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Formulation and Evaluation of Fast Dissolving Film of Melatonin

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ABSTRACT:

This research work was aimed to provide faster onset of action of Melatonin (provide faster onset of action and avoid problem of dysphasia) by formulating its fast-dissolving film. The FDF of Melatonin was prepared by solvent casting method using HPMC (film forming agent), Glycerol (plasticizer), Citric acid (saliva stimulating agent), Mannitol (sweetening agent). The formulation was optimized by two factors, three levels (32) was used for the formulation optimization of fast dissolving film of Melatonin and experimental trials are performed on all 9 formulations. In which the amount of HPMC, Glycerol was selected as independent variables (factor) varied at three different level: low (-1), medium (0), and high (+1) levels. The drug release and disintegration time used as dependent variables (response). and formulation was evaluated for weight variation, thickness, folding endurance, drug content, in- vitro disintegration, in vitro dissolution study and stability study. Based on results it was concluded that FDF (F6) showed faster onset of action.

Key words – FDFs, Melatonin , Polymers, dysphasia, HPMC.

INTRODUCTION

The oral route is one of the most preferred routes for drug administration because it is more convenient, cost-effective, and ease of administration leads to a high level of patient compliance. Sometimes the oral route is problematic because of the swallowing difficulty for paediatric and geriatric patients who have fear of choking. Patient convenience and compliance-oriented research have resulted in introducing newer and safer drug delivery systems. Recently, fast-dissolving or rapid dissolving drug delivery systems have started gaining popularity and acceptance as one such example with increased consumer choice, for the reason of rapid disintegration or dissolution, self-administration possible even without water or chewing.[1]

Fast dissolving drug-delivery systems were first developed in the 1970s as an alternative to tablets, capsules, and syrups for paediatric and geriatric patients for experienced difficulties in swallowing traditional oral solid dosage forms. The oral fast-dissolving film is one of such a novel approach to increase consumer acceptance by rapid dissolution, self administration, easy to handle, convenient packaging, alleviates, and pleasant taste. Oral fast - dissolving film (OFDF) is also known as mouth dissolving film (MDF), oral strips, Oro dispersive films (ODF), and quick-dissolving film. FDDS is easy to administer and provides better patient compliance in the elderly, pediatric, mentally retarded, nauseated, and uncooperative patients. This drug delivery system was developed based on the technology of the transdermal patch. Fast dissolving film solely placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. Mouth dissolving films have the property to dissolve the drug within seconds by saliva and thereby passing the first-pass hepatic metabolism; dissolved drugs are dropped into systematic circulation by a buccal mucosa. To achieve this, some of the criteria have to be maintained such as the polymers used in film preparation should be hydrophilic in nature. The drug should have a low loading dose with enhanced bioavailability [2]

MATERIALS AND METHOD

1. MATERIALS

Melatonin and β – cyclodextrin was obtained as Yarrow chem. pvt. Ltd. HPMC , Glycerol , Citric acid ,Mannitol, was obtained from loba chemicals.

2. EXPERIEMENTALS

2.1 Identification of Drug :

2.1.1 By UV Spectroscopy: 10 mg of Melatonin was weighed and dissolved into 10 ml ethanol to prepare stock solution (1000µg/ml) from which a 10µg/ml dilution was prepared. Baseline correction was performed using ethanol and sample was scanned between 200-400nm and wavelength of maximum absorbance (λmax) was determined..[3]

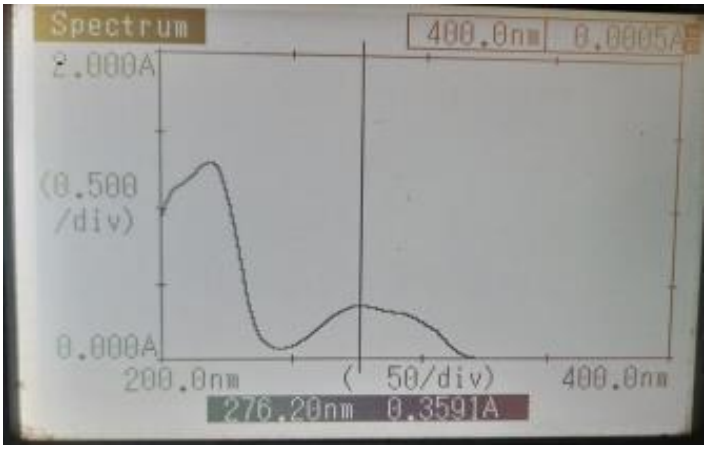

Figure 1: UV Spectrum of Melatonin

2.1.2 By melting point determination: Melting point of drug sample was determined by using melting point apparatus. Powdered drug sample was taken and filled in a thin walled capillary tube; the tube was approximately 10-12 cm in length with 1mm in diameter and closed at one end. The capillary was placed in melting point apparatus and heated and when drug sample was melted the melting point of sample powder was recorded.

Table no.1: Melting Point of Melatonin

Drug	**Observed**
Melatonin	116-1180C

2.1.3 Preparation of Calibration Curve :

The calibration curves of Melatonin were prepared in distilled water and phosphate buffer pH 6.8 by using Shimadzu 1800 UV visible spectrophotometer. Accurately weighed 50 mg of Melatonin was transferred into a 50 ml volumetric flask and the volume was made up by using co-solvent (ethanol) with distilled water to obtain a 1000µg/ml stock solution of Melatonin. From the stock solution 1 ml was taken and transferred into a 10 ml volumetric flask and rest of the volume was made up with solvent to obtain a 100µg/ml of solution from which 5, 10, 15, 20 and 25 µg/ml dilutions were prepared. Then each solution was separately analyzed. Same procedure was followed for phosphate buffer 6.8 to prepare calibration curve respectively.[4]
The calibration curves of Melatonin in various solvents e.g. Distilled water, 6.8 pH phosphate buffer were prepared and shown in Table

Table no.2 Absorbance data of Melatonin in distilled water at 276 nm

S. No.	**Concentration (µg/ml)**	**Absorbance**
1.	0	0
2.	5	0.240
3.	10	0.460
4.	15	0.650
5.	20	0.860
6	25	1.110

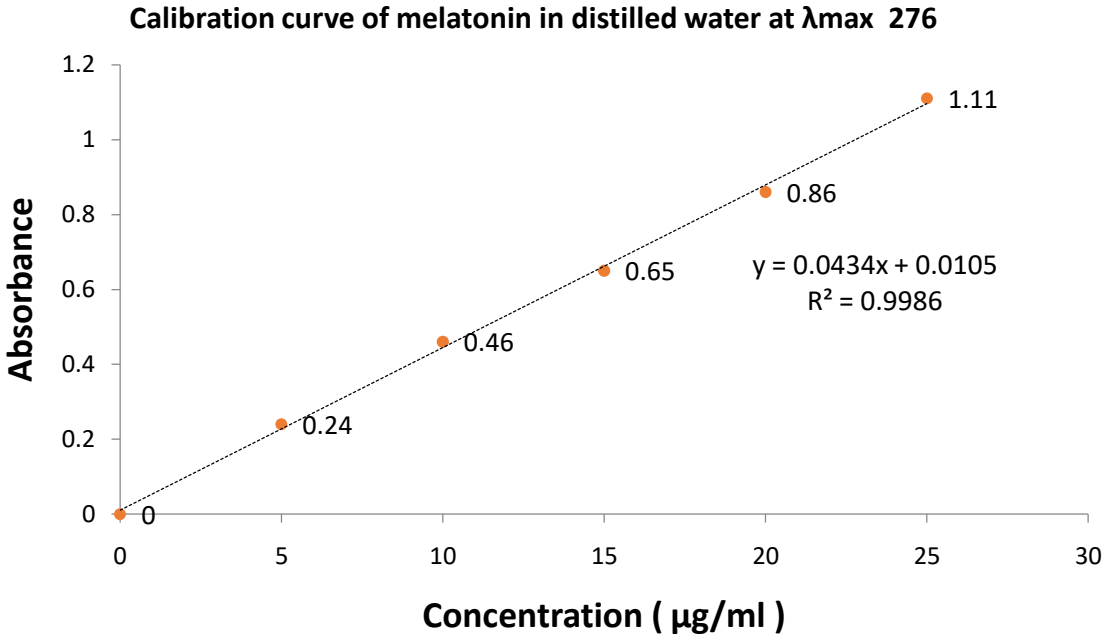

Figure 2 Calibration curve of Melatonin in distilled water at 276 nm

Table no. 3 Absorbance data of Melatonin in phosphate buffer pH 6.8 at 276 nm.

S. No.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	5	0.220
3.	10	0.476
4.	15	0.699
5.	20	0.886
6.	25	1.142

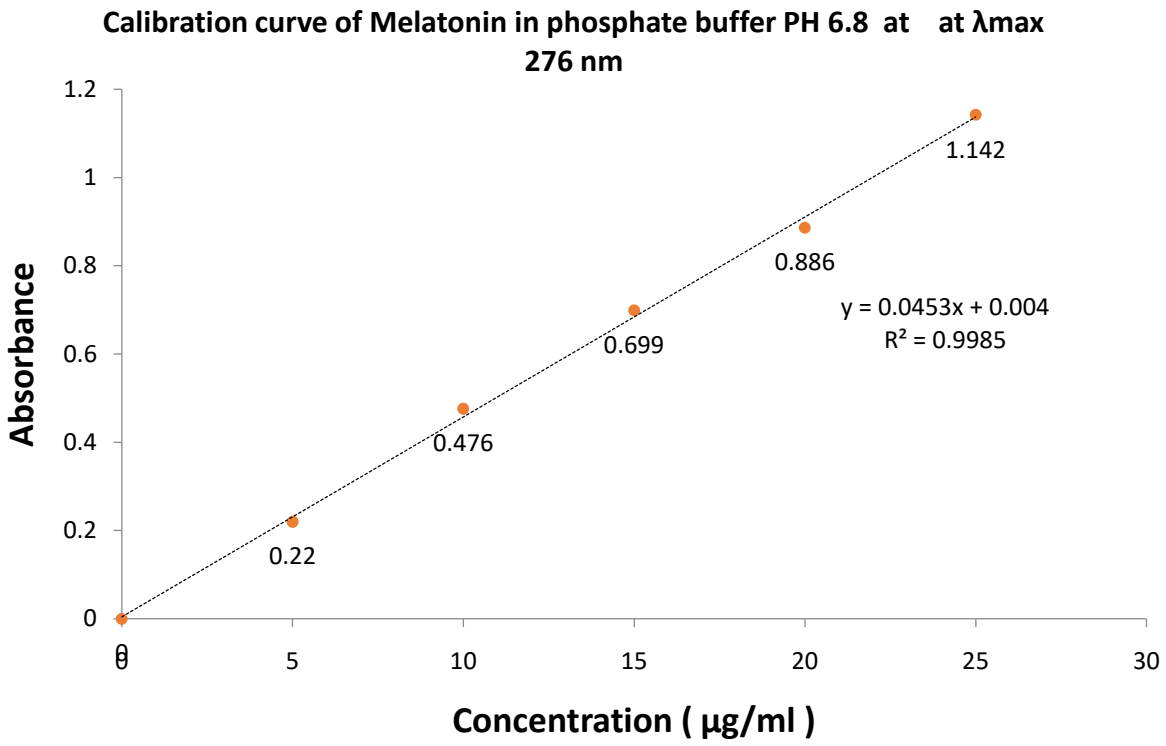

Figure 3 Calibration curve of Melatonin in phosphate buffer PH 6.8 at 276 nm

2.1.4 Determination of solubility of pure drug in various medium (n=3):

The solubility of Melatonin in various medium was determined by equilibrium solubility method. In this method 5 ml of each solvent was taken into a separate vial and excess amount of Melatonin was added in to vials containing distilled water and phosphate buffer pH 6.8. The vials put on mechanical stirrer at 37±2^{0}C for 12 hrs. The solutions were allowed to equilibrate for next 24 h. The solution was transferred into eppendroff tubes and centrifuged for 5 min. at 2000 rpm. The supernatants of each vial were filter through 0.45 micron membrane filter, make appropriate dilutions and analyzed by UV visible spectrophotometer (UV-1800 Shimadzu ,japan), the studies was performed in triplicate. [5]

Table no.4 Solubility data of Melatonin in different mediums

Name of drug	Medium (n=3)	
	Distilled water (mg/ml) Mean± SD	Phosphate buffer pH 6.8 (mg/ml) Mean± SD
Melatonin	0.109 ±0.003	0.540 ±0.005

The solubility of solid dispersion of Melatonin (1:1, 1:2, 1:3) in distilled water and phosphate buffer pH 6.8 were studied and the results of study were shown in below table no.5.

Table no.5 Solubility data of solid dispersion of Melatonin in different medium

Name of drug	Ratio	Medium	
		Distilled water (mg/ml) Mean± SD	Phosphate buffer pH 6.8 (mg/ml) Mean± SD
Melatonin+ β cyclodextrin solid dispersion	1:1	0.920 ±0.004	8.478±0.007
	1:2	1.160±0.002	11.330±0.002
	1:3	3.540±0.86	15.140±0.006

2.1.5 Drug-excipient interaction study:

FTIR absorption spectra of pure drug and physical mixture were recorded in the range of 400 to 4000$cm^{-1}$by KBR disc method using FTIR spectrophotometer. FTIR study was carried out individually for drug and polymer and physical mixture of drug with polymer. FTIR spectra of physical mixture of drug with all polymers were compared with FTIR spectra of pure drug and polymers. [6]

2.1.6 Preparation of solid dispersion of Melatonin: Solid dispersion of Melatonin was prepared with β- Cyclodextrin in different ratio (1:1, 1:2 and 1:3) by physical mixture method. In this method accurately weighted quantity of drug and β –cyclodextrin was taken in morter and pestel. Drug and β-cyclodextrin mixed thoroughly in motor by trituration. This mixture was then passed through sieve number #60.[7]

2.1.7 Preparation of fast dissolving films :

The fast dissolving film of Melatonin was prepared by solvent casting technique using HPMC as film forming polymer and Glycerol as a plasticizer. Citric acid as saliva stimulating agent and mannitol as a sweetening agent. The formulation were prepared as pr composition given in table no. (6.6).The hydrophilic polymer HPMC accurately weight and dissolved in distill ed water in a beaker and continouslly stirred on magnetic stirrer for 2 hours. Then the wighted quantity of drug and β –cyclodextrin solid dispersion, Glycerol , citric acid mannitol was dissolved in distilled water in another beaker then this mixture was added to the polymeric solution and stirred well using a magnetic stirrer to obtain homogenous solution.This solution allow to stand 12 h for the de-areation of the solution. The solution was then cast in petridish and kept n room temperature for 10 to 12 hours. After drying films were removed and cut into area 2×2 cm2. The film was coverd with aluminium foil and stored in dessicater for further use.[8,9]

TABLE no. 5 COMPOSITION OF MELATONIN FAST DISSOLVING FILM

BATCH NO. **INGREDIENTS**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Melatonin + β cyclodextrin solid dispersion(mg)	80	80	80	80	80	80	80	80	80
HPMC	250	250	250	350	350	350	450	450	450
Glycerol (ml)	0.05	0.075	0.09	0.05	0.075	0.09	0.05	0.075	0.09
Citric acid (mg)	20	20	20	20	20	20	20	20	20
Mannitol(mg)	20	20	20	20	20	20	20	20	20
Distilled water(ml)	10	10	10	10	10	10	10	10	10

3.1 EVALUATION OF FAST DISSOLVING FILM:

Thickness of films: It is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose distribution in the film. Thickness of the film was measured by micrometer screw gauge (Acculab)[10]

Weight variation: For the evaluation of weight variation of the fast dissolving film area 2×2 cm2cut and 3 films of each formulation were taken and weight individually using electronic balance. The average weight was calculated.[11]

Folding endurance: Folding endurance is related to the flexibility of a film. The folding endurance expressed as the number of folds (number of times of film is folded at the same plain) required breaking the film or developing visible cracks. This gives an indication of brittleness of the film. A small film 2×2cm2 was subjected to this test by folding the film at the same plane repeatedly several times until a visible crack was observed. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance. [12]

Surface pH: The surface pH of fast dissolving film was determined to investigate the possible side effects due to change in pH in vivo, since an acidic or alkaline pH may irritate the oral mucosa. The surface pH was determined by using pH meter This test was evaluated by placing the film in a petri dish. Then it was moistened with 0.5 ml of phosphate buffer and kept for 30s. The pH was noted after bringing the electrode of the PH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was taken.[13]

Drug Content Uniformity: The films were tested for content uniformity. Films of size 2×2 cm^2 were cut, placed in 100 ml volumetric flask and dissolve in phosphate buffer 6.8. Volumetric flask was shaken continuously for 10 min. Then solution was filtered through whatmanfilter paper membrane filter paper. After filtration, 1 ml of solution was withdrawn from the above solution in 10 ml volumetric flask and dilute up to 10 ml of phosphate buffer 6.8. Solution was analyzed on UV spectrophotometer at desired wavelength to calculate the concentration of drug present in the film. [14]

In- vitro disintegration test: disintegration time of fast dissolving film measured by placing the film area (2×2cm^2) in a petridish 6 cm in diameter containing 6 ml phosphate buffer of ph 6.8. Time required for complete disintegration of the film was noted.[15,16]

In- vitro Dissolution test: In-vitro dissolution of fast dissolving film of melatonin was studied in USP Type II (Paddle type) dissolution test apparatus using phosphate buffer pH 6.8 (250 ml) as the dissolution medium. Each film area 2×2 cm^2 was cut and fixed to a piece of metal wire slab and placed at the bottom of the dissolution vessel. The temperature was maintained at 37±0.5ºC with paddle speed rotation 50rpm. 5ml Sample was withdrawn at specific intervals and the same quantity was replaced with phosphate buffer of pH 6.8 to maintain sink condition.(Khatoon et al., 2014) The sample were filtered immediately through whatsman filter paper and analyzed spectophotometrically for the drug concentration and calculated the % of drug dissolved or release. [17]

Table no. 6 Thickness, Weight variation, Folding endurance, Drug content &Disintegration time of Formulation F1-F9.

Formulation	Thickness (mm) Mean± SD	Weight variation (mg) Mean± SD	Folding endurance (Times)	Drug Content (%) Mean± SD	Surface pH	Disintegration Time (sec) Mean± SD
F1	0.07±0.02	39.15±0.02	117	85.28±1.61	6.82	24±0.26
F2	0.09±0.07	38.40±0.11	122	91.37±1.42	6.93	18±0.34
F3	0.08±0.04	36.25±0.05	126	94.22±0..52	6.78	20±0.34
F4	0.09±0.07	35.43±0.09	134	86.81±1.30	6.84	25±0.27
F5	0.07±0.06	48.58±0.04	142	85.16±1.15	6.92	22±0.94
F6	0.08±0.02	47.35±0.04	148	97.36±1.74	6.88	15±0.39
F7	0.10±0.08	48.64±0.07	140	87.72±1.75	6.66	28±0.22
F8	0.11±0.02	46.12±0.04	146	92.80±0.65	6.78	30±0.18
F9	0.11±0.04	49.22±0.03	152	92.49±0.82	6.65	34±0.40

4.CONCLUSION

In the present research work an attempt has been made to , formulate and evaluate Fast dissolving film of Melatonin. Melatonin has poor bioavailability and low solubility. Melatonin is a hormone derived from 5- hydroxytryptamine which is secreted primarily in pineal gland and the retina of vertebrates during dark hours. Its importance lies in its ability to regulate normal physiological processes related to biorhythms and neuroendocrine function. In the present work solubility and bioavailability of drug was enhanced using solid dispersion. The solid dispersion of Drug: β-cyclodextrin was prepared in different ratio by physical mixure method. The solvent casting method was used to formulate and evaluate fast dissolving film of Melatonin. The drug–excipients compatibility by FT-IR studies revealed no physicochemical interaction. Addition of Drug: β-cyclodextrin solid dispersion leads to improve the dissolution characteristics and solubility of drug at optimum concentration (1:3). So, considering the above results it was found that the formulation F6 was found to be optimized formulation from the data obtained. It is observed from the formulation F6 which shown disintegration time 15 sec. and percentage cumulative drug release shown 97.12% within 180 second. Thus, it can be concluded that the drug given in the form of Fast dissolving films should be advantageous for patients suffering from sleep disorder, provide fast onset of action, avoid problem of dysphasia and an effective mode of treatment

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