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Preparation and In-Vitro Evaluation of Mirtazapine Oral Films

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Research Article

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ABSTRACT

Mirtazapine is an antidepressant drug, which affects chemical pathway in the brain that is unbalanced in people with depression. In Mirtazapine oral films HPMC (Hydroxy propyl methyl cellulose) is used as a polymer. The films are prepared by solvent casting method. The prepared batches of films were evaluated for durability, proportion elongation, folding endurance and dissolution. Formulation F3 was found to be promising and it was tested for In-vitro drug release pattern which showed 100% drug release 8mins. The formulation F3 has shown better control over drug release compared to marketed product.

INTRODUCTION

Oral route has achieved such popularity over alternative routes system due to its administration, pain prevention and numerous benefits. Hence, oral administration is that the most generally used technique for general impact, while not being affected of tremendous advancement in drug delivery system. problem in swallowing, resulting in patient's incompliance significantly just in case of paediatric and geriatric, disabled, offensive patients is that the most evident downside of oral indefinite quantity forms like tablets and capsules. Associate improved interest has been addressed to oral solid indefinite quantity forms designed for precise convenience of therapeutic dose. Oral dissolve merchandise (tablets and films) show high levels of patient acceptableness and convenience. Fast-dissolving oral delivery systems are solid indefinite quantity forms, that disintegrate or dissolve within 1min once placed within the mouth while not drinking of water or chewing [1,2]. after disintegration in mouth, increases the clinical potency of the drug through pre-gastric absorption from mouth tubular cavity and muscle system because the secretion passes down into the abdomen. In such cases, bioavailability of drug is considerably above those ascertained from standard pill dosage type.

More recently, Fast-dissolving buccal film drug delivery systems have quickly gained acceptance as a very important new method of administering medication. Fast-dissolving buccal films are usually used for pharmaceutical and Nutraceutical product. It's the most recent frontier in drug delivery technology that has a very convenient suggests that of taking medications and supplements. FDF's are applicable once native action within the mouth is fascinating like local anesthetic for toothaches, oral ulcers, cold sores, or teething [3-5]. Quick dissolving films ready by victimization hydrophilic polymers that quickly dissolve within the mouth within

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few seconds and eliminate the fear of chocking as an alternate to quick dissolving tablets. Primarily the quick dissolving film may be thought of as AN ultra-thin strip of item size with an active pharmaceutical ingredient and alternative excipients. Most quick dissolving films are having taste masking active ingredients. These masked active ingredients are swallowed by the saliva of patients along with the soluble and insoluble excipient [6-7].

Formulation of quick dissolving film involves both aesthetic and performance characteristics similar to strip-forming polymers, plasticizers, API's, flavoring agents, sweetening agents, saliva stimulating agent, coloring agents, stabilizing and thickening agents. From the regulative views, all excipients used in the formulation of oral drug strips should be approved to be used of oral pharmaceutical dosage forms. quick dissolving films evolved over the past few years from the confection and oral care market within the kind by consumers for delivering vitamins and personal care product.

MATERIALS AND METHODS

Materials

Mirtazapine a sample from Aurobindo pharmaceuticals inc. Hyd. Glycerin and Hydroxy Propyl Methyl Cellulose E3, E5, E15 are from SD fine chem. Ltd, Mumbai, India and Tween 80, Propylene glycol, Eudragit 100 are from Merck Ltd, Mumbai, India.

Fabrication of drug free oral films

Oral films are prepared by Solvent Casting Technique (SCT). Applying 'O' shape ring placed on a glass surface as substrate by using different polymers like Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl cellulose (EC), Glycerin. The solution was mixed often to urge semisolid physical property. Then the solution was subjected to sonication in a bath to remove the air bubbles. Then this were casted on a glass surface applying 'O' shape ring having 3.6 cm in diameter is coated with funnel to dominant the evaporation of solvent and allowed to dry at room temperature overnight. The dried films were separated and also the backing membrane used was tin foil. Then the formulations were hold on in desiccators till additional use [8-15] **(Table 1)**.

Fabrication of mirtazapine oral films

The oral films were set up by the method for dissolvable throwing method applying "O" shape ring put on a glass surface as substrate by utilizing distinctive polymers like Hydroxy Propyl Methyl Cellulose - (HPMC), Ethyl cellulose (EC), Glycerin.

Table 1: Formulation of different composition

Ingredients	F1	F2	F3	F4	F5	F6
Hpmc	50	75	--	--	--	--
Glycerine	31	06	31	06	31	06
Ethyl cellulose	--	--	50	75	--	--
Eudragit / 100	--	--	--	--	50	75
Tween 80	04	04	04	04	04	04
Methanol	Qs	Qs	Qs	Qs	Qs	Qs
Total film weight	100	100	100	100	100	100

The arrangement was blended once in a while to get semisolid consistency. At that point the arrangement was subjected to sonication in a bath sonicator to evacuate the air bubbles. Then this were placed on a glass surface utilizing "O" shape ring having 3.6 cm in width is secured with pipe to controlling the dissipation of dissolvable and permitted to dry at room temperature overnight. The dried films were isolated and the support film utilized was aluminum foil. At that point the details were put away in desiccators until further utilize. The pieces of definition of both medication free and Mirtazapine oral films were given in **Table 2** [16-22]

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Table 2: Formulation of different composition.

Ingredients	F1	F2	F3	F4	F5	F6
Drug	15	15	15	15	15	15
Hpmc	50	75	--	--	--	--
Glycerine	31	06	31	06	31	06
Ethyl cellulose	--	--	50	75	--	--
Eudragit / 100	--	--	--	--	50	75
Tween 80	04	04	04	04	04	04
Methanol	Qs	Qs	Qs	Qs	Qs	Qs
Total film weight	100	100	100	100	100	100

The composition of oral films prepared using mirtazapine

Drug –polymer compatibility studies by FTIR

Drug polymer similarity studies were performed by FTIR57 (Fourier change infrared spectroscopy). Keeping in mind the end goal to affirm that the capture of medication inside the polymeric frameworks include just the physical procedure and no association in the middle of medication and polymer. FTIR absorption spectra of pure drug and polymers utilized like HPMC, EC, Glycerin and the mix of drug and polymer demonstrates no huge significant in the middle of drug and polymers [23-28] **(Figure 1).**

EVALUATION

Mechanical Properties like tensile strength, young's modulus, percent elongation and folding endurance [27-31].
Tensile strength = Load at breakage / Strip thickness × Strip Width
% Elongation = Increase in length × 100 /Original length
Folding endurance $F = \log_{10} d$

PHYSICO-CHEMICAL EVALUATION

Surface pH

Acidic or basic pH may cause disturbance in the buccal mucosa and impact the rate of hydration of the polymers, the surface pH of the films was resolved. The observed surface pH of the plans was observed to be in the scope of 6.61 to 6.81. The results are found that there is no significant distinction of surface pH in every one of the plans and the pH range exists in the scope of salivary pH i.e. 6.5 to 6.8, consequently don't bring about bothering and accomplish understanding consistence. Surface pH values of all the formulations are represented in **table 3** [32-36].

Percentage Moisture Absorption and Percentage Moisture Loss

Checking physical stability of the film at high humid conditions and integrity of the film at dry conditions, the films were evaluated for PMA and PML (**Table 3**).The percentage Moisture uptake in the formulation F4 (1:1 ratio (35mg + 35mg) of HPMC E3 and HPMC E5, 11 mg CP) has shown the highest value of moisture absorption 10.32. This may be due to the presence of equal concentrations of HPMC E3 and E5. The formulation F8 (50mg and 20mg HPMC E3 and E15, 11 mg CP) shows higher value of Moisture loss 7.13 which is due to presence of higher concentration of HPMC E3 and formulation F6 (1:1 ratio (35mg + 35mg) of HPMC E5 and HPMC E15, 11 mg CP) shows low value of 3.88. The Results were tabulated in table 3 [37-41].

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Swelling percentage

Table 3 shows the swelling percentage of the formulated buccal films. The swelling behavior of the polymer was reported to be crucial for its bioadhesive character. The adhesion occurs shortly after swelling but the bond formed is not very strong. The adhesion increases with the degree of hydration till the point of disentanglement at the polymer tissue surface, which leads to abrupt drop in adhesive strength due to over hydration [42-46].

The formulation F6 (1:1 ratio (35mg+35mg) of HPMC E5 and HPMC E15, 11 mg CP) shows higher value of Swelling percentage 138.4 which is due to presence of higher concentration of carbopol. The Results were tabulated in table 3.

Water Vapour Transmission

Water vapor transmission studies indicated that all the films were permeable to water vapour (**Table 3**).

Table 3: Standard graph of Mirtazapine.

Concentration	Absorbance at 290 nm
0	0
10	0.186
15	0.259
20	0.36
25	0.41
30	0.501
35	0.625
40	0.671
45	0.821
50	0.853

Thickness and Weight of films

The film thicknesses were observed by using digital vernier calipers and found to be in the range of 0.47 mm to 0.81 mm. The weight of the films was found to be in the range of 97.69 mg to 96.35 mg. The Results were in table 3.

Drug content estimation

The observed results of content uniformity indicated that the drug was uniformly dispersed and with minimum intra batch variability. Recovery was possible to the tune of 3.60 to 3.97. The Results were tabulated in table 3 [47-51]

Disintegration time

The disintegration time limit of 30s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast disintegrating films strips, this may be used as a qualitative guideline for quality control test or at development stage [52-57]. Pharmacopoeia disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30 s[38].

Dissolution test

Test performed using Standard Basket or Paddle apparatus method. The dissolution medium will be selected as per the sink conditions and highest dose of the active pharmaceutical ingredients. The dissolution test can be difficult due to tendency of the strip to float onto the medium when the paddle apparatus is employed [39] **(Figure 2).**

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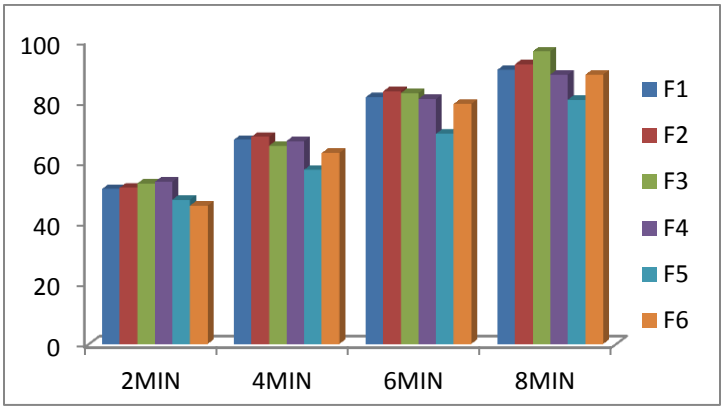
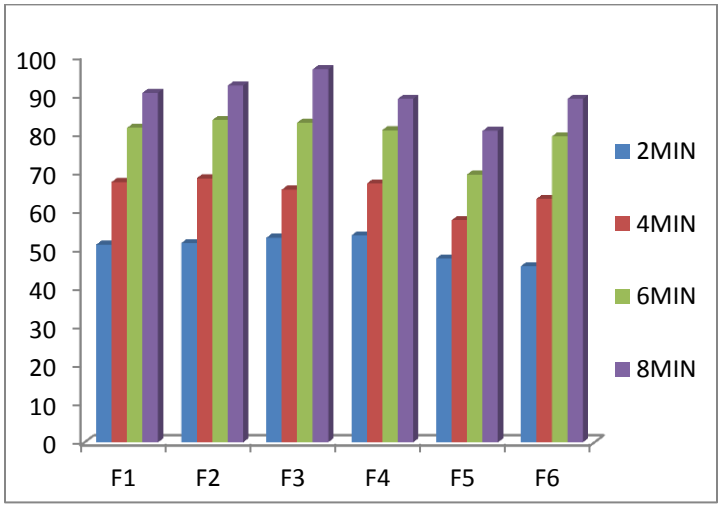
Figure 1 and 2: Dissolution and Disintegration time of Mirtazapine.





RESULTS AND DISCUSSION

Evalution

Mechanical properties of oral dispersible films of mirtazapine (**Table 4**)

Table 4: Mechanical properties of different formulations.

Formulation	Tensile strength	Percentage elongation (%)	Folding endurance
F1	0.75	15.25	78
F2	0.73	20.54	76
F3	0.68	22.89	79
F4	0.70	23.86	77
F5	0.61	30.5	72
F6	0.58	29.56	71

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Young's modulus

HPMC films are brittle then EC and demonstrate a high tensile strength and young's modulus with small elongation (**Table 5-7**).

Table 5: Physicochemical evaluation of oral films of mirtazapine.

Formulation code	Surface PH	PMA	PML	Swelling index	WVT	Thickness	Weight variation	Drug content
F1	6.73	5.21	5.97	69.4	10.58	0.44	98	96%
F2	6.79	7.23	5.14	99.67	7.67	0.62	101	97.1%
F3	6.8	9.24	4.74	118.4	7.17	0.47	104	98.2%
F4	6.61	10.32	4.14	107.2	6.4	0.59	99	99.1%
F5	6.78	3.56	4.08	132.6	5.94	0.81	103	100.1%
F6	6.65	7.02	3.88	138.4	6.39	0.76	101	97.4%

Table 6: Disintegration time of different formulations.

Formulation	Dt (sec)
F1	49
F2	56
F3	54
F4	57
F5	60
F6	61

Table 7: in vitro drug release of different formulations

Formulation	2min	4min	6min	8min
F1	51.23	67.45	81.49	90.6
F2	51.62	68.43	83.47	92.42
F3	53.01	65.47	82.87	96.66
F4	53.6	67.05	80.9	88.98
F5	47.67	57.56	69.42	80.7
F6	45.7	63.1	79.28	88.98

CONCLUSION

Mirtazapine is an anti-depressant drug. Concept of formulating orally dissolved films contains mirtazapine for rapid action of drug. Oral administration is the most widely used method for systemic effect, without being affected of tremendous advancement in drug delivery system. Difficulty in swallowing, leads to patient's incompliance particularly in case of Pediatric and geriatric. Oral dissolved films (ODFs) have several advantages over conventional forms of fast dissolving tablets. These are new emerging novel drug delivery system (NDDS). So, they are great importance during the emergency cases whenever immediate onset of action is desired. In the present work, oral dissolved films of mirtazapine were designed with a view to enhance patient compliance by solvent casting method. In this HPMC is used as a polymer. Prepared batches of Films were evaluated for durability, proportion elongation, folding endurance and dissolution. Among the films

prepared by solvent casting method formulation F3 found to be promising. The formulation was tested for In-vitro drug release pattern which showed 100% drug release 8 mins. The formulation F3 has shown better control over drug release of marketed product.

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