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FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILM OF MEMANTINE HYDROCHLORIDE

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ABSTRACT

Mouth dissolving films are solid dosage form that disintegrates or dissolves within a minute when placed in the mouth facilitating the rapid absorption thereby reducing the first pass metabolism. The aim of this study is to formulate and evaluate the fast dissolving oral film of Memantine hydrochloride which is used in the treatment of Alzheimer's disease. The films were prepared by using hydroxyl propyl methyl cellulose E5 as a film based synthetic polymers by solvent casting method. The formulated Memantine hydrochloride fast dissolving oral films were found to be acceptable when evaluated for weight uniformity, thickness, drug content, in-vitro drug release, folding endurance and disintegration time. The film was disintegrated within thirty seconds to release drug rapidly.

Keywords: Memantine hydrochloride, mouth dissolving film, solvent casting method and hydroxyl propyl methyl cellulose

INTRODUCTION

Oral drug delivery system is most preferred route as it aids in non-invasiveness, compliance by the patient, easy administration, self-medication, acceptability and adaptability **[1, 2]**. In oral route of drug administration many alternatives have continuously been presented by using recent novel technologies for pediatrics, geriatrics, nauseous and non-compliance patients **[3, 4]**. Quick dispersing or dissolving oral drug

delivery systems is a novel technique serves as an alternative to conventional route of drug administration. It is defined as an oral drug delivery systems that dissolve or disintegrate within seconds after placement in the mouth or the oral cavity and do not require water to aid in swallowing **[5, 6]**. These systems include tablets, caplets, wafers, films, granules and powders. Among various dosage forms, the use of polymeric films for delivering medication into oral cavity has developed great potential recently **[7, 8]**.

The development of mouth dissolving films of Memantine hydrochloride for Alzheimer's disease which is a chronic neurodegenerative disease initially starts slowly and over time worsens **[9]**. 60-70% cases of dementia are caused by Alzheimer's disease includes difficulty in remembering recent events as an early symptom. With advancement in diseased condition symptoms such as problems with language (including easily getting lost), mood swings, and behavioral issues are observed. Death occurs when the body functions are lost in severe conditions **[10]**. Memantine is used to treat moderate to severe dementia related to Alzheimer's disease and improves memory, awareness, and the ability to perform daily functions **[11]**. The aim of the present work was to formulate and evaluate mouth dissolving film of Memantine hydrochloride.

MATERIALS AND METHOD

Drugs and chemicals

Memantine hydrochloride was procured from Medley Pharmaceuticals Ltd., Mumbai and other excipients such as (Hydroxyl propyl methyl cellulose) HPMC E- 3, HPMC E - 5, HPMC E - 6, HPMC E - 15, PVA (Poly vinyl alcohol), PEG (Polyethylene glycol), Phullulan of analytical grade, Glycerin, Methanol, distilled water were purchased from vendors.

Development of formulation

Solvent casting method was used for the formulation of films **[12, 13]**. A polymeric solution (solution A) and drug solution (solution B) were prepared and mixed by magnetic stirrer for 15 minutes followed by addition of glycerin and citric acid and kept on magnetic stirring for 1 hour **[14, 15]**. Then the solution was casted on petri-plate which was then dried in oven at 60° Celsius for about 5 - 6 hours until a dried film was obtained **[16]**. Different trial batches were made by using water and methanol as solvent as shown in the **Table 1, 2, 3, 4, 5 and 6**.

Table 1: Trial with Methocel E5 and methanol as a solvent

Objective	Feasibility trial with HPMC E-5			Observation
Trial	A	B	C	
Memantine HCl	10.0 mg	10.0 mg	10.0 mg	Separation of drug is observed in all three trials
HPMC E- 5	400.0 mg	600.0 mg	800.0 mg	
Glycerine	2 ml	2 ml	2 ml	
Citric Acid	225 mg	225 mg	225 mg	
Methanol	20 ml	20 ml	20 ml	

Table 2: Trial with Pullulan and methanol as solvent

Objective	Feasibility trial with Pullulan			Observation
Trial	A	B	C	
Memantine HCl	10.0 mg	10.0 mg	10.0 mg	Feathery Crystallization is observed in above trials
Pullulan	400.0 mg	600.0 mg	800.0 mg	
Glycerine	2 ml	2 ml	2 ml	
Citric Acid	25 mg	25 mg	25 mg	
Methanol	20 ml	20 ml	20 ml	

Table 3: Trial with PVP K-30 and methanol as solvent

Objective	Feasibility trial with PVP K-30			Observation
Trial	A	B	C	
Memantine HCl	10.0 mg	10.0 mg	10.0 mg	Crystallization is observed in all three trials
PVP K-30	400.0 mg	600.0 mg	800.0 mg	
Glycerine	2 ml	2 ml	2 ml	
Citric Acid	25 mg	25 mg	25 mg	
Methanol	20 ml	20 ml	20 ml	

Table 4: Trial with PVA and methanol as a solvent

Objective	Feasibility trial with PVP K-30			Observation
Trial	A	B	C	
Memantine HCl	10.0 mg	10.0 mg	10.0 mg	Slight Crystallisation is observed in all three trials.
PVA	500.0 mg	700.0 mg	1000.0 mg	
Glycerine	2 ml	2 ml	2 ml	
Citric Acid	25 mg	25 mg	25 mg	
Methanol	20 ml	20 ml	20 ml	

Table 5: Trial with PVA and HPMC and methanol as solvent

Objective	Feasibility trial with PVP K-30			Observation
Trial	A	B	C	
Memantine HCl	10.0 mg	10.0 mg	10.0 mg	Trial A and B were Transparent and clear. C was with slight separation of drug. So only Trial A and B were evaluated.
PVA	600.0 mg	400.0 mg	200.0 mg	
HPMC	200.0 mg	400.0 mg	600.0 mg	
Glycerine	2 ml	2 ml	2 ml	
Methanol	20 ml	20 ml	20 ml	

Table 6: Trial with optimized formula

Objective	To execute trial batch to study reproducibility of optimized formulation			Observation
Trial	A	B	C	
Memantine HCl	10.0 mg	10.0 mg	10.0 mg	All the optimized trial batches were clear and transparent and further evaluated for acceptance criteria.
PVA	600.0 mg	600.0 mg	600.0 mg	
HPMC	200.0 mg	200.0 mg	200.0 mg	
Glycerine	2 ml	2 ml	2 ml	
Methanol	20 ml	20 ml	20 ml	

RESULT AND DISCUSSION

Determination of λ max of Memantine hydrochloride in phosphate buffer pH 6.8

Standard Stock solution was prepared by dissolving 100 mg of drug in 100 ml of suitable solvent to get the concentration of 1000 µg/ml. From the stock solution 10 µg/ml was prepared and UV scan was taken between 400 to 800 nm. The absorption maximum was found to be 546 nm. The spectrum is shown in the **Figure 1**.

Study of IR spectrum of Memantine hydrochloride

The compatibility of drug in formulation was confirmed by IR spectra of pure drug and formulations using Shimadzu FTIR. The FTIR spectrum of pure drug of Memantine hydrochloride shows peak according to chemical groups present as shown in the **Figure 2 and Table 7**.

Preformulation studies of Memantine hydrochloride and excipients compatibility by IR spectroscopy

Interpretation of IR Spectrum of Memantine hydrochloride + E5 shows the peak according to chemical groups as shown in the **Figure 3 and Table 8**. Interpretation of IR Spectrum of Memantine hydrochloride + E5 + PVA shows the peak according to chemical groups as shown in the **Figure 4 and Table 9**. From the overlay FTIR spectra of pure drug Memantine hydrochloride and excipients used in film, it was observed that there was no considerable change in peak of pure Memantine hydrochloride and combination of Memantine hydrochloride and excipients indicating the absence of defined interaction between drug and excipients.

Evaluation parameters:

Uniformity of Weight: Films were weighed individually at weighing balance and results were obtained in terms of average. A significant difference in weight is reported as change in uniformity of weight **[17]**.

Thickness: Thickness was measured by calibrated dial gauge having as correction factor of 0.01 mm and average is taken by measuring three times. Thickness of film was checked form all the corners of film. 5% mean thickness variation is acceptable in case of thickness testing **[18]**.

Folding Endurance: This test was applied to check integrity and rigidity of oral film. It also gives an idea about the brittleness of film which ultimately suggests the excess or less use of plasticizer. The films were checked for folding endurance by folding it at same point until it breaks **[19]**.

Surface pH: Surface pH plays a key role in formulation of oral film as it is meant to be placed in to mouth. A significant increase or

decrease in the pH of the surface of film may cause irritations to the patient while administration of dosage forms. To find out surface pH of film, it was kept into the petri-dish containing 0.5 ml distilled water for 30 sec. Then the pH of moisten film surface was calculated by using pH electrode or pH paper. Minimum three pH studies were carried out for accurate results **[20]**.

Disintegration test: In this test the 8 cm diameter petri-plate was used which was filled with 10 ml simulated salivary solution. Time was noted after complete dispersion of film in fluid. 6 samples were studied for mean in vitro dispersion time **[21]**.

Elongation test: Elongation test is the stress applied to the film until film gets deformed by means of strain. It can be calculated as

% Elongation = (Increase in film length / original length of film) × 100

In-vitro Drug Release: Dissolution study was done using USP apparatus type II. A dissolution medium of 900 ml of phosphate buffer (pH 6.8) was prepared and maintained at 37 ± 0.5 ºC with stirring speed of 150 rpm. At an interval of 1 min, 5 ml of the sample was withdrawn replacing with same volume of fresh dissolution medium. The absorbance was determined to measure the % drug release by using UV-spectroscopy at 546 nm. **[22]**.

Evaluation Observation

Physical observation complies at all trials except C. The assay of the drug in trial A and B is within specified limits. There is a drop in assay of drug in trial C due to crystallization of drug in the formulation. According to dissolution data, trials A and B are within the limit for in-vitro drug release. The percentage of drug release decreases as drug forms crystals in trial C hence fails in dissolution. Except trial C, other concentrations can be used because of decrease in the in-vitro drug release. For the purpose of Physical appearance of film Trial A was selected as shown in the **Table 10**.

Results of Trial with optimized formula

Reproducibility batches of optimized formula were subjected to respective evaluation parameters. Absorbance of Assay and Dissolution study was carried out at 546 nm. Physical observations were acceptable. All the evaluation parameters were within the range. The percent cumulative drug release was found to be appropriate for kinetics of drug. There was no crystallization in optimized batches. The formulation with optimized batch was stable **(Table 11 and Figure 5)**.

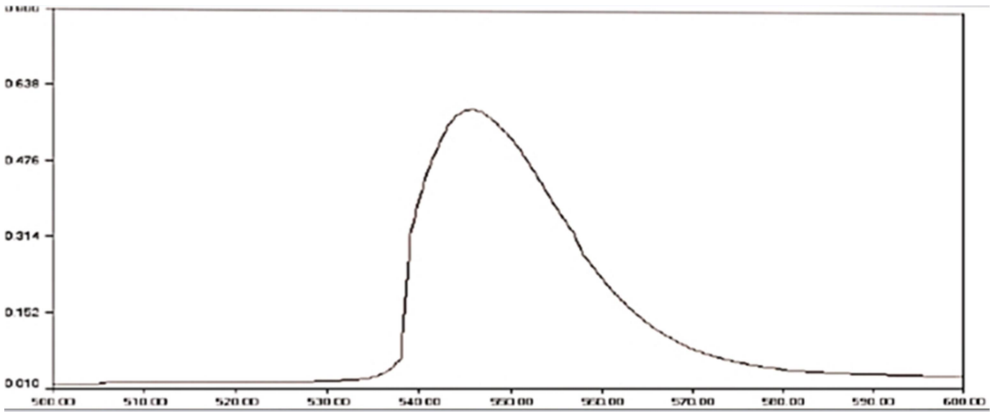

Figure 1: Absorption spectrum of Memantine hydrochloride with eosin

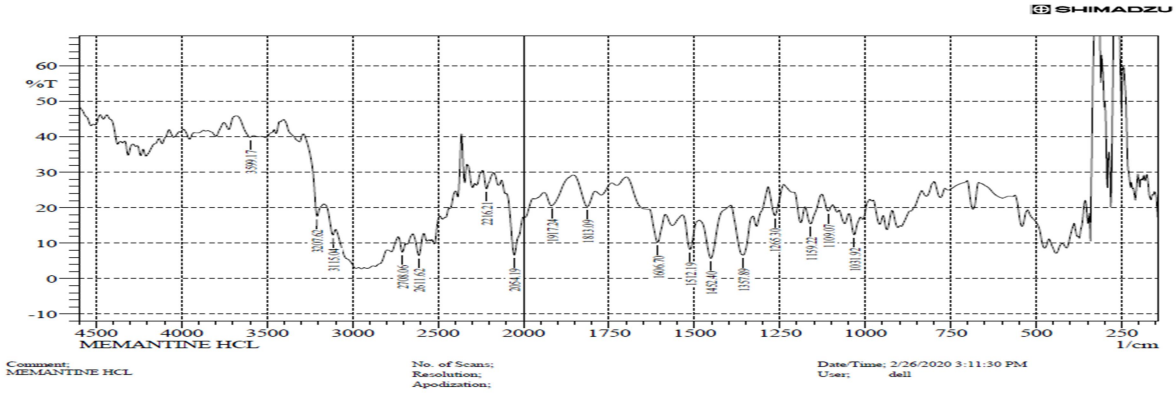

Figure 2: IR Spectrum of Memantine hydrochloride

Table 7: Interpretation of IR data of Memantine hydrochloride

IR Signals (cm^{-1})	Functional groups	Observed Value
3150-3050	CH Stretching	3120
3300-3500	NH Stretching	3350

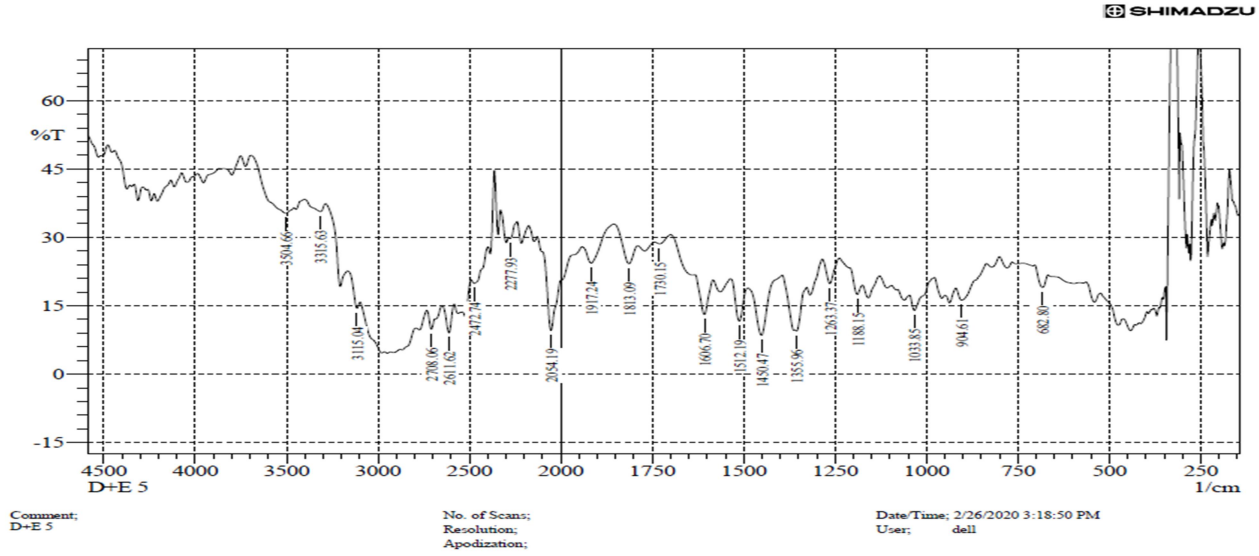

Figure 3: IR Spectrum of Memantine hydrochloride + E5

Table 8: Interpretation of IR spectra of Memantine hydrochloride + E5

Polymer	Wavelength (nm)	Interpretation	Observed Value
HPMC E5	2950, 2900, 2850	Aliphatic C-H stretch	2830
Memantine HCl	3300-3500	N-H strech	3400

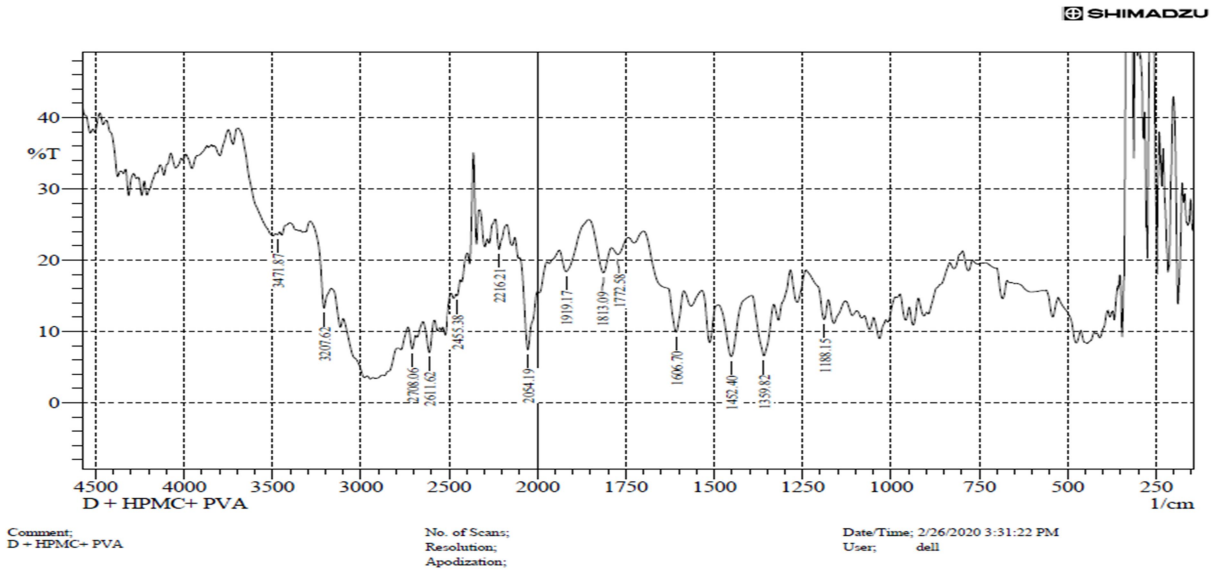

Figure 4: IR Spectra of Memantine hydrochloride + HPMC E5 + PVA

Table 9: Interpretation of IR spectra of Memantine hydrochloride, HPMC E5, Memantine hydrochloride + E5 + PVA

Polymer	Wavelength (nm)	Interpretation	Observed Value
Memantine	3300-3500	N-H stretch	3400
	3150-3050	C-H stretch	3120
HPMC E5	2950, 2900, 2850	Aliphatic C-H stretch	2959
PVA	2900,	Aliphatic C-H stretch	2903
	3400,	O-H stretch for alcohol	3385
	1300	C-O stretch for alcohol	1304

Table 10: Trial with PVA and HPMC using methanol as solvent

Tests	Trials		
	A	B	C
Physical observation	Complies	Complies	Non- Compliance
Weight Uniformity (mg)	120 ± 7	114 ± 11	113 ± 4
Thickness (mm)	0.11 ± 0.05	0.17 ± 0.04	0.23 ± 0.06
Folding Endurance	173	191	205
Percent Elongation	9.66%	11.33%	7.33%
Disintegration (sec)	24	31	48
Assay	80.2%	85.6%	68.2%
In-Vitro Drug Release	101.17%	99.17%	78.4 %

Table 11: Results of Trial with optimized formula

Tests	Trials			
	A	B	C	D (Average)
Physical observation	Complies	Complies	Complies	Complies
Weight Uniformity (mg)	111 ± 5	109 ± 13	114 ± 9	111.3 ± 6
Thickness (mm)	0.17 ± 0.1	0.21 ± 0.02	0.20 ± 0.03	0.19 ± 0.04
Folding Endurance	154	171	179	168
Percent Elongation	9.62 %	6.27 %	8.47 %	8.12 %
	32	29	24	28.33

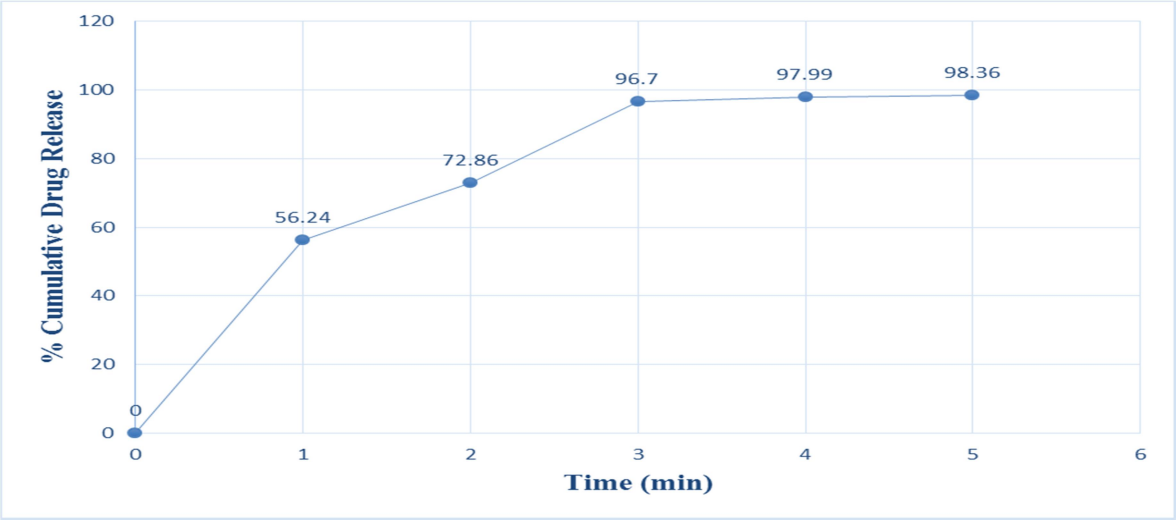

Figure 5: % Cumulative Drug Release (D) of selected optimized batch

CONCLUSION

In present study mouth-dissolving film containing Memantine hydrochloride by solvent casting technique was formulated and evaluated. Compatibility of Memantine hydrochloride with polymers was confirmed by FT-IR studies. Percentage elongation, Tensile strength and folding endurance of the films were enhanced with increase in the concentration of polymer due to rise in the elasticity nature of the polymer. Disintegration time and mouth dissolving time of the films were enhanced with rise in the concentration of the polymer, as extra fluid is required to wet the film in the mouth. Content uniformity analysis revealed that the drug is uniformly distributed in the film. No differences were observed in *in-vitro* dissolution of drug from the film A, B, C and pure drug as the film instantly get wet by dissolution medium. Present study reveals that all the three formulated films showed satisfactory film parameters. Hence Mouth dissolving film containing Memantine hydrochloride exhibited required evaluation parameters and can be a potential novel drug dosage form for pediatric, geriatric and also for general population.

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