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Formulation and evaluation of mouth-dissolving films of memantine

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Abstract

This present research aims to formulate and evaluate mouth dissolving films using Memantine as model drug to improve bioavailability and facilitate rapid onset of action to relieve vomiting and nausea. The thicknesses of the films were in the range of 0.234 mm to 0.271mm. The weights of the films were found to be in the range of ±10%. The folding endurance of the films was found to be in the range of 38± 1 to 57 ± 2. The surface pHs of all the films were neutral, as there was no color change in the litmus paper. All the films were found to be 98 to 102. The disintegration time of the prepared films ranged from 21sec to 32sec. Acceptable mechanical properties were obtained in batch F-9, and the in vitro disintegration time was below 27 sec. It has been determined that formulations F-9 were found to be satisfactory batches and were optimized for the desirable properties.

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INTRODUCTION

Oral medication administration is the most practical, economical, and widely used method of drug delivery. The small intestine is often the primary site of drug absorption, and the amount of drug absorbed via the intestinal epithelium affects the medication's bioavailability. One crucial factor to take into account when administering drugs orally is the first-pass effect. It describes the process of drug metabolism, which frequently results from liver metabolism, in which the drug concentration is greatly reduced prior to entering the systemic circulation [1]. For individuals who can swallow and tolerate oral medication, the oral route is recommended as it is convenient. Some short-half-lives drugs are taken orally in sustained-release or timed-release formulations, which dissolve over several hours. The most common form of treatment for gastrointestinal disorders, both local and systemic, is oral administration. The harsh gastrointestinal tract (GIT) milieu and several physiological barriers, such as gastrointestinal anatomy, biochemistry, and physiology factors, make oral medication administration difficult, even with apparent benefits [2]. Food digestion and medication

Table 1 Formulation of Memantine fast disintegrating films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Memantine	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPMC E15	25	30	35	40	45	50	10	20	30
HPMC E5	-	-	-	-	-	-	30	20	10
Propylene glycol	10	10	10	10	10	10	10	10	10
Sorbitol	34	29	24	19	14	9	19	19	19
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
Flavoring agent	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total wt. (mg)	85	85	85	85	85	85	85	85	85

absorption are significantly influenced by the many components of the gastrointestinal tract (GIT), which include the stomach, esophagus, colon, small intestine, and mouth cavity. Given the extremely low oral bioavailability of oral distribution, nanoparticles have shown considerable promise for drug delivery. Studies have been conducted on inorganic and organic nanoparticles to enhance oral medication targeting, pharmacologic specificity, biodegradability, and tolerability. Oral medications have been administered using a variety of nanocarriers, such as liposomes, emulsions, and nanoparticles. Most nanocarriers have shown benefits in ensuring a regulated release, enhancing absorption from the GIT into the circulatory system, shielding medications from the harsh environment in the GIT, and focusing on specific areas [3].

MATERIALS AND METHODS

MATERIALS

The gift sample Memantine is from Hip Pharma Labs, Hyderabad, and other selected excipients such as HPMC E15, HPMC E5, Propylene glycol, Sorbitol, Aspartame, Tween 80, citric acid, and Flavouring agent are from S.D. Fine chemicals, Mumbai.

METHODS

Fourier Transform – Spectroscopy

FT-IR spectra were recorded on samples prepared in potassium bromide disks using thermal electron FTIR. Samples were prepared in potassium bromide discs using a hydrostatic press. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}. IR spectroscopy has been to quantify the interaction between drug and carrier FTIR spectra of pure drug and best formulation [7].

Formulation of Memantine Mouth dissolving film:

The MDF of Memantine using polymers was prepared using a solvent casting method. An aqueous solution of the polymers was prepared in distilled water. Memantine was added to the aqueous polymeric solution. The addition of plasticizers like Propylene glycol followed this. Sweeteners like aspartame and peppermint flavor were also added to the above solution. The solution was cast on a Petri dish (diameter 9 cm) and dried at room temperature for 24 hr. The film was carefully removed from the Petri dish, checked for imperfections, and cut into the required size to deliver the equivalent dose (2 x 2 cm^2) per strip. The samples were stored in a desiccator at 30-35 % relative humidity until further analysis.

Evaluation of oral disintegrating films

Morphological properties

These criteria were easily verified through visual assessment of the films' physical appearance and sensory or feel evaluation of their texture.

Thickness uniformity

A calibrated Vernier caliper was used to measure the thickness of each of the eight batches, with a minimum count of 0.01mm. Three distinct locations on the films were measured for thickness, and the average was determined.

Weight uniformity of films

Each formulation trial's three 2 cm by 2 cm films were removed and weighed separately on an

electronic balance, and the average weights were determined [9].

Folding endurance

For the prepared films, the folding endurance was measured by hand. The folding endurance of films can be used as a quantitative indicator of their flexibility. A 2*2cm strip of film was cut, then repeatedly folded in the same spot until it broke. The value of folding endurance was determined by counting how many times the film could be folded in the same direction without breaking.

Surface Ph

The surface pH was determined by laying the film on the surface of one millilitre of distilled water. Bringing pH paper close to the film surface and letting it acclimate for a minute allowed us to measure the surface pH. The change in the color of the pH paper was observed

In-vitro disintegration test

In vitro, disintegration time is measured visually in a glass dish filled with 25 milliliters of distilled water, with a 10-second swirl. The disintegration time is the time when the film starts to break or disintegrate [10].

Invitro dissolution studies

A paddle dissolution device was used for the in vitro dissolution test. The 900 mL 6.8 pH phosphate buffer solution was the dissolving medium, which was swirled at 50 rpm and kept at 37±0.5°C. Every test used a single film. At predetermined intervals, five milliliter samples of the dissolving liquid were removed using a syringe equipped with a pre-filter, and the drug release was measured spectrophotometrically at 280 nm. Every time a volume withdrawal occurred, a new dissolving medium was added. Memantine's cumulative percent drug release was computed and shown against time.

9. In vitro Release Kinetics Studies

Analyzing the drug release mechanism from a pharmaceutical dosage form is an essential but complicated process and is practically evident in the case of matrix systems. The order of drug release from IR was described using zero-order kinetics or first-order kinetics [11].

A. Zero Order Release Kinetics

It defines a linear relationship between the fractions of drug released versus time.

$Q=k_0t$.

B. First Order Release Kinetics

Assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process, Wagner suggested that the first-order kinetics could adequately describe the drug release from most of the slow-release pellets. The equation that describes first-order kinetics is

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

A graph of log cumulative of log % drug remaining Vs. Time yields a straight line. It will be linear if the release obeys the first-order release kinetics.

STABILITY STUDIES

Understanding the pharmacological substance's intrinsic stability is essential while creating a solid dosage form. To have an idea of what excipients to use, as well as how best to put them together with the drug and to know that no toxic substances are formed. Limits of acceptability and, therefore, compromises must be reasonably defined. Because the measurements of these stability aspects and the determination of shelf life or expiration date for the final dosage form require long term stability studies for confirmation, they can be expensive and time-consuming. Consequently, it is necessary to define those study designs and conditions that show the most excellent probability of success. Therefore, a stability study's objective is to identify and help avoid or control situations where the stability of the active ingredient may be compromised. For a drug substance to be developed into a tablet dosage form, this objective may be achieved by investigating the stability of the drug under the following three categories: (1) solid-state stability of the drug alone, (2) compatibility studies in the presence of excipients, (3) solution phase stability [12].

RESULTS AND DISCUSSION

Compatibility Studies: FTIR Study

FTIR spectroscopy has been to quantify the no interaction between drug and carrier.

Table 2 Evaluation parameters of Memantine FDF

Formulation code	Appearance	Thickness (mm)	Weight variation	Folding endurance	% Assay	Dintegration time (sec)
F1	Smooth and Transparent	0.234	87	42	99.13	19
F2	Smooth and Transparent	0.271	91	51	98.79	24
F3	Smooth and Transparent	0.263	83	38	99.82	21
F4	Smooth and Transparent	0.247	85	57	100.17	27
F5	Smooth and Transparent	0.257	87	54	99.48	32
F6	Smooth and Transparent	0.234	90	49	101.07	28
F7	Smooth and Transparent	0.238	86	45	100.29	26
F8	Smooth and Transparent	0.265	91	39	99.37	23
F9	Smooth and Transparent	0.268	87	48	100.53	27

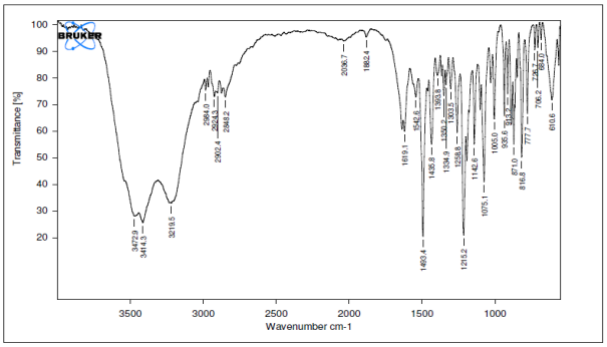

Figure 1 FTIR Spectrum for Memantine

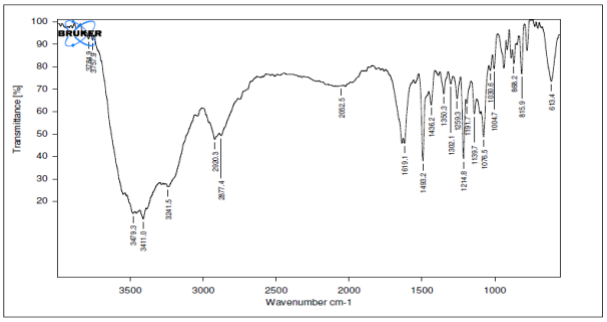

Figure 2 FTIR Spectrum for Memantine best formulation

Evaluation of oral disintegrating films

The observation by visual inspection of films and by feel or touch explains that the films have smooth surfaces and are elegant enough to see. The thicknesses of the films were in the range of *0*.234 mm to *0*.271mm. The weights of the films were found to be in the range of ±10%. The folding endurance of the films was found to be in the range of 38± 1 to 57 ± 2. The surface pHs of all the films were neutral, as there was no color change in the litmus paper. Three films were taken for each formulation trial to ensure drug content homogeneity, and the average drug content was determined. All the films were discovered to be between 98 and 102. The prepared films had a disintegration time of between 21 and 32 seconds.

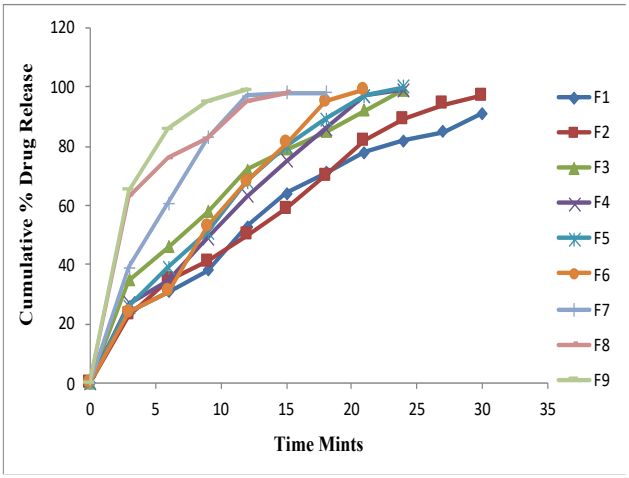

Figure 3 Dissolution profile for all formulations

Table 3 In-vitro drug release data of formulation F1 to F6

TIME (min)	% DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
3	24	23	35	27	26	24	39	63	65
6	31	35	46	35	39	31	61	76	86
9	38	41	58	49	51	53	83	83	95
12	53	50	72	63	68	68	97	95	99
15	64	59	79	75	80	81	98	98	-
18	71	70	85	86	89	95	98	-	-
21	78	82	92	97	97	99	-	-	-
24	82	89	99	99	100	-	-	-	-
27	85	94	-	-	-	-	-	-	-
30	91	97	-	-	-	-	-	-	-

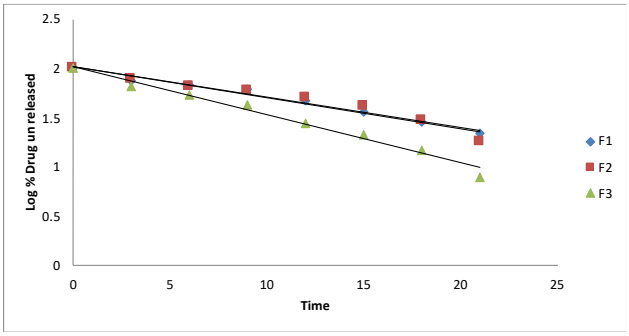

Figure 4 First-order plot for the F1, F2, and F3 formulae

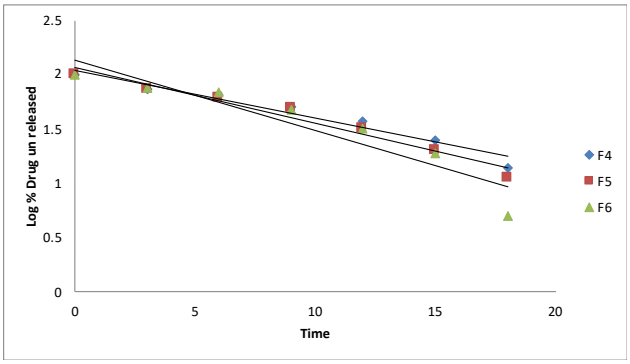

Figure 5 First-order plot for the F4, F5, and F6 formulae

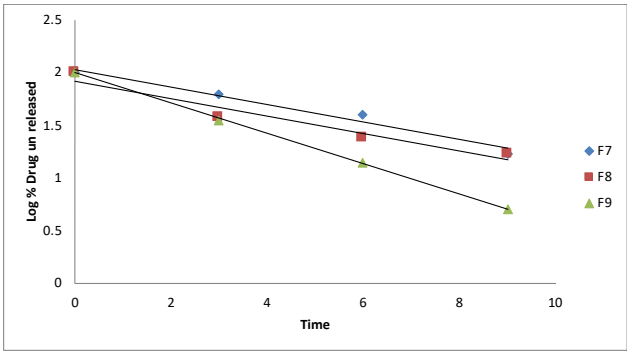

Figure 6 First-order plot for the F7, F8 and F9 formulae

Table 4 R2 Values for best formulation F9

Formulation code	Zero-order	First order
F9	0.789	0.999

STABILITY STUDIES OF PHYSICAL AND CHEMICAL PARAMETERS

Selected formulation F4 was strip packed and stored at 40°C ± 2°C / 75% ± 5% RH for one month. Samples were analyzed and evaluated after storage for one month.

Table 5 In-vitro release profile of F9 during Stability studies (40°C ± 2°C / 75% ± 5% RH)

TIME	Initial	1 Month
0	0	0
3	65	64
6	86	87
9	95	95
12	100	100

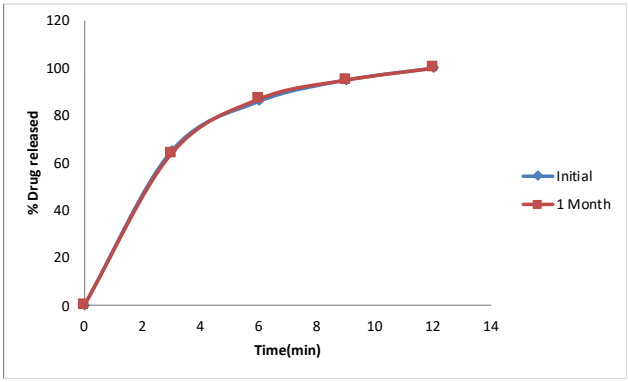

Figure 7 In-vitro release profile of F9 during Stability studies (40°C ± 2°C / 75% ± 5% RH)

CONCLUSION

Memantine orally disintegrating films were effectively made with HPMC E15CPS and HPMC

E15, as well as the HPMC E5 combination. The observation by visual inspection of films and by feel or touch explains that the films have smooth surfaces and are elegant enough to see. The thicknesses of the films ranged from 0.234mm to 0.271mm. The film weights ranged from ±10%. The folding endurance of the films ranged from 38±1 to 57±2. The surface pHs of all the films were neutral, as there was no color change in the litmus paper. And all of the flicks were found to be 98-102. The disintegration times of the prepared films ranged from 21 to 32 seconds. Acceptable mechanical properties were obtained in batch F-9, and the in vitro disintegration time was less than 27 sec. It was determined that formulas F-9 were satisfactory batches optimized for desirable qualities.

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