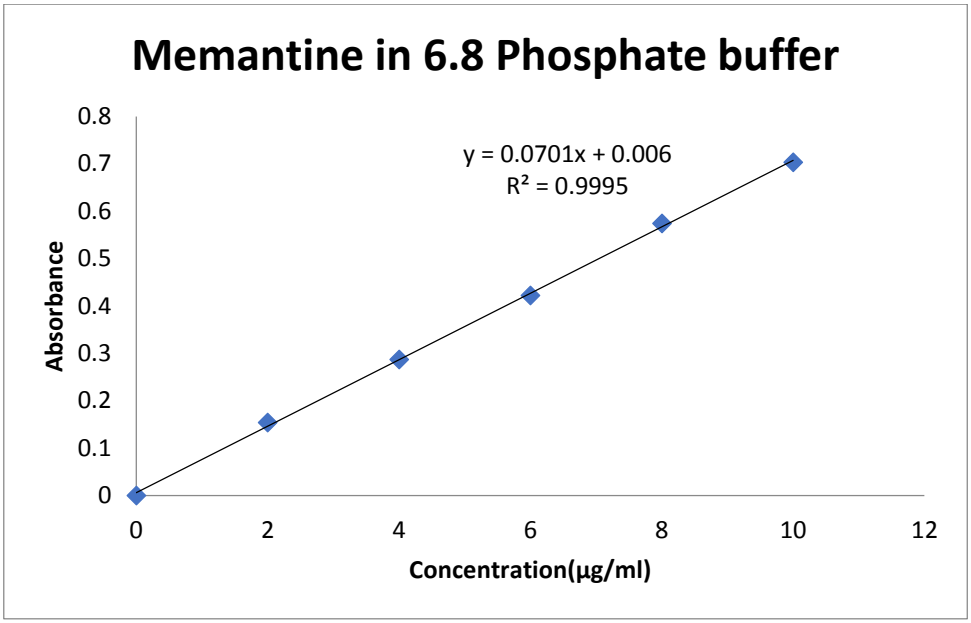

Fig. 1: Standard calibration curve of Memantine in 6.8 phosphate buffer

Inference

The standard calibration curve of Memantine in 6.8 phosphate buffer showed good correlation with regression value of 0.998.

Table 5: Evaluation parameters of Memantine Oral disintegrating films

Formulation code	Appearance	Thickness (mm)	% Weight variation	Folding endurance	% Assay	Disintegration time(sec)
F0	Smooth and Transparent	0.234	3.4	41	99.94	102
F1	Smooth and Transparent	0.234	4.1	42	99.13	19
F2	Smooth and Transparent	0.271	0.5	51	98.79	24
F3	Smooth and Transparent	0.268	3.3	48	100.53	27
F4	Smooth and Transparent	0.247	3.3	57	100.17	27
F5	Smooth and Transparent	0.257	4.2	54	99.48	32
F6	Smooth and Transparent	0.234	4.3	49	101.07	28
F7	Smooth and Transparent	0.229	2.1	45	100.29	26
F8	Smooth and Transparent	0.265	3.6	39	99.37	23
F9	Smooth and Transparent	0.263	2.3	49	99.93	21

Inference

The observation by visual inspection of films and by feel or touch, it explains that the films are having smooth surface and they are elegant enough to see.

The thicknesses of the films were in the range of 0.229 mm to 0.271mm.

The weights of the films were found to be in the range of ±10%.

Folding endurance of the films was found to be in the range of 39 to 57.

The surface pH of all the films were found to be neutral as there was no colour change in the litmus paper.

The drug content uniformity is performed by taking three films in each formulation trial and the average drug content was calculated. And all the films were found to be 98 to 102.

The disintegration time of the prepared films were in the range of 19sec to 102sec.

Table 6: In-vitro drug release data of formulation

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	**0**
5	22.47	23.68	25.15	25.49	25.89	31.61	27.31	32.58	**36.12**
10	45.51	52.37	55.89	48.62	54.24	59.45	52.55	57.79	**77.45**
15	62.68	80.49	81.18	71.53	77.68	78.62	78.41	79.38	**99.72**
20	79.11	99.74	99.83	95.62	99.31	99.55	89.62	95.21	
25	94.71			99.92			99.45	99.85	
30	99.52								

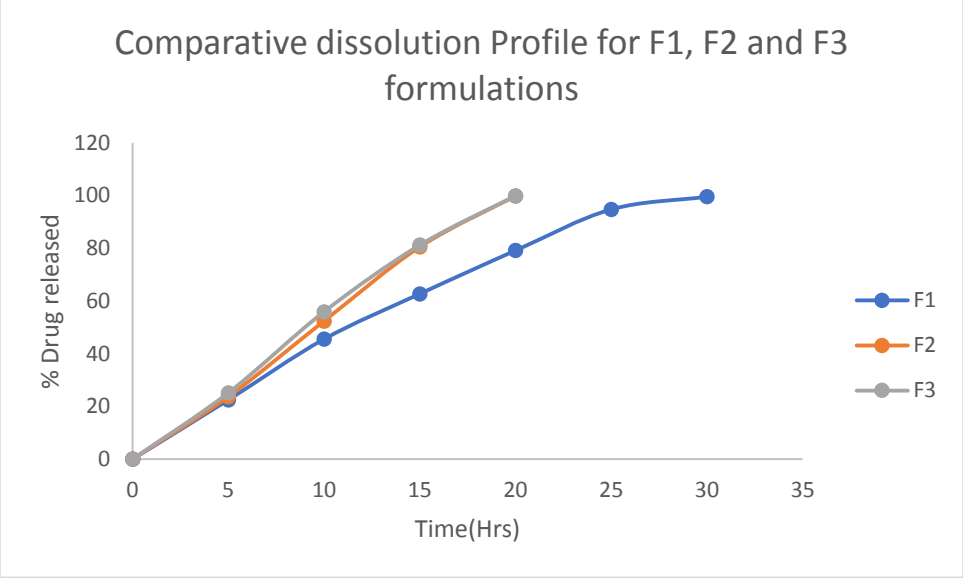

Fig. 2: Comparative Dissolution profile forF1, F2 and F3 formulations

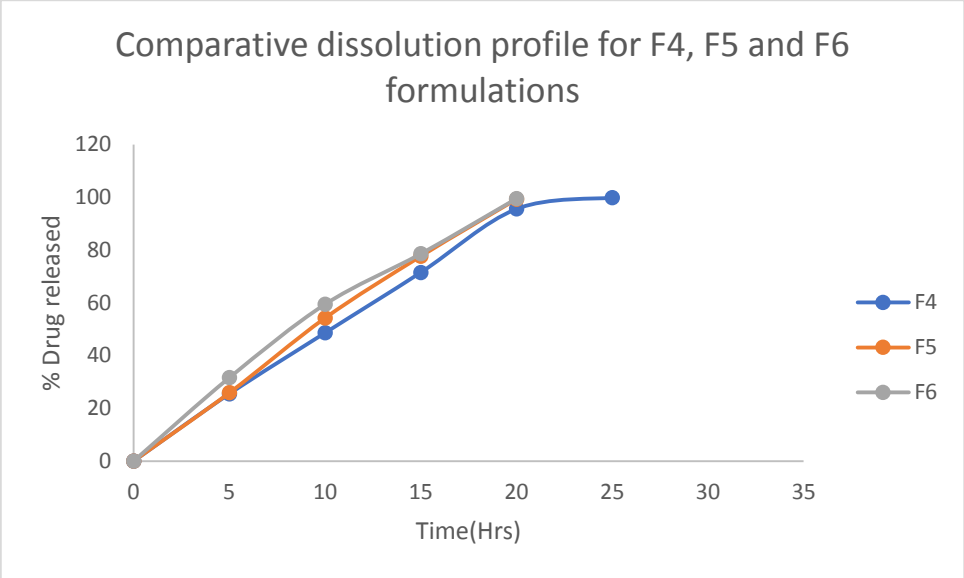

Fig. 3: Comparative Dissolution profile for F4, F5 and F6 formulations

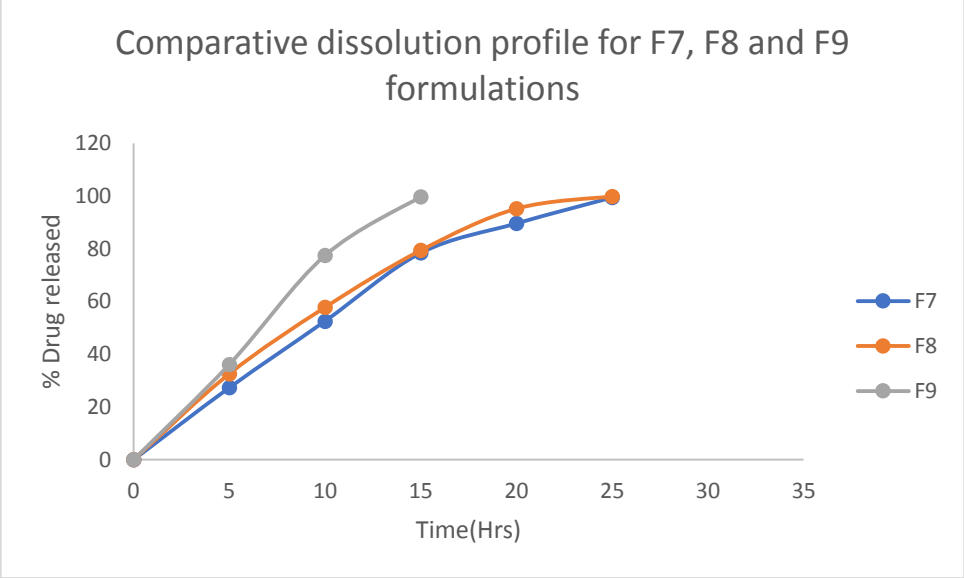

Fig. 4: Comparative Dissolution profile for F7, F8 and F9 formulations

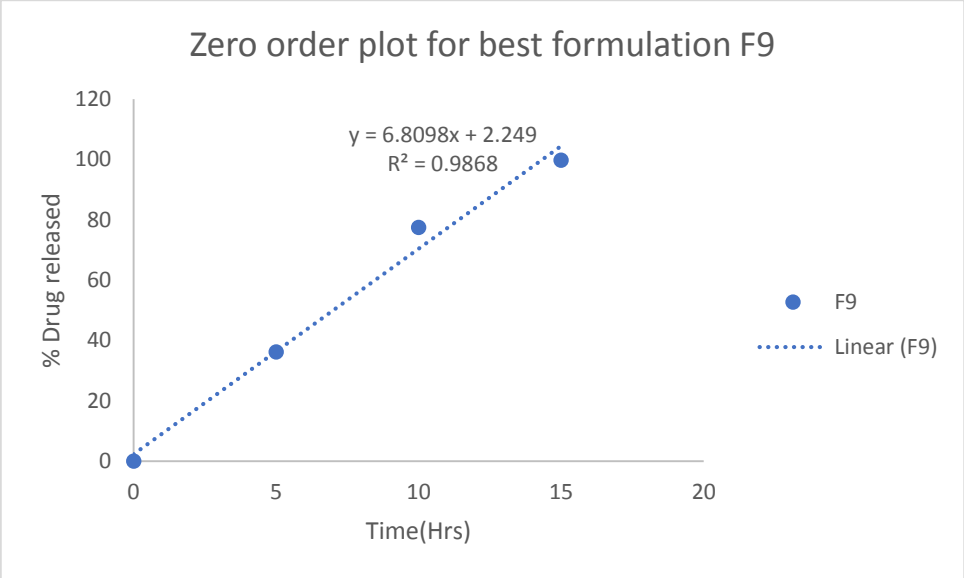

Fig. 5: Zero order plot for best formulation F9

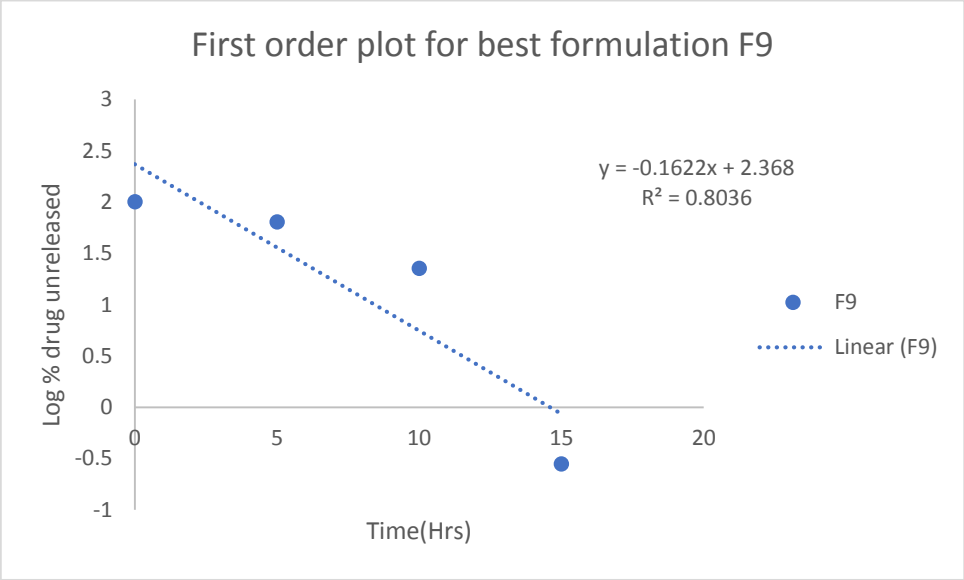

Fig. 6: First order plot for best formulation F9

Table 7: R^2 Values for all formulations

Formulation code	Zero order	First order
F9	0.986	0.803

SUMMARY AND CONCLUSION

- Memantine orally disintegrating films were successfully prepared with HPMC E15 and HPMC E5 combination.
- The observation by visual inspection of films and by feel or touch, it explains that the films are having smooth surface and they are elegant enough to see.
- *The thicknesses of the films were in the range of* 0.229 m*m to 0.*271m*m.*
- *The weights of the films were found to be in the range of* ±10%*.*
- *Folding endurance of the films was found to be in the range of* 39 to 57*.*
- *The drug content uniformity is performed by taking three films in each formulation trial and the average drug content was calculated. And all the films were found to be 98 to 102.*
- The disintegration time of the prepared films were in the range of 19sec to 102sec.

- Acceptable mechanical properties were obtained in the batch F-3 and the in - vitro disintegration time was below of 21 sec.
- It was concluded that formulations F-3 were found to be satisfactory batch and were optimized for the desirable properties.
- Formulation F3 follows First order.

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