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MELATONIN ORAL FAST DISSOLVING FILM FORMATION AND EVALUATION

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Abstract: Melatonin, a hormone secreted in pineal glands and vertebrates' retinas, regulates biorhythms and neuroendocrine function. However, it has limited solubility due to first-pass metabolism. Solvent casting can be used to form a solid dispersion of melatonin that prevents first-pass metabolism, permits quick action, and keeps elderly individuals from experiencing dysphasia. The solubility and interactions of melatonin, a drug having a melting point of 276.2 nm, with different excipients were investigated. A study developed an oral quick dissolving film of melatonin using solid dispersion. With a disintegration time of 15 seconds and a cumulative drug release percentage of 97.12% over 180 seconds, formulation F6 was determined to be the best. Patients with sleep disorders benefit from this formulation because it has a rapid onset of action, prevents dysphasia, and is an efficient therapeutic mechanism.
Keywords: Melatonin, First-pass metabolism, Solid Dispersion, Dysphasia.

1. INTRODUCTION

The oral route is the most popular method of administering medications since it is more economical, easy, and increases patient compliance. For young and elderly patients who are frightened of choking, the oral route can be challenging to swallow at times. Research focused on patient convenience and compliance has led to the creation of safer and more efficient drug delivery systems. Oral fast-dissolving drug delivery methods (quick dissolving tablets, fast dissolving films) have lately acquired popularity and acceptability as a result of expanded consumer choice, because rapid disintegration or dissolution allows for self-administration even without water or chewing.[1,2]

ANATOMY & PHYSIOLOGY OF THE ORAL MUCOSA

1.1.1 Structure: The tongue, lips, hard and soft palates, and cheeks make up the oral cavity. The lamina propria, the submucosa, the foundation membrane, and the topmost layer of stratified squamous epithelium make up the oral mucosa. [3]

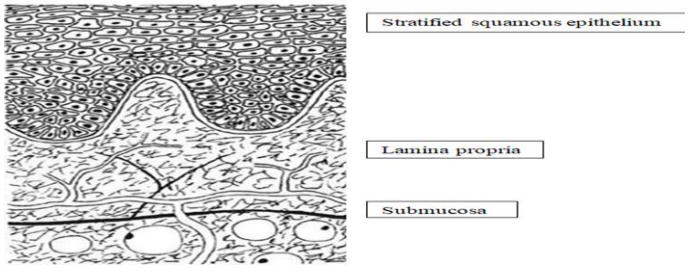

Figure 1.1 Structures of Oral Mucosa1.1.1 Anatomy and Organization

The oral cavity's masticatory mucosa, which covers stress-prone regions like the gingival and hard palate, has a keratinised or cornified epithelium. It provides chemical resistance and mechanical strength. It is separated into four layers:

- Keratinized
- Granular
- Prickle-cell
- Basal layer

The non-cornified surface epithelium that covers the lips, cheeks, floor of the mouth, and soft palate makes up the lining mucosa, which offers flexibility. It can be separated into four layers:

- Superficial
- Intermediate
- Prickle-cell
- Basal layers

The third type of mucosa is the specialized mucosa, which has both keratinized and non-keratinized layers and is limited to the tongue's dorsal surface. Water, lipids, and proteins can all be found in intercellular gaps. [4,5]

1.1.2 Physiological Importance of Mucins and Saliva:

Mucus, composed of negatively charged glycoproteins called mucins, protects mucosal tissues and maintains saliva's pH between 5.8 and 7.4 by contributing to its viscoelastic character. [6] Salivary glands secrete mucus and produce saliva, which protects soft tissues from chemical and mechanical damage. Mucus is crucial for effective buccal delivery and medication delivery systems. The mouth's surface area is divided into teeth, keratinized epithelium, and non-keratinized epithelium. Sublingual, buccal, and gingival routes can all be used to distribute drugs through the mouth mucosa. [7]

1.1.3 Permeability of oral mucosa:

Between the intestinal mucosa and the epidermis is a type of leaky epithelial tissue called the oral mucosa. Compared to the skin, the buccal mucosa is 4–4000 times more porous. The distinct structure and function of the oral mucosa are responsible for the variance in permeability. Sublingual > buccal > palatal is the order in which the mouth mucosa's permeability diminishes. The sublingual mucosa is relatively thin and non-keratinized, the buccal mucosa is thicker and non-keratinized, and the palatal mucosa is intermediate in thickness but keratinized. This order is dictated by the thickness and degree of keratinization of these tissues. [8]

1.1.4 Barriers to Permeation:

Membrane coating granules (MCG), which attach to the plasma membrane during cell development, create the permeability barrier of the oral mucosa. The top third layer of the epithelium receives the contents of these granules. Flattened surface cell layers constitute the primary barrier, according to permeation tests, whereas more isodiametric cell layers are comparatively porous. Ten The hurdle function is not anticipated to be considerably affected by keratinization alone. Non-keratinized epithelia contain glycosphingolipids, cholesterol, and cholesterol esters, whereas keratinized epithelia possess MCG lipids. [9,12]

1.1.5 Routes of permeation: The oral mucosa's squamous stratified epithelium allows drugs to enter the body through two different pathways:

• Transcellular (moving through the cell, intracellular)

• Paracellular (moving throughout the cell, intercellular) [11]

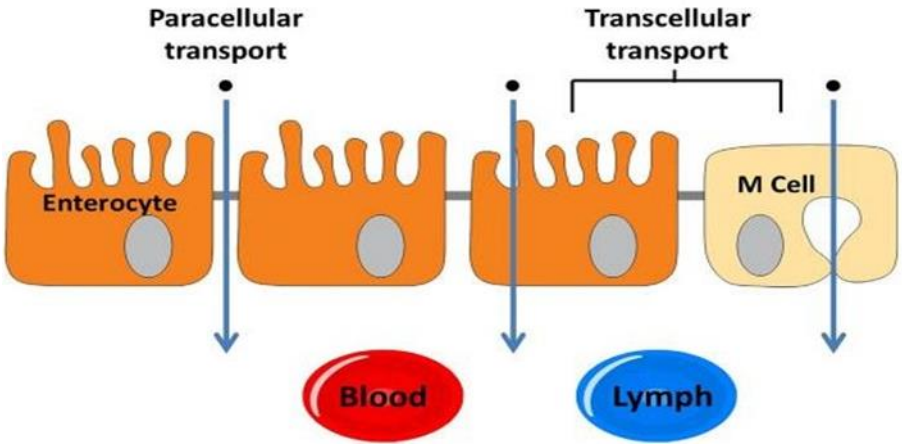

Figure 1.2 Routes of Permeation

One important location for medication penetration is the buccal mucosa, mostly by passive diffusion. Peptides, oligonucleotides, and polysaccharides are examples of hydrophilic macromolecular agents that can be distributed using it. But because of their poor permeability, these medications require absorption enhancers and treat salivary enzymes and proteases. [1,14]

1.2 DISSOLVING DRUG DELIVERY SYSTEM QUICKLY

For patients who have trouble swallowing, fast dissolving medication delivery systems, which were created in the 1970s, provide an alternative to conventional oral dose forms. Oral fast-dissolving films, also known as mouth dissolving films, are used to improve patient compliance in various populations. Developed using transdermal patch technology, these films dissolve medications in seconds via saliva, avoiding hepatic processing. The polymers used in film production are hydrophilic, ensuring low loading doses and increased bioavailability. [16,17]

1.2.1 Oral Fast Dissolving Film Benefits

- Requires no water for administration.
- Ideal for pediatric, geriatric, and dysphagia patients with difficulties swallowing.
- Films dissolve quickly in the oral cavity due to their enormous surface area.
- them easier to handle, transport, and store, as well as more cost-effective.Ease of administration to mentally retard, disabled, uncooperative patients and the patients who are on reduced liquid intake plans or are nauseated.
- Helps with motion sickness, severe discomfort, allergies, asthma, and coughing that demand immediate relief.
- Improved bioavailability by avoiding hepatic first-pass effect, resulting in faster commencement of action.
- Improves therapeutic efficacy, safety, and reduces side effects.Portable and flexible, making
- Maintain stability throughout time.
- Higher dosing accuracy compared to liquid dosage forms.
- Experience a pleasant mouthfeel with minimal or no residue after administration. [18,19]

1.2.2 Oral Fast Dissolving Film's Drawbacks

- It is not possible to provide medications that are unstable at salivary pH.
- This method cannot be used to give medications that cause mucosal irritation.
- Only low-dose medications can be given.
- Taste masking is necessary because the majority of drugs have a bitter taste.
- Because OFDFs are delicate and need to be protected from water, they

need special packaging. [22]

1.3 OVERALL ORAL FAST DISSOLVING FILM COMPOSITION [21,25,38]

Table 1.1 Oral fast-dissolving film's general composition

S. No.	Ingredients	Concentration percentage (%)
1.	API (drug)	01–25
2.	Hydrophilic polymer/film former	40–50
3.	Plasticizer	01–20
4.	Flavoring agents	02–10
5.	Sweetening agents	03–06
6.	An agent that stimulates saliva	02–06
7.	Agent for colouring	01
8.	Active agent on the surface	Q.S.

The ideal characteristics of the polymers utilized in the oral FDF [38]

- It shouldn't be annoying or toxic.
- It shouldn't be bitter.
- It ought to have no taste.
- Leachable pollutants should not be present.
- It needs to be accessible and reasonably priced.
- The disintegration process shouldn't be hampered by it.
- Polymers should have good wetting and spreadability properties.
- The material should have enough peel, shear, and tensile strength.
- Ensure acceptable shelf life.

• It shouldn't result in oral cavity secondary infections. [26]

Table 1.2 List of polymers utilized in oral FDF [12,18]

Collective	The Class	For instance,
Natural	Carbohydrate	Maltodextrin, pullulan, pectin, sodium alginate, and sodium starch glycolate (SSG)
	Proteins	Gelatin
	Resin	Polymerized rosin (novel film former)
	Cellulose derivatives	Methylcellulose (A3, A6, A15), hydroxypropyl methylcellulose (HPMC) (E3, E5, E15, K3, K15, K50), carboxy methyl cellulose secekol-30, sodium carboxy methyl cellulose, microcrystalline cellulose, and croscarmellose sodium (CCS).

Synthetic	Vinyl polymer	Polyvinyl pyrrolidone (K-90, K-30), Polyvinyl alcohol, polyethylene oxide
	Acrylic polymer	Eudragit (RD-100, 9, 10, 11, 12 and RL-100)

1.5 METHODS OF PREPARATION [36]

- Conventional Methods
- Method of Solvent Casting
- Method of Semisolid Casting
- Method of Hot Melt Extrusion
- Method of Solid Dispersion Extrusion
- Rolling method

Solvent Casting Method:-

The oral thin film is made using the solvent casting process, which dissolves the water-soluble ingredients to produce a transparent, viscous solution. Before being combined with the bulk, the API and excipients are dissolved in small amounts of solution. Next, the mixture is added to the viscous aqueous solution. The entrapped air is evacuated using a vacuum. The resultant solution is then cast as a film, dried, and cut into little pieces. [27]

Semisolid Casting Method:- [35]

This procedure begins with the creation of a water-soluble film-forming polymer solution. An acid-insoluble polymer solution (such as cellulose acetate phthalate or cellulose acetate butyrate) made in sodium hydroxide or ammonium hydroxide (NH4OH) is then combined with this solution.The plasticizer is then added at a proper concentration to produce a gel mass. Finally, the gel mass is pressed onto the films with heat-controlled drums. The ratio between the acid-insoluble polymer and the film-forming polymer should be 1:4. [26]

Hot Melt Extrusion Method:-

In this approach, polymers of low molecular weight and viscosity are employed. The medicine is mixed with the carrier in solid form, resulting in granular material. The granules are then dried and fed into the extruder. The screw's speed should be around 15 rpm. 80°C, 115°C, 100°C, and 65°C are the suggested processing temperatures. A film was created by pressing the extrudate (T=65°C) into a cylindrical calendar. [28]

Extrusion Method of Solid Dispersion: -

The solid dispersion extrusion procedure creates solid dispersions by extruding medications with immiscible components. Lastly, dies are used to shape the solid dispersions into films. [16]

5. Rolling method:-

The rolling method involves rolling a solution or suspension containing medication (API) on a carrier. Water and a mixture of water and alcohol are the main solvents used in this method. The film is dried on the rollers and then cut into acceptable shapes and sizes. [18]

1.5 ORAL FAST DISSOLVING FILM CLASSIFICATION

Three distinct subcategories exist.

a) Flash release,
b) Mucoadhesive melt-away films,
c) Mucoadhesive sustained-release films. [27]

Table 1.3 Oral fast-dissolving film classification [29]

Properties	Flash release Mucoadhesive	melt- away films	Mucoadhesive sustained released films
Area (cm^2)	2-8	2-7	2-4

Thickness(μm)	20-70	50-500	50-250
Structure	Single-layer	Single or multilayer	Multilayer system
Excipients	Soluble hydrophilic polymers	Soluble hydrophilic polymers	Low/nonsoluble polymers
Drug phase	Solid solution	Suspended drug particles or solid solutions	Solid solution or suspension
Application	Tongue (upper palate)	The buccal or gingival area	Gingival and other oral cavity areas
Dissolution	60 seconds	Creating a gel in a matter of minutes	8–10 hours at most
Place of activity	Local or systemic	either local or systemic	Local or systemic

2. EXPERIMENTAL WORK

Table 2.1 List of Material

S. No.	Material Used	Manufacturer name
1.	Melatonin	Yarrow chem. pvt. Ltd
2.	HPMC E5	Lobachem Pvt. Ltd
3.	PEG-400	Lobachem Pvt. Ltd.
4.	Citric acid	Lobachem Pvt. Ltd.
5.	Mannitol	Lobachem Pvt. Ltd
6.	β –cyclodextrin	Yarrow chem. Pvt. Ltd

Table 2.2 List of Instruments

S. No.	Instrument Used	Model Name
1.	UV Spectrophotometer	Schimadzu 1800
2.	Melting point apparatus	Remi Pvt. Ltd.
3.	Dissolution Test Apparatus	Electro lab Pvt. Ltd.
4.	Hot air Oven	S.M. scientific instrument (p) Ltd.
5.	Digital weighing balance	Shimadzu
6.	Centrifuge apparatus	Remi 12c
7.	pH – Meter	MK VI

2.1 PREFORMULATION STUDY [24]

2.1.1 Identification study of drug

- **Determination of wavelength (λmax) using UV-visible spectroscopy: [26]**
  Melatonin (10 mg) was weighed and diluted in 10 mL of ethanol to provide a stock solution (1000µg/mL) and a 10µg/mL dilution. Baseline correction was conducted using ethanol, and the sample was scanned between 200-400nm to determine the wavelength of maximum absorbance (λmax).
- **Calibration curve of Melatonin in ethanolic distilled water at 276.2 nm [3,5]**
  Melatonin calibration curves were constructed in distilled water using a UV visible spectrophotometer (Shimadzu 1800, Japan). To create a 1000µg/ml stock solution of Melatonin, accurately weigh 50 mg and transfer it to a 50 ml volumetric flask. Fill the flask with co-solvent (ethanol) and distilled water (2:8) to get the desired volume. A 10 ml volumetric flask was filled with 1 ml of the stock solution to create dilutions of 5, 10, 15, 20, and 25 µg/ml. The remaining volume was filled with solvent to achieve a 100µg/ml solution. The solutions were examined individually at λmax 276.2 nm.
- **Melatonin calibration curve at 276.2 nm in phosphate buffer pH 6.8 [26]**
  A Shimadzu 1800 UV visible spectrophotometer was used to create melatonin calibration curves in phosphate buffer pH 6.8. Weigh out 50 mg of melatonin precisely, then pour it into a 50 ml volumetric flask to make a 1000µg/ml stock solution. Pour phosphate buffer (pH 6.8) into the flask. A 10 ml volumetric flask was filled with 1 ml of the stock solution to create dilutions of 5, 10, 15, 20, and 25 µg/ml. A 100µg/ml solution was obtained by filling the remaining volume with solvent. Each solution was analysed separately at λmax 276.2 nm..

2.1.2 Determination of Melting Point: [38]

The melting point of a pharmacological sample was tested using a melting point testing equipment. A powdered drug sample was collected and placed in a thin-walled capillary tube, which was roughly 10-12 cm long, 1mm in diameter, and closed at one end. The capillary was inserted in the melting point device and heated. When the drug sample was melted, the melting point of the sample powder was recorded.

2.1.3 Solubility studies [36]

Determination of solubility of Melatonin in various medium (n=3): The equilibrium solubility approach was used to assess melatonin's solubility in different media. This process involved adding an excess of melatonin to vials containing distilled water and phosphate buffer pH 6.8, and placing 5 ml of each solvent in a different vial. For twelve hours, the vials were kept at 37±20C on a mechanical stirrer. For the next twenty-four hours, the solutions were left to equilibrate. After being moved to Eppendorf tubes, the solution was centrifuged at 2000 rpm for five minutes. Each vial's supernatants were filtered through a 0.45-micron membrane filter, diluted appropriately, and assessed with a UV visible spectrophotometer.

2.1.4

Drug-excipient interaction study: [22]

Melatonin and excipients' FTIR absorption spectra were acquired in the 400 to 4000 cm-1 range using the KBR disc technique and an FTIR spectrophotometer. Melatonin and its physical combination with excipients were studied using FTIR. The FTIR spectra of Melatonin's physical combination with all polymers were compared to Melatonin's FTIR spectrum .

2.2 FORMULATION DEVELOPMENT:-
Melatonin solid dispersion was synthesized using β- Cyclodextrin in various ratios (1:1, 1:2, 1:3, and 1:4) using a physical mixed approach. Melatonin and β-cyclodextrin were carefully weighted in a mortar and pestle. Trituration was used to thoroughly mix melatonin and β-cyclodextrin in the motor. After that, the mixture was run through sieve number 60. [6,14]

Table 2.3 List of excipients selected

S. No.	Excipients	Purpose
1.	HPMC E5	Polymer that forms films
2.	PEG-400	Plasticizer
3.	Citric acid	An agent that stimulates saliva
4.	Mannitol	Sweetning agent
5.	β- cyclodextrin	Solublising agent

Making oral fast-dissolving films: [19,22]
Using HPMC as the film-forming polymer, PEG as a plasticiser, citric acid as a saliva-stimulating agent, and mannitol as a sweetener, the oral quick dissolving film of solid dispersion of melatonin was created using the solvent casting technique.The formulation was made according to the composition listed in table 2.7. The hydrophilic polymer HPMC was precisely weighed, dissolved in distilled water in a beaker, and continuously swirled on a magnetic stirrer for 2 hours. Melatonin, β-cyclodextrin solid dispersion, PEG-400, citric acid, and mannitol were dissolved in distilled water in a separate beaker. To create a homogenous solution, the mixture was then added to the polymeric solution and thoroughly stirred using a magnetic stirrer. To de-areate, the solution was left to stand for 12 hours. The solution was then cast on petridish and stored at room temperature for 10 to 12 hours. After drying, the films were removed and cut into 2×2 cm2 pieces. For subsequent usage, the film was put in a desiccant and sealed with aluminum foil..

2.2.1 Optimization of oral fast dissolving film [37,39]
The polymer-plasticizer ratio was optimized using a 32 complete factorial design. In this design, two variables were assessed at three levels each, and experimental trials were conducted in all nine conceivable combinations. The quantity of polymer HPMC (X1) and plasticizer PEG-400 (X2) were chosen as independent variables, with each factor tested at a low (-1), medium (0), and high (+1) level. Tables 2.4 and 2.5 illustrate the amounts of independent variables, as well as the drug release and disintegration time that were employed as dependent variables (response). Table 2.6 shows the whole factorial design arrangement, whereas table 2.7 shows the composition of several rapid dissolving films.

Table 2.4 Selected factors and there levels (Independent variables)

S. No.	Name of factors	Levels (concentration of factor)		
		Low(-1)	Medium (0)	High (+1)
1.	X1: Concentration of HPMC (mg)	250	350	450
2.	X2: Concentration of PEG-400(ml)	0.05	0.07	0.09

Table 2.5 Dependent (Response) variables

S. No.	Name of response	Unit
1.	% medication release	%
2.	Disintegration time	Second

Table 2.6 32 layout of a full factorial design

Formulation code	Variable levels	
	X1 (Polymer)	X2 (plasticizer)
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

TABLE 2.7 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 E5 (mg)	250	250	250	350	350	350	450	450	450
PEG-400(ml)	0.05	0.07	0.09	0.05	0.07	0.09	0.05	0.07	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

2.3 ORAL FAST DISSOLVING FILM EVALUATION: [18,26]

- **Thickness of films:** A micrometer screw gauge was used to measure the film's thickness at three different sites; the averages of the three measurements were calculated.
- **Weight variation:** A 2x2cm2 fast dissolving film was cut, and three films of each formulation were weighed independently on an electronic scale to assess weight variation. An average weight was calculated. [38]
- **Folding endurance:** The flexibility of a film is related to its folding endurance. The number of folds (the number of times a film is folded in the same plane) required to shatter the film or cause observable fractures is known as folding endurance. This shows how brittle the film is. A 2x2cm2 material was repeatedly folded in the same plane during the test until a noticeable break emerged. The number of times the film could be folded in the same spot without cracking or breaking was used to calculate its folding endurance.
- **Surface pH:** Since an acidic or alkaline pH can irritate the oral mucosa, the surface pH of a quickly dissolving film was examined to investigate the possible negative effects of pH variations in vivo. A pH meter was used to measure the surface pH. The film was placed in a petri dish for this test. After that, 0.5 mL of phosphate buffer was added, and it was left for 30 seconds. After contacting the formulation's surface with the pH meter's electrode and allowing one minute for equilibration, the pH was measured. For every formulation, the mean of three measurements was utilized. [25]
- **Drug Content Uniformity:** The consistency of the films' content was assessed. Cut 2x2 cm2 films, put them in a 100 mL volumetric flask, and let them dissolve in phosphate buffer with a pH of 6.8. For ten minutes, the volumetric flask was continuously shaken. Whatman filter paper was then used to filter the mixture. After filtering, 1 ml of the previously mentioned solution was taken out and diluted with 10 ml of phosphate buffer pH 6.8 in a 10 ml volumetric flask. To ascertain the drug concentration in the film, the solution was analyzed using a UV spectrophotometer at λmax 276.2.
- **In-vitro disintegration test:** A rapid dissolving film (2x2cm2) was placed in a petridish with 6 ml of phosphate buffer pH 6.8 to measure the disintegration time. The amount of time required for the film to completely disintegrate was noted. [26]
- **In-vitro drug release:** Phosphate buffer pH 6.8 (250 ml) was used as the dissolve medium in a USP Type II (Paddle type) dissolution test apparatus to examine the in vitro drug release of a rapidly disintegrating film of melatonin. A 2x2 cm2 film was cut, attached to a slab of metal wire, and placed at the bottom of the dissolving tank. With a paddle speed of 50 rpm, the temperature was kept at 37±0.5ºC. Five millilitres of the sample were removed at certain intervals and replaced with phosphate buffer pH 6.8 in order to maintain the volume of the dissolving media. The sample was quickly filtered through Whatman filter paper, and the drug concentration and percentage of dissolved or released drug were measured using UV spectrophotometry at λmax 276.2..

3. OUTCOMES AND TALK

3.1 PREFORMULATION STUDIES

3.1.1 Identification study of drug

- **Determination of wavelength (λmax) using U.V. spectroscopy** Melatonin's absorbance maxima in ethanol were determined to be 276.2 nm, which is

consistent with previous reports. Figure 3.1 shows the UV spectrum of melatonin .

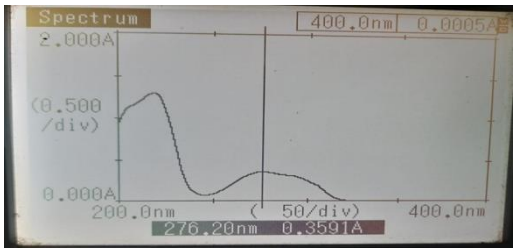

Figure 3.1 UV Spectrum of Melatonin

- **Preparation of calibration curves:** Tables 3.1 and 3.2, along with Figures 3.2 and 3.3, show the melatonin calibration curves that were produced in ethanolic distilled water and phosphate buffer pH 6.8..

- **Table 3.1 Absorbance data of Melatonin in ethanolic distilled water at 276.2 nm (n=3)**

S. No.	Concentration (µg/ml)	Absorbance Mean± SD
1.	0	0
2.	5	0.239±0.003
3.	10	0.465±0.009
4.	15	0.659±0.006
5.	20	0.846±0.012
6	25	1.112±0.018

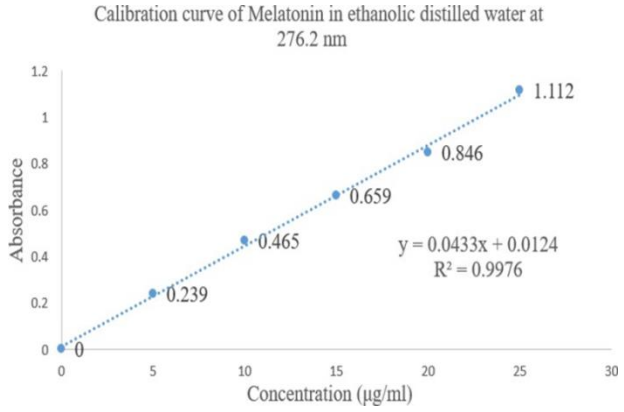

Figure 3.2 Calibration curve of Melatonin in ethanolic distilled water at 276.2 nm

Table 3.2 Melatonin absorbance values at 276.2 nm in phosphate buffer pH 6.8 (n = 3)

S. No.	Concentration (µg/ml)	Absorbance Mean± SD

1.	0	0
2.	5	0.219±0.002
3.	10	0.474±0.001
4.	15	0.698±0.001
5.	20	0.885±0.004
6.	25	1.143±0.002

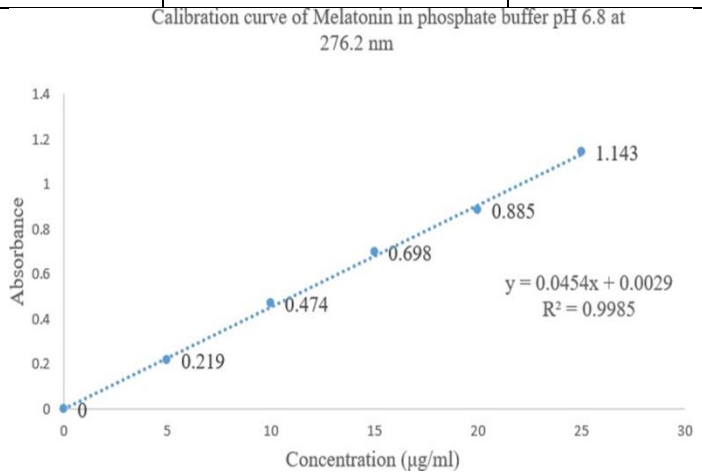

Figure 3.3 Melatonin calibration curve at 276.2 nm in phosphate buffer pH 6.8

3.1.2 Melting point determination:

Melatonin's melting point was determined to be 1170C ±0.001, consistent with previous studies.

3.1.3 Determination of solubility of Melatonin

The solubility of Melatonin in distilled water and phosphate buffer pH 6.8 was investigated, and the findings are presented in table 3.3. The study's findings revealed that Melatonin has low aqueous solubility in distilled water and phosphate buffer pH 6.8.

Table 3.3 Melatonin solubility data in phosphate buffer pH 6.8 and distilled water (n=3)

Name of drug	Medium	
	Distilled water (mg/ml) Mean± SD	pH 6.8 phosphate buffer (mg/ml) Mean± SD
Melatonin	0.110 ±0.002	0.538 ±0.006

The study examined the solubility of Melatonin solid dispersion with β-cyclodextrin (1:1, 1:2, 1:3, 1:4) in distilled water and phosphate buffer pH 6.8. The findings are provided in Table 3.4.

Table 3.4 Solubility data of solid dispersion of Melatonin in distilled water and phosphate buffer pH 6.8 (n=3)

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	0.936 ±0.004	8.471±0.007
	1:2	1.257±0.002	11.327±0.002
	1:3	3.632±0.003	15.136±0.006
	1:4	3.636±0.002	15.183±0.004

3.1.4 Drug-excipient interaction study using FTIR

Figures 3.4, 3.5, 3.6, 3.7, and 3.8 show the FTIR spectrum of Melatonin, a physical combination of Melatonin with HPMC-E5, a solid dispersion of Melatonin with β-cyclodextrin, and a physical mixture of HPMC-E5 with Melatonin and β-cyclodextrin solid dispersion. Tables 3.5, 3.6, 3.7, and 3.8 provide peak information .

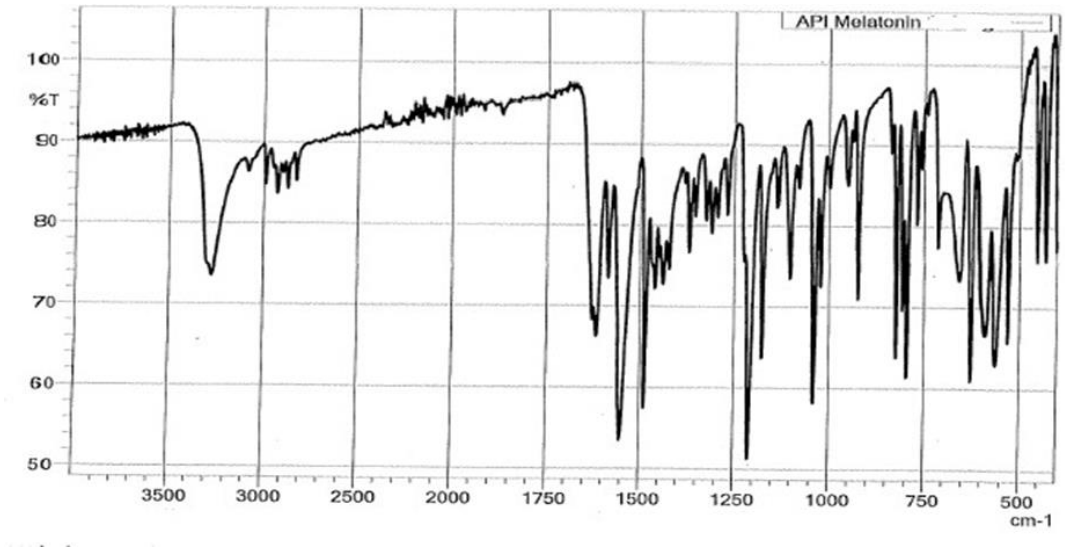

Figure 3.4 FTIR spectrum of Melatonin

Table 3.5 FTIR Spectra Peaks of Melatonin

Groups	Observed Value cm^{-1}	Reported Value cm^{-1}
N-H (stretch)	3300.12	3500-3300

=C-H(stretch)	2991.3	3100-3000
C-N(Amine)	1211.14	1350-1000
C=C(Aromatic)	1488.54	1600-1400
C=O(Amide)	1552.89	1700-1500
C-O-C(Ether)(stretch)	1079.59	1250-1050

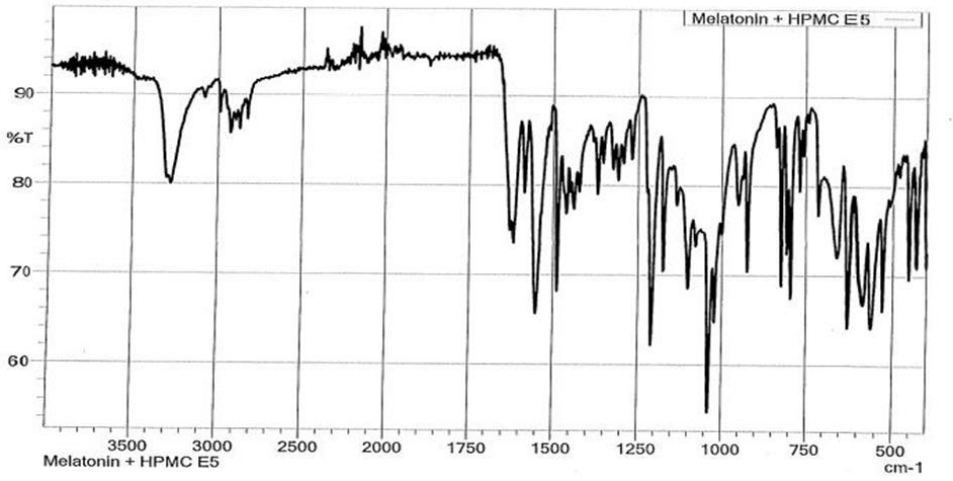

Figure 3.5 FTIR spectrum of physical mixture of Melatonin and HPMC-E5

Table 3.6 FTIR Spectra Peaks of Melatonin and HPMC-E5

Groups	Observed Value cm^{-1}	Reported Value cm^{-1}
N-H(stretch)	3300.12	3500-3300
=C-H(stretch)	2989.96	3100-3000
C-N(amine)	1211.14	1350-1000
C=C(aromatic	1488.54	1600-1400
C=O(amide)	1551.46	1700-1500
O-H(stretch)	3320.25	3400-3200
C-O-C(Ether)	1079.59	1250-1050

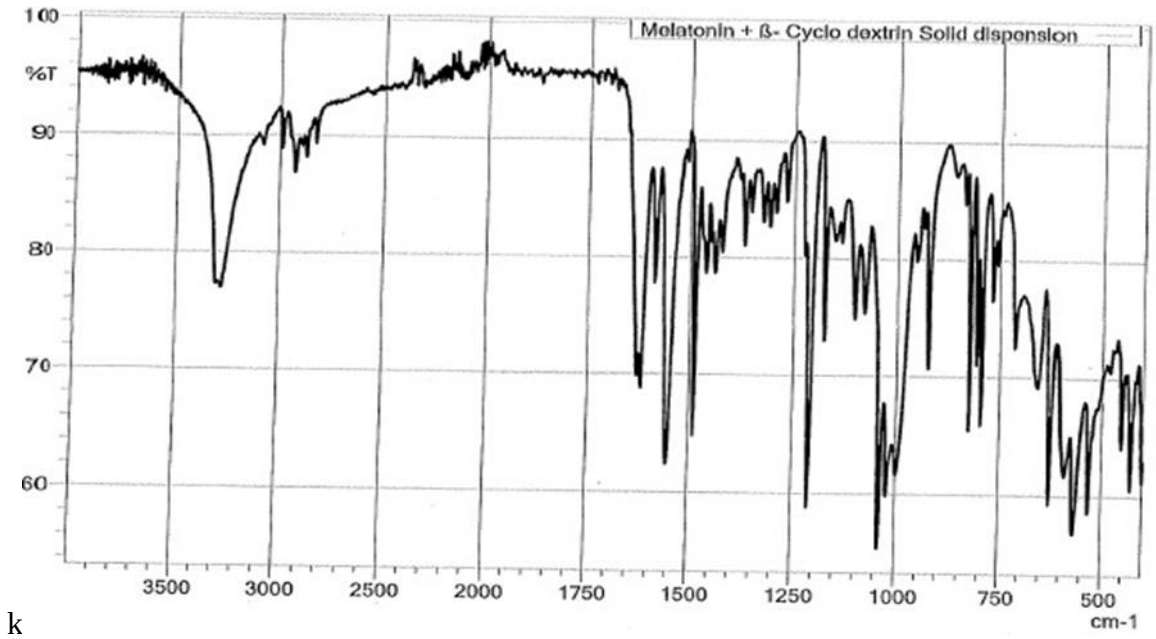

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Figure 3.6 FTIR spectra of Melatonin and β-cyclodextrin solid dispersion

Table 3.7 FTIR Spectra Peaks of Melatonin and β-cyclodextrin solid dispersion

Groups	Observed Value cm^{-1}	Reported Value cm^{-1}
N-H(stretch)	3300.12	3500-3300
=C-H(stretch)	2991.39	3100-3000
C-N	1212.57	1350-1000
C=C	1488.54	1600-1400
C=O(amide)	1554.32	1700-1500
O-H(Strech)	3320.15	3400-3200
C-O	1079.59	1250-1050
CH_2(bend)	1461.38	1480-1440

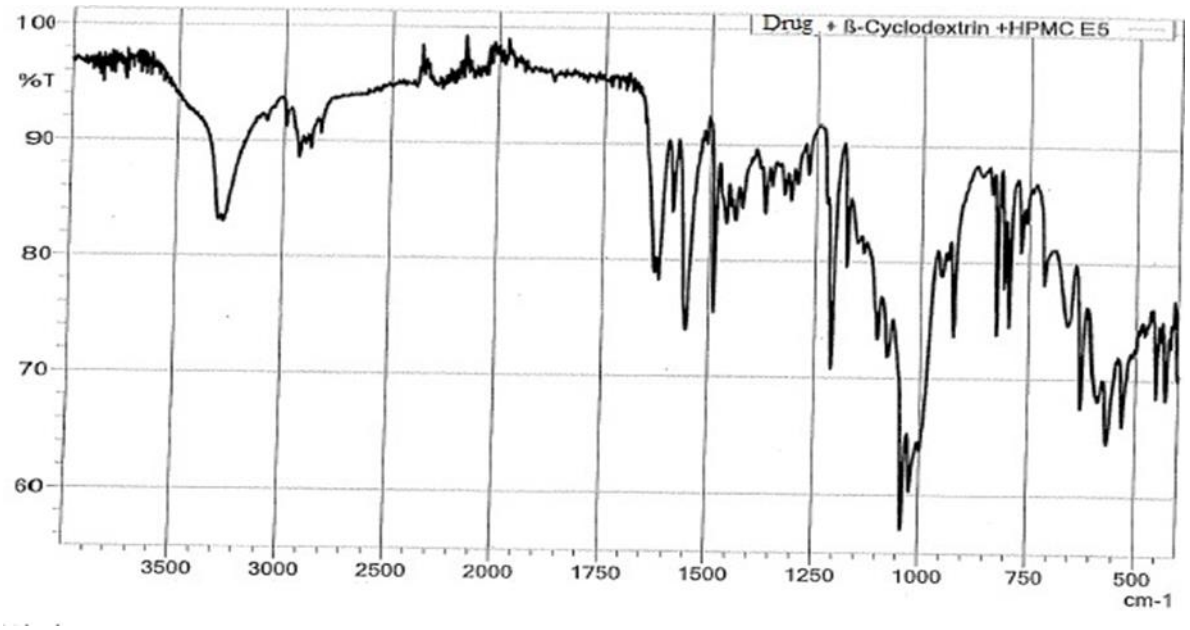

Figure 3.7 FTIR spectrum of HPMC-E5 with Melatonin and β-cyclodextrin solid dispersion

Table 3.8 FTIR Spectra Peaks of HPMC-E5 with Melatonin and β-cyclodextrin solid dispersion

Groups	Observed Value cm^{-1}	Reported Value cm^{-1}
N-H(stretch)	3300.12	3500-3300
=C-H(stretch)	2989.96	3100-3000
C-N	1212.57	1350-1000
C=C	1488.54	1600-1400
C=O (amide)(stretch)	1554.32	1700-1500
C-O	1079.59	1250-1050
O-H(stretch)	3320.15	3400-3200
CH_2(bend)	1461.38	1480-1440

The FTIR spectrum of Melatonin, physical mixture of Melatonin with HPMC-E5, solid dispersion of Melatonin with β-cyclodextrin, and physical mixture of HPMC-E5 with Melatonin and β-cyclodextrin was recorded and found in conformity with the stated peaks displayed in the figures. The FTIR spectra of a physical combination of Melatonin and HPMC-E5 revealed the major peaks of both components. Melatonin and HPMC-E5 showed no incompatibility or interaction in their physical combination. The FTIR spectrum of Melatonin dispersion with β-cyclodextrin revealed the main peaks of both components. Melatonin and β-cyclodextrin exhibited no incompatibility or interaction in their solid dispersion form.

The FTIR spectrum of a combination of HPMC-E5 with Melatonin and β-

cyclodextrin solid dispersion revealed the main peaks of both components. Melatonin and β-cyclodextrin solid dispersion showed no incompatibility or contact with HPMC-E5 in their physical combination.

3.2 Evaluation parameters of oral fast dissolving film:

Melatonin sheets containing β-cyclodextrin solid dispersion were examined for thickness, weight fluctuation, folding durability, drug content, surface pH, and disintegration time. Table 3.9 summarizes the study outcomes. Table 3.10 shows the in-vitro% drug release data for F1 to F9 formulations of oral fast dissolving film, whereas Figure 3.7 shows the in-vitro% drug release graph.

Table 3.9 Formulation's thickness, weight fluctuation, folding durability, drug content, and disintegration time 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±0.04	38.15±0.02	116	85.26±1.60	6.81	24±0.22
F2	0.08±0.07	39.38±0.11	122	91.37±1.42	6.92	18±0.36
F3	0.07±0.02	35.26±0.05	127	86.82±1.32	6.83	25±0.27
F4	0.09±0.05	36.43±0.09	134	94.21±0.52	6.76	20±0.34
F5	0.09±0.06	48.52±0.06	141	85.16±1.15	6.95	22±0.94
F6	0.08±0.02	47.35±0.04	148	97.36±1.74	6.88	15±0.40
F7	0.10±0.09	48.62±0.05	139	87.73±1.76	6.78	23±0.22
F8	0.11±0.03	49.22±0.07	144	92.82±0.68	6.69	30±0.16
F9	0.11±0.02	46.12±0.04	153	92.53±0.83	6.67	28±0.42

Table 3.10 Drug release % in vitro for oral fast-dissolving film formulations F1 to F9.

S.No.	Time (in sec.)	Drug Release % data								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	0	0	0	0	0	0	0	0	0	0
2.	30	25.65± 0.13	29.14± 0.42	23.12± 0.09	25.23± 0.14	20.28± 1.24	26.56± 0.12	22.84± 0.14	24.43± 0.70	25.92± 0.06
3.	60	35.47± 1.21	36.53± 0.46	39.24± 0.33	32.27± 0.84	35.18± 1.34	38.29± 0.12	31.93± 0.24	38.85± 0.07	40.63± 0.07
4.	90	46.45± 0.23	50.17± 0.26	59.29± 0.09	49.13± 1.36	46.37± 0.07	48.31± 0.38	42.15± 0.45	45.67± 0.02	53.23± 1.24
5.	120	62.23± 2.24	67.57± 0.09	69.46± 1.39	57.34± 1.63	65.25± 0.07	66.79± 2.16	68.91± 0.72	52.82± 1.53	67.10± 1.75
6.	150	76.14± 2.02	71.69± 2.12	84.10± 0.63	80.35± 0.19	79.54± 0.78	82.15± 0.70	75.32± 0.91	67.27± 0.16	86.82± 0.02
7.	180	94.42± 0.33	92.23± 0.42	96.68± 0.32	94.43± 0.35	90.38± 0.16	97.12± 0.91	91.59± 0.53	88.47± 0.96	93.76± 0.12

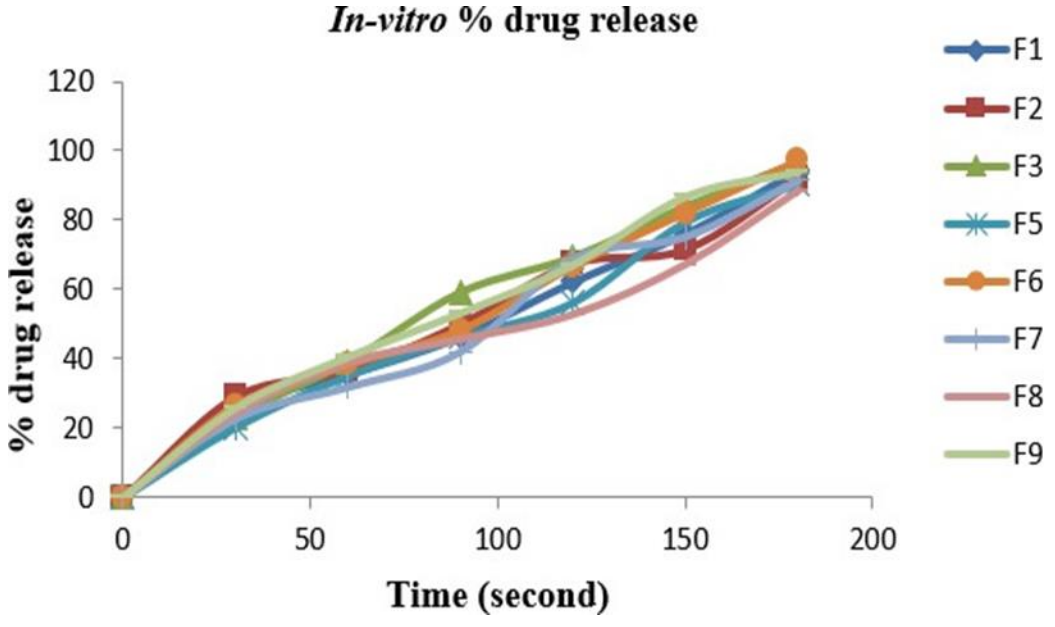

Figure 3.8 In-vitro % drug release profile of film formulations F1-F9

3.2.1 Evaluation of optimized formulation (F6):

Melatonin sheets containing β-cyclodextrin solid dispersion were examined for thickness, weight fluctuation, folding durability, drug content, surface pH, and disintegration time. Table 3.11 shows the study outcomes.

Table 3.11 The optimized formulation's thickness, weight fluctuation, folding durability, drug content, and disintegration time (F6).

Formulation	Thickness(mm) Mean±SD	Weight variation (mg) Mean±SD	Folding endurance(Times)	Drug Content(%) Mean± SD	Surface pH	Disintegration Time (sec) Mean± SD
F6	0.08±0.02	47.35±0.04	148	97.36±1.74	6.88	15±0.40

In-vitro % drug release study of optimized batch (F6)

The table below shows the in-vitro% drug release statistics for the optimised batch (F6) formulation of oral rapid dissolving film, and the image below shows an in-vitro% drug release graph. Within 180 seconds, the formulation F6 exhibits the highest release (97.12%).

Table 3.12 In-vitro % drug release data of optimize formulation (F6) of oral fast dissolving film.

S. no.	Time (in seconds)	*In-vitro* % drug release
		Optimized formulation F6
1.	0	0
2.	30	26.56±0.12
3.	60	38.29±0.12
4.	90	48.31±0.38
5.	120	66.79±2.16
6.	150	82.15±0.70
7.	180	97.12±0.91

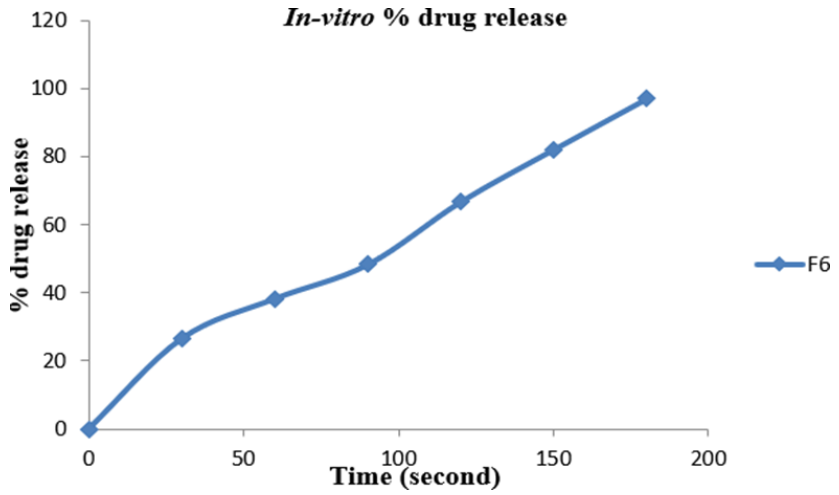

Figure 3.9 In-vitro % drug release profile of optimized formulations F6

4. SUMMARY AND CONCLUSION

First-pass metabolism limits the solubility and bioavailability of melatonin. In older individuals who have trouble digesting solid dosage forms (dysphasia), melatonin in standard dosage forms (tablets, capsules) has a slow onset of action. Solvent casting will be used to create an oral rapid dissolving film that contains melatonin. Melatonin can be made into a solid dispersion to overcome its limited water solubility. The creation of a solid dispersion oral fast-dissolving film of melatonin may minimize dysphasia, provide a quick onset of action, and avoid first-pass metabolism, which is the main reason for restricted bioavailability. The oral rapid-dissolving film of melatonin helps with sleep problems.

Melatonin's λmax, as measured by UV spectrophotometry, is 276.2 nm. Melatonin was discovered to have a melting point that was relatively near to the normal value. Every observation and piece of information gathered agreed with the values reported in the literature. A twin beam UV-visible spectrophotometer (Shimadzu 1800) was used to create melatonin calibration curves in ethanolic distilled water and phosphate buffer pH 6.8. FTIR was used in preformulation studies to examine the solubility of the drug and its interactions with different excipients. There were no physicochemical interactions between the medicines and excipients, according to FT-IR testing. Distilled water and phosphate buffer pH 6.8 were used to examine the solubility of a sample of melatonin medicine. Melatonin is poorly soluble in phosphate buffer (pH 6.8) and water. The goal of this study was to create, manufacture, and evaluate a melatonin oral quick-dissolving film. Solid dispersion was employed in the current investigation to improve the bioavailability and solubility of the medicine. Physical mixing was used to form a solid dispersion of melatonin: β-cyclodextrin in different ratios (1:1, 1:2, 1:3, 1:4). Melatonin enhances the solubility and dissolution of β-cyclodextrin at the ideal concentration when added to its solid dispersion.

When compared to 1:1 and 1:2, the melatonin: β-cyclodextrin ratio of 1:3 produced the greatest improvement in water solubility. Nevertheless, when the ratio of melatonin to β-cyclodextrin was raised to 1:4 from 1:3, SDPs did not considerably improve melatonin solubility. Thus, formulation F6 was found to be the best formulation based on the data collected. Formulation F6, which has a disintegration time of 15 seconds and a total drug release percentage of 97.12% over 180 seconds, makes this clear. Therefore, patients with sleep disorders should benefit from the drug administered in the form of oral rapid dissolving films since it has a quick start of action, prevents dysphasia, and is an effective therapeutic method.

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