https://doi.org/10.15218/zjms.2024.029

Formulation and evaluation of melatonin as fast dissolving oral strips using combined polymers

Received: 18/09/2022 Accepted: 24/11/2022

Muhannad Omer Taher [1*] Huner Kamal Gardy [1]

Abstract

Background and objective: Fast-dissolving oral thin film (FDOF) is a novel and most advanced form of solid dosage form that dissolves or disintegrates in 1 minute when put in the mouth without water or chewing. Pre-gastric absorption of FODFs from the mouth, pharynx, and esophagus as saliva flows down into the stomach would improve the therapeutic benefit of the drug as oral films disintegrated in the mouth. The study is designed and purposed to use most water soluble, best type and concentration of polymers to be selected for use in combination to formulate melatonin oral thin films. Different types of synthetic water soluble polymers were utilized the preparation of films (hydroxypropyl methyl cellulose HPMC15M, sodium carboxy methyl cellulose NACMC).

Methods: Solvent casting method was performed for preparation of twelve placebo films at the beginning, to obtain and select suitable polymer type and concentration for use in combination to be formulated for drug loading. The films were evaluated for their characteristics like mechanical properties (thickness and folding endurance), surface pH and disintegration time. Percentage of release and assay of melatonin was taken. Comparison studies were performed on melatonin films from this study with melatonin oral disintegrating tablets release profiles. Best batch could be selected. Drug-excipient compatibility carried out as pre formulation study to see whether there is interaction between the drug and excipients used.

Results: Results from FT-IR showed no interaction between melatonin and polymers used, the prepared formulations were clear, transparent, non-sticky and easily removed from the plate surface with the thickness ranging from (0.04-0.07) mm depending on the polymer concentration. The times required for the films to disintegrate was ranging from 21-26 seconds, and the majority of melatonin was released within first 2 minutes within the dosage form.

Conclusion: Melatonin can be formulated as fast dissolving oral films using combination of water-soluble polymers by solvent casting method to obtain ease of administration without using water during administration, fast onset of action resulted from rapid disintegration.

Keywords: Fast dissolving oral films FDOF; Hypromellose; Sodium carboxy methyl cellulose; Melatonin.

Introduction

Because of the low cost of treatment and ease of delivery, the oral route remains the best route for administering therapeutic agents. Oral dosage forms are the most popular among other dosage forms since it has ease of application, accuracy in the dosage, self-administration, better patient compliance, and cost effective. Oral solid dosage forms account for roughly 60% of all dosage forms available. Tablets and capsules are the most popular solid dosage forms.[1] Fast dissolving oral drug delivery systems were first introduced in the 1970s as an alternative to pills, capsules, and syrups for pediatric and

[1] Department of Pharmaceutics, College of Pharmacy, Hawler Medical University, Erbil, Iraq.
Correspondence: muhannadpharmacist91@gmail.com

https://doi.org/10.15218/zjms.2024.029

geriatric patients who had trouble swallowing standard oral solid-dosage formulations. Fast dissolving oral dosage form has becoming significantly important due to their pleasant characteristics.[2]

Fast dissolving oral thin film is an example of an innovative way to maximize market adoption by the virtues of rapid dissolution, self- administration, ease of handling, compact packaging, and a good taste. Fast dissolving oral films also known as mouth dissolving films (MDF), oral thin films (OTF), oral strips, oro-dispersive films.[1]

Orally fast dissolving films are new drug delivery system that consist of thin oral films (solid dosage form) that dissolves in oral mucosa within seconds as it come in contact with patient's saliva.[3] Oral Thin Films are now a well-established and widely used technology for the systematic delivery of active pharmaceutical ingredients (APIs) in over-the-counter (OTC) and prescription medications.[4]

A fast-dissolving film is a thin, 5- to 20-cm2 film containing an active ingredient, film forming polymers, plasticizer, saliva stimulating agent, surfactant, super disintegrant, flavoring and sweetening agents.[1]The study aimed at finding best type and proper polymer concentration to be used in combination for drug incorporation.

Pineal gland during the night, secretes an indole amine called melatonin which plays an important role in regulating circadian rhythm. Melatonin is an indole amine neurohormone whose levels vary in a daily cycle. biologic effects of melatonin are performed through melatonin receptors MT1, MT2, and MT3.[5] The administration of this neurohormone is very useful for treating sleep disorders in both children and elderly. Melatonin secretion and synthesis is inhibited by light and enhanced by darkness.[6]

After intravenously administering of melatonin is rapidly distributed since its 100% bioavailable and its half-life is (0.5 to 5.6 minutes) and eliminated. After orally administering of melatonin, plasma concentration arises peak within 60 minutes. After intravenous or oral administration, melatonin is quickly metabolized, mainly in the liver and secondarily in the kidney.[7] In general melatonin is available in various dosage forms in the market from different origins, most of them are available in a form of oral dosage forms such as solid oral dosage forms; tablet, capsule, effervescent tablet, gummies, and mouth dissolving tablets. And also liquid oral dosage forms are available as melatonin syrups.

Methods

Materials

Pure melatonin powder was purchased from material USP 12601. Film forming polymers HPMC k1500, NACMC, CMC, and HPC, plasticizers glycerol, PEG400, and propylene glycol, sweeteners as sodium saccharine, saliva stimulating agent as citric acid and mannitol DC400 as diluent were all obtained as a gift from Awamedica company, Erbil.

Drug-excipient compatibility

Fourier Transformation Infrared Spectroscopy (FTIR)

This study was carried out by using FT-IR, to obtain whether the drug is compatible with the excipients specially polymers or not and assure that melatonin functional groups will remain without disappearing, at which the study is conducted on pure drug alone and a mixture of drug and polymers. Spectra of melatonin and polymers were obtained.[8]

Characterization of melatonin

Determination of melatonin melting point

The basic and most common method for determination of melting point is capillary tube method by using electrical melting point apparatus which was also performed in the study.

Determination the λmax of melatonin

A stock solution of 100 m/ml melatonin was prepared by dissolving 5mg of pure (reference standard) powder of melatonin in 50ml 0.1N HCL by using sonicator,

https://doi.org/10.15218/zjms.2024.029

which was then completed to 100ml in a volumetric flask. After suitable dilutions from stock solution by using UV spectrophotometer, the sample solution taken from stock solution is scanned in the range of 200-400 nm, and the l max was detected.

Determination of Calibration Curve

From the stock solution 100µg/ml of melatonin, a series of diluted solutions were prepared, with concentrations 2.5µg/ml, 5, 7.5, 10, 11, 12, 15µg/ml. from these solutions samples were taken and scanned at melatonin l max by using double beam UV Spectroscopy (UV-VIS SPECTROPHPTOMETER, shimadzu), and the absorbance of diluted solutions were recorded and average absorbance was calculated. In order to obtain linearity, absorbance's of samples were plotted versus concentration, usually the linearity of calibration curve is expressed through correlation coefficient (R^2).

Method

Formulation of melatonin films using solvent casting method

Melatonin thin films were prepared by using the solvent casting method according to the formula in Table 1. In the beginning, a polymeric solution was prepared by adding and dissolving polymers to 25 ml of water in a beaker mixed gently to form a homogenous solution, Other excipients were added slowly to the polymeric solution.

Table 2 shows the composition of preliminary batches without melatonin. The drug was dissolved alone in the ratio of 2:1 water and ethanol, then the drug solution was added to the solutions of polymers and excipients with continued and gentle stirring on a magnetic hot plate using a magnetic stirrer till a clear solution was formed, Table 3 shows the composition and amount of each ingredients of prepared melatonin. The formed solution is kept aside; thus, all formed bubbles are removed. Then the solution is cast on the surface of the petri dish and dried either at room temperature or put in an oven at 50 Cº for 12 hours.[9] The formed films were gently removed from the surface and cut into the desired size (22cm^2).

Different concentration of polymers (40%, 45%, and 50%) were used alone (according to reference concentration of polymers used. 25). Based on the peel ability, surface texture, and mechanical properties of films best type and concentration of polymers were selected. In this study,45% of combined HPMC K1500 and NACMC was used.

Table 1 Concentration of ingredients used in fast dissolving oral film formulations[10]

Ingredients	Concentrations % (w/w)
Polymers	40, 45, and 50
Plasticizer	0-20%
Saliva stimulating agent	3-5
Sweetener	3-5
Diluents	q.s

https://doi.org/10.15218/zjms.2024.029

Table 2 composition of preliminary batches (films without melatonin)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
HPMC *	40	45	50	-	-	-	-	-	-	-	-	-	-	-	-
NACMC *	-	-	-	40	45	50	-	-	-	-	-	-	-	-	-
CMC *	-	-	-	-	-	-	40	45	50	-	-	-	-	-	-
HPC *	-	-	-	-	-	-	-	-	-	40	45	50	-	-	-
HPMCK1500 , NACMC combined polymers *	-	-	-	-	-	-	-	-	-	-	-	-	30/15	22.5/22.5	15/30
citric acid *	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Sodium saccharine *	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
GLYCERIN *	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Mannitol q.s up to 100 *	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml

*amounts expressed as %w/w

Table 3 Composition of melatonin fast dissolving films in this study

Ingredients	Amounts
Melatonin	5 mg
HPMC	22.5%
NACMC	22.5%
Citric acid	5%
Glycerol	15%
Sodium saccharine	5%
Mannitol	q.s
Water	18 ml
Ethanol	2-3 ml

*amounts expressed as %w/w

https://doi.org/10.15218/zjms.2024.029

Evaluation of the prepared films

Organoleptic evaluations

Films were evaluated for color, transparency, surface texture, peel ability and flexibility by visual inspection. Fast dissolving oral films FDOFs were also evaluated for taste and odor.[11]

Mechanical properties

Thickness

The thickness of the film measured using a Digital Vernier Caliper which was carried out in AWAMEDICA manufacture for the ones with melatonin and without melatonin. The films which contain tears and bubbles were not analyzed. The thickness was measured at five distinct crucial spots: our corners and center.[12]

2.3.3.3. Folding Endurance

Folding endurance was measured by folding the film in the same place over and over until it broke. The folding endurance value is the number of times a film can be folded without breaking, for all types of the films folding and unfolding the film at the same place was performed manually.[13] Films with a folding endurance value of 300times or more are considered to be ideal.[14]

Surface pH

The surface pH of the films must be determined because either the highly acidic or highly basic pH of ODF cause irritation and discomfort during administration. Determination of surface pH is necessary for evaluation of acceptability of FDOFs administration in the mouth. Films of melatonin formulation placed in petri dish filled with 2ml of distilled water for wetting of the films, pH meter is used to determine surface pH, at which ends of electrode touched the surface of films. The surface pH of ODF should be within the normal range of salivary pH 6.2–7.6.[15]

***In – Vitro* Disintegration Time of the Films**

The Center for Drug Evaluation and Research CDER guidance's disintegration time requirement of 30 seconds or fewer for orally disintegrating tablets can be applied to fast dissolving oral films. Various method available to determine the disintegration time of FDOF, to perform the disintegration of oral thin film of melatonin and without melatonin petri dish method was performed, 5mL of water was added in a petri dish then the film was put in the center of the petri dish. The time at which the film starts to disintegrate or break was recorded as disintegration time.[16]

***In–Vitro* dissolution study**

This approach was used to determine cumulative drug release and cumulative percentage of drug retained. A USP paddle type equipment was used to perform in-vitro drug dissolution. The experiments were carried out in a 900 ml 0.1N HCL at 37°C with a 50-rpm stirring speed.[17] At predefined intervals of 2, 4, 6, 8, 10, 12, 15 minutes respectively, samples of 5 ml taken at each interval and replaced with the same volume of 0.1N HCL. The samples were collected, and the concentration was measured using a UV-visible spectrophotometer at the 277nm wavelength.[18]

Comparison studies between melatonin films of this study and other melatonin dosage forms.

Release profiles of melatonin and oral disintegrating tablets (ODT) were compared. A USP paddle type equipment was used to perform the comparison. Release profile of melatonin films and melatonin conventional tablets were compared. Disintegration time of two fast dissolving oral dosage forms were compared (melatonin thin films and melatonin ODT).

Statistical Analysis

Comparison of results of the study was done by using the Statistical Package for Social Sciences (SPSS, version 25) by using paired sample t-test and ANOVA test for statistical analysis. The evaluated parameters were expressed as mean and standard deviation. Difference was considered statically significant ($P \leq 0.05$).

https://doi.org/10.15218/zjms.2024.029

Results

Drug-excipient compatibility studies

The study was performed using FT-IR, Figure 1 below explains the compatibility of melatonin with polymers used.

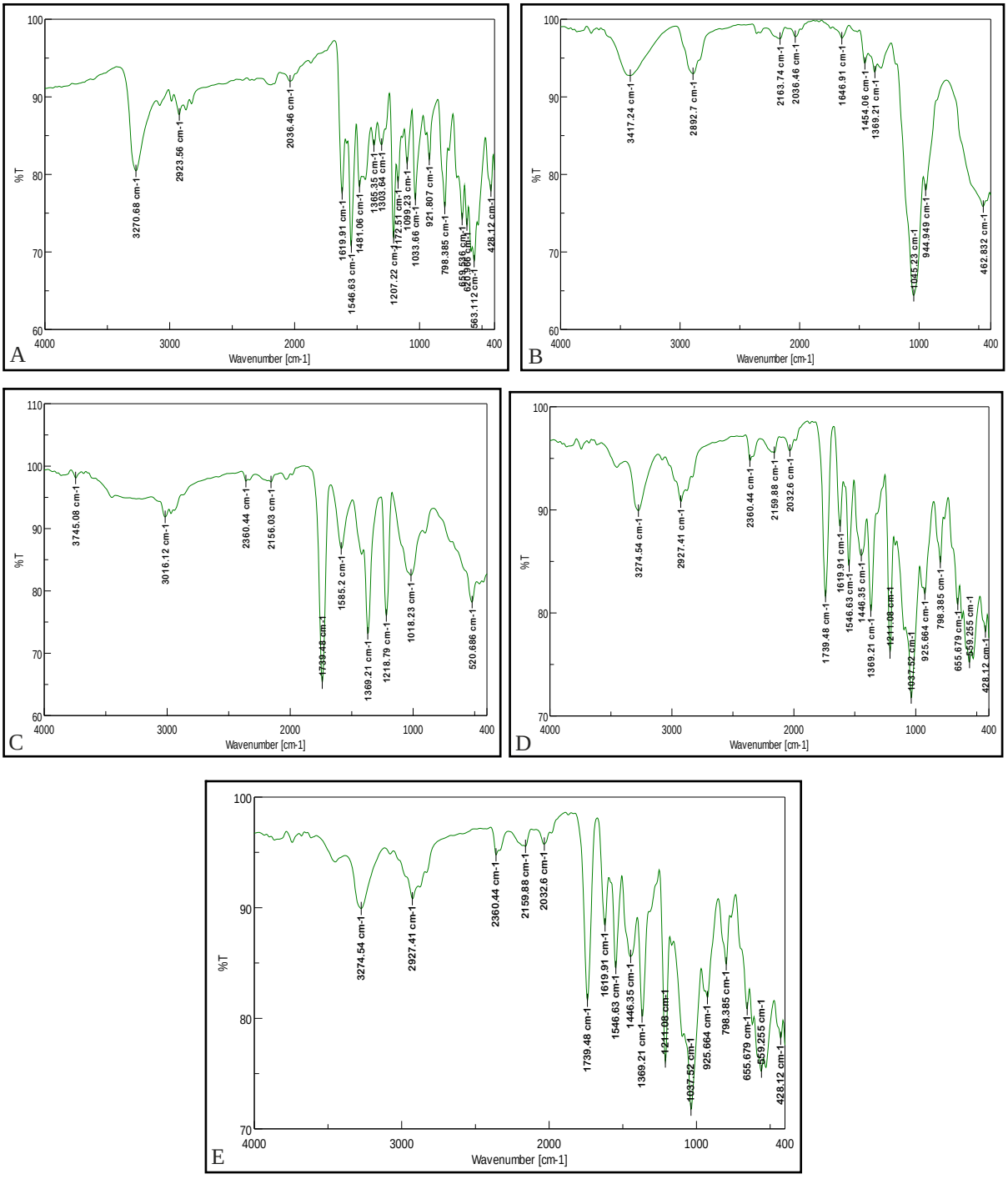

Figure 1 shows spectra of melatonin and excipients (melatonin spectra A, HPMC spectra B, NACMC spectra C, melatonin with HPMC spectra D, melatonin with HPMC k15 and NACMC E)

https://doi.org/10.15218/zjms.2024.029

Meting point measurement

Melting point of pure melatonin measured, starts melting from (114-117.2ºC)

Determination of lmax of melatonin

After scanning of sample solution by using UV spectroscopy, the maximum absorbance was detected at the range 277nm which recorded as lmax and showed in Figure 2.

Determination of calibration curve

Figure 3 explains the calibration curve of melatonin as a result of plotting absorbance against concentration which shows the linearity at (2.5-15mg/ml) concentrations, which was an indication of following Beers-Lambert low of linearity, with correlation coefficient R 0.9994.

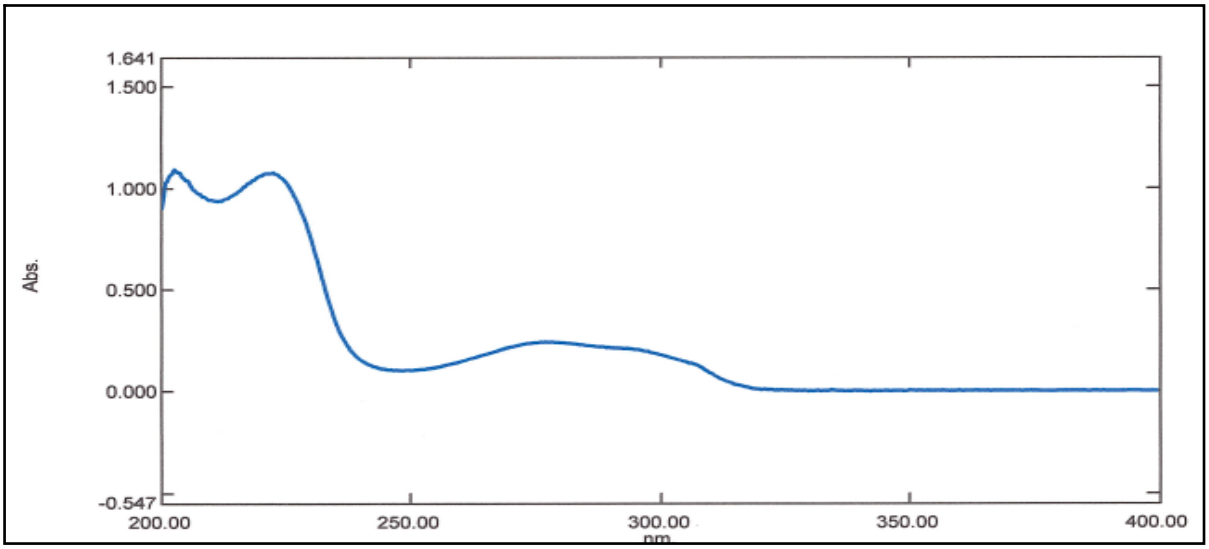

Figure 2 l max of melatonin

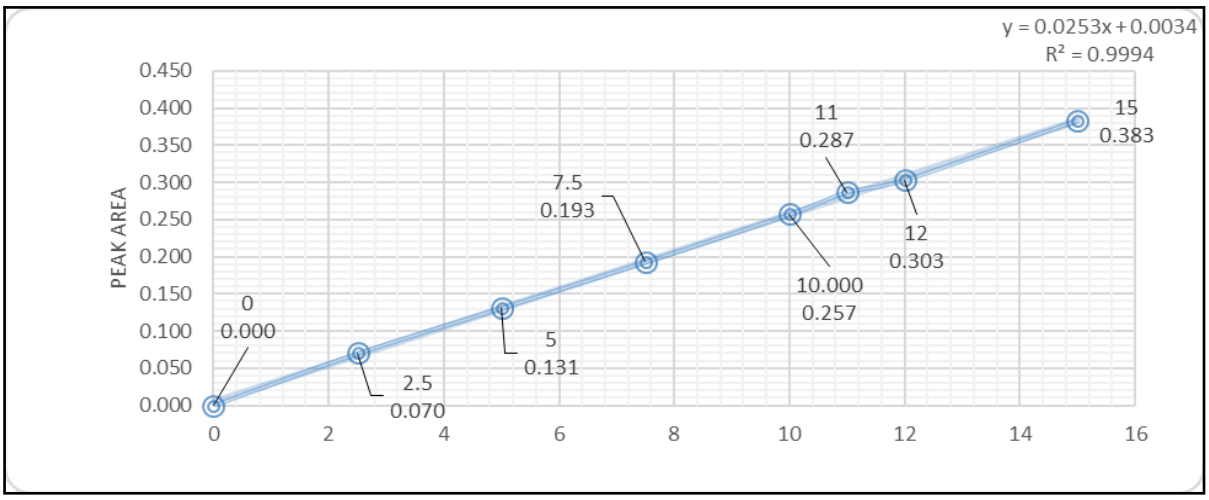

Figure 3 calibration curve of melatonin

https://doi.org/10.15218/zjms.2024.029

Evaluation of fast dissolving films (with and without melatonin)

Results of evaluation parameters are tabulated below in Table 4, which includes (thickness, folding endurance, *in-vitro* disintegration time, surface pH, and film properties), films with same type of polymer with different concentrations were compared with each other, based on the parameters the best formula was selected for melatonin incorporation (drug-loaded formulation).

Table 4 Evaluation of preliminary batches and melatonin films

Formulation	Film forming capacity	Organoleptic properties	Surface pH	* Folding endurance (no. of folds)	* Thickness (mm)	* In-vitro disintegration time (sec)
F1	Very good	Transparent, odorless	6.73±0.12	398±1.52	0.04±0.006	21±0.85
F2	Very good	Transparent, odorless	6.78±0.045	399±1.52	0.05±0.016	23±1.79
F3	Very good	Milky Transparent, odorless	6.75±0.095	399±0.57	0.06±0.014	25±0.5
F4	Very good	Clear transparent	6.76±0.15	400±0.57	0.05±0.014	23±1.41
F5	Very good	Clear transparent	6.77±0.079	400.6±1.52	0.06±0.01	25.6±1.23
F6	Very good	Clear transparent	6.91±0.055	405±1.15	0.07±0.013	28.1±0.14
F13	Very good	Clear transparent	6.69±0.17	430±0.57	0.058±0.011	24.24±0.53
F14	Very good	Clear transparent	6.93±0.075	440±1	0.06±0.012	24.2±0.83
F15	Very good	Milky transparent	7.05±0.13	455±0.52	0.073±0.006	26±0.21
Melatonin films	Very good	Milky transparent	7.1±0.12	430±0.52	0.061±0.007	24.3±0.78

Results were expressed as mean ± SD, (surface pH n=3, folding endurance n=3, thickness n=6, disintegration time n=5). The (*) indicates that there was statistical significant difference between polymer concentration and those parameters. (*P <0.05).*

https://doi.org/10.15218/zjms.2024.029

In-vitro dissolution test in 0.1N HCL

Figure 4 shows the release profile of melatonin in (22.5% HPMC and 22.5% NaCMC) in 0.1N HCL at different time intervals. At which 90% of melatonin was released within the first two minutes, which indicates the dosage form fast disintegration time.

Comparison studies

Comparison of melatonin films of this study and other melatonin dosage forms was performed on *in-vitro* disintegrating time of prepared melatonin films with melatonin ODT shown in Figure 5 and *in-vitro* dissolution test using 0.1N HCL of prepared melatonin films with melatonin ODT and melatonin conventional tablets shown in Figures 6 and 7 respectively.

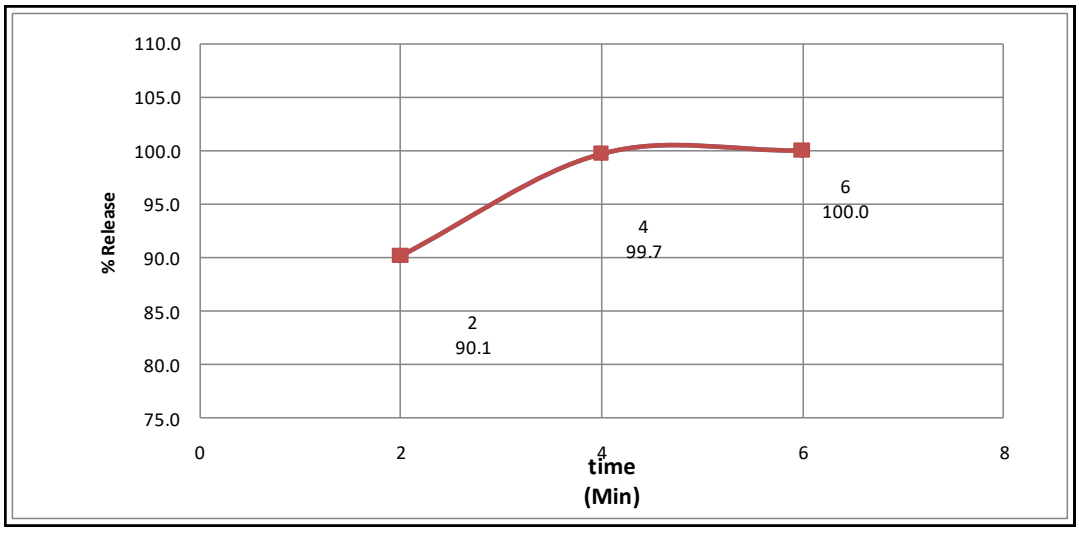

Figure 4 *In-vitro* dissolution (percentage of release per time interval) of melatonin in (22.5% HPMC K15 and 22.5% NACMC)

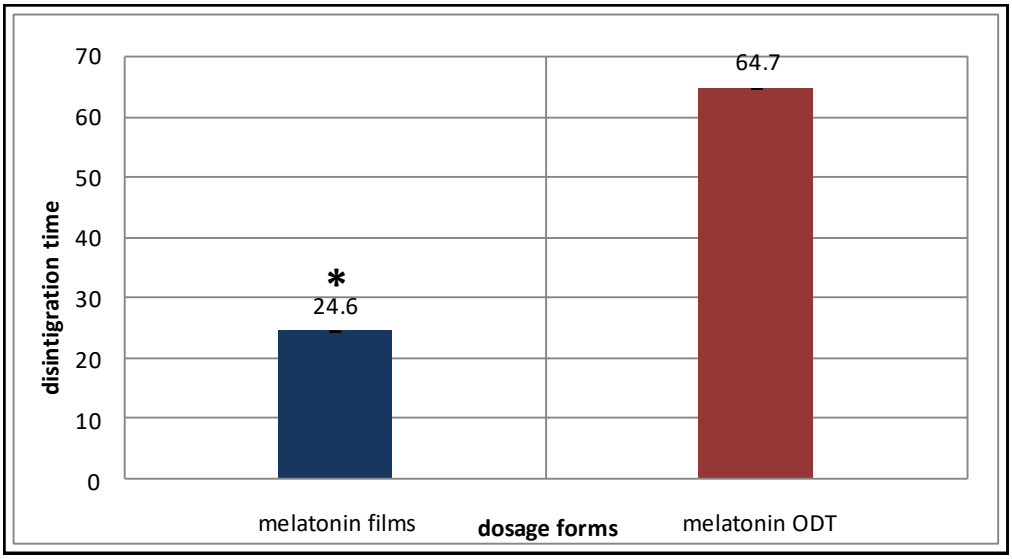

Figure 5 *In- vitro* disintegration time of the prepared melatonin film versus Melatonin ODTs. The (*) indicate there is a significant difference in disintegration time between melatonin film and melatonin ODTs *(P <0.001).*

https://doi.org/10.15218/zjms.2024.029

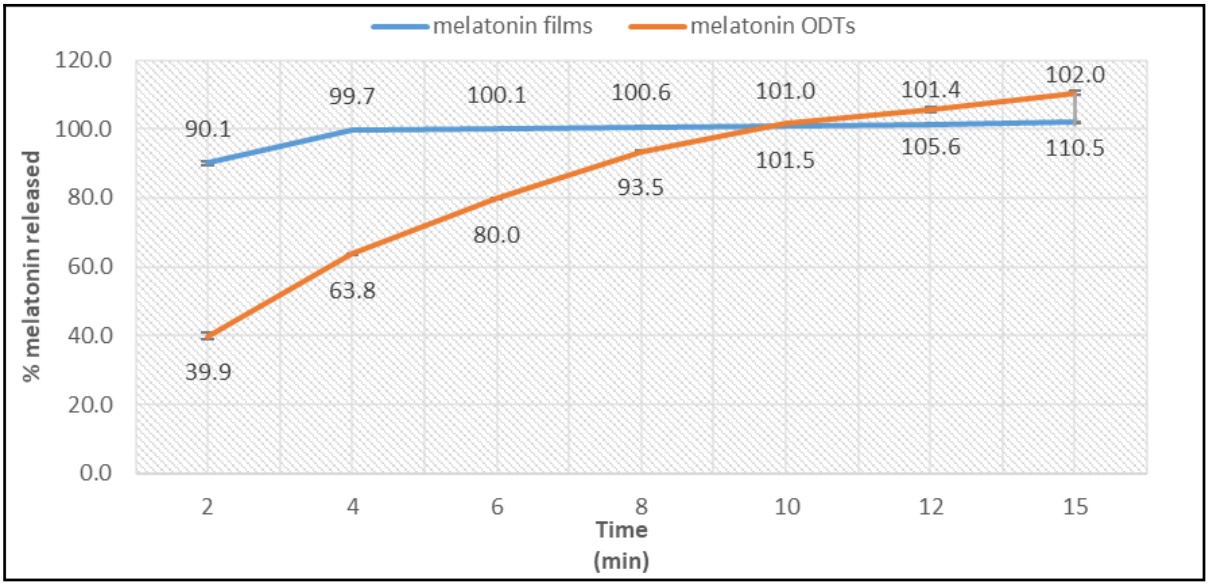

Figure 6 Comparison of release profile of melatonin films and melatonin ODTs
Results expressed as mean ± SD, *(P <0.002)*

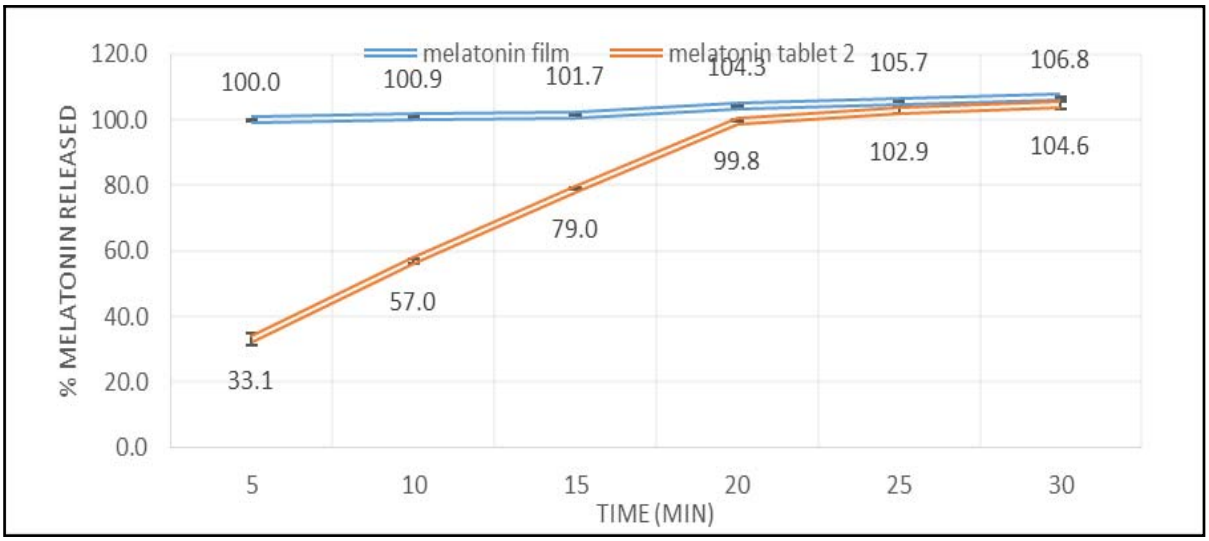

Figure 7 Comparison of release profile of melatonin films and melatonin conventional tablet
Results expressed as mean ± SD, *(P <0.0001)*

https://doi.org/10.15218/zjms.2024.029

Discussion

FTIR spectrum of drug. drug-excipient mixture and excipients alone are shown in the Figure 1 respectively. FTIR of melatonin complies with its chemical structure and shows peaks for its functional groups without disappearing. The study demonstrates that there is no loss of the main functional groups, which are responsible for biologic activity and water solubility of the melatonin, when the melatonin is combined with the polymers. The slight shifts of peaks may due to hydrogen bonding between hydrophilic groups the melatonin and polymers.

In the formulation of melatonin thin films, various preliminary trials were done to select a suitable type and concentration of polymers, capable of forming films with desirable organoleptic and mechanical properties with acceptable and good disintegration time. Preliminary batches were prepared using different type and concentration of polymers (HPMC, NACMC, HPC, CMC at 40%, 45%, 50% w/w) with same plasticizer concentration. F1-F6 batches at which HPMC and NACMC alone were used, showed suitable physical properties, clear transparent, odorless and good surface texture to be selected for drug loading, however in the formulation of atenolol films using NACM, films were brittle with rough surface.[11]

In this study CMC and HPC placebo films (F7-F12) were brittle and breakable during removing from the plate with poor physical and mechanical properties which were all excluded from the study, this may resulted from incompatibility of plasticizer with the polymers. HPMC and NACMC placebo batches were all had acceptable appearance with good peel ability except 40% of both polymers were somewhat difficulty removed from plate surface.[19]

Regarding mechanical properties and thickness, all three used concentrations of polymers were within acceptable limit (less than 0.3mm), with thickness ranging from (0.04-0.07), with greater thickness for 50% polymer concentration of NACMC and least for 40% HPMC, folding endurance all greater than 300 times. Based on the ease of peeling and acceptable thickness of both polymers (NACMC and HPMC) decision was made to prepare combined polymer formulations with 45% for both. various trails have been done, Preliminary batches (F13-f15) prepared with HPMC K1500 and NACMC at 2:1 (F13), 1:1 (F14), and 1:2 (F15) polymers to polymer ratios showed good properties acceptable transparency easily removable, enough to be formulated for drug loading.

After selection of polymer type and ratio, further evaluation tests were performed, all prepared films of combined polymers were within acceptable range of thickness ranging from (0.058-0.07 mm), folding endurance (>300 times), and disintegration time less than 1 min. In the evaluation of FDOF, the thickness homogeneity is an essential mechanical factor as it has consequential implication for the precision of dose distribution of FDOF. The uniformity of thickness has a direct association to the content uniformity and weight of films.[20]

Polymers (HPMC K15, NACMC) are good film former for the preparation of acceptable film thickness, folding endurance and disintegration time which they were used in combination in this study and showed by the results. the slight change in the thickness among formulations due to using different concentration of polymers, since increasing polymer concertation resulted in increase in the thickness parameter which in turn results in different time required for disintegration, and this may also due to the different type of polymers, using NACMC as film forming polymer may exhibit a variation in the thickness of the films, probably this condition may result from high viscous solution formed from NACMC which makes somewhat difficulty in pouring and casting process,[21] otherwise NACMC films were thicker than those prepared with HPMC. variation in thickness may result from uneven surface of the Petri dish, variation in drying time and inherent experimental studies.[22,8]

Identifying the suitable and acceptable thickness for drug loading is potentially

https://doi.org/10.15218/zjms.2024.029

necessary since it has a great impact on the disintegration time and mechanical properties of FDOF. Hence there is a proportionality between thickness and disintegration time, from which thickness greatly affected by polymer concentration.[19] Statistical analysis showed that there was a significant difference between (F1-F3), (F4-F6) batches (*P* <0.05), since higher concentration of polymers used in both F3 and F6. Regarding combined polymers placebo films (F13-F15), there was no significant difference between them (*P* >0.05). the reason behind the selection of F14 in which 1:1 polymer ratio was used for incorporation of melatonin was that regarding F13 concentration of HPMC k15 used was higher than that of NACMC, during evaluation obtained that there was greater variation among thickness, disintegration time and weight of single films as compared to F14. The F15 formulation have greater thickness, since in F15 formulations higher NACMC concentration was used and results in thicker and more viscous solution which makes difficulty in casting on plate surface. Combination of polymers does not show great influence on the thickness of the films.

According to the results, the folding number of formulations were from the range (398-430 times), it means that all prepared formulation (placebo and drug-loaded films) have acceptable mechanical strength and met the requirement of folding endurance of FDOF (more than 300). From statistical analysis there was no significant difference between types of polymers and folding number *(P >0.05),* also statistically there was no significant difference among formulation with different polymer concentrations. The slight change and different in folding number was due to concentration of plasticizer, although same plasticizer concentration was used but during preparation it was difficult to weigh and measure the exact amount of plasticizer, thus, some formulations have increased number of folding. As the concentration of plasticizer increase the number of folding and mechanical properties will increase.[7] from our study concentration of plasticizer was same for all preparation. Folding number was also affected by concentration of polymers, as concentration increase number of folding increase. In this study increasing polymer concentration did show significant difference *(P >0.05).* preliminary batches with combined polymers showed greater ability to withstand breakage and higher folding number than those films prepared with single polymers and statistical analysis revealed that there was significant difference when oral films prepared with combination of polymers *(P <0.05).*

In the formulation of FDOF, the surface pH was evaluated to previse its possible effect on the oral mucosa during its administration, since acidic or alkaline pH of oral formulation may result in irritation of oral mucous membrane. In this study pH of all formulation was within the acceptable range and exhibit neutral pH (6.7-7.1), this will not be causing irritation and spitting out the dosage form.[23]

Determining in vitro disintegration time is greatly affected by the physicochemical properties of the selected polymers.[24] By increasing concentration of polymers, disintegration time will increase which in turn thickness increased. All preliminary batches have acceptable disintegration less than (1 min). statically analysis showed that there is significant difference between batches with higher concentration of polymers (F3 and F6) (*P* <0.05).

disintegration times of formulations with combined polymers (F13, F14, and F15) were also different and there was significant difference between them (*P* <0.05), since F13 concentration of HPMC was high while F15 concentration of NACMC was higher. Although 40% of both used polymers had the faster disintegration time (21 seconds for HPMC, 23 seconds for NACMC) but decision was made to select and formulate 45% of combined polymers based on peel ability and smooth surface.

Melatonin release profile was taken in HCL, at which 90% of melatonin was released within the first two minutes, this indicates 45% concentration of combined polymers rapidly disintegrates with

https://doi.org/10.15218/zjms.2024.029

acceptable thickness and readily releases its content into dissolution medium.

The disintegration of both novel fast dissolving oral dosage form (melatonin FDOFs and melatonin ODT) was compared, with faster disintegration time for melatonin films, statistical analysis showed significant difference between disintegration time of both novel dosage forms (*P <0.05)*.as shown in figure 4.

Release profile of melatonin films was compare with melatonin ODT and melatonin conventional tablets. From the results as shown in the figures 5 and 6 respectively, Figure 5 illustrates the comparison of melatonin films with melatonin ODT during first two minutes at which 90% of melatonin was release from films of this study while only 40% of melatonin released from oral disintegrating tablets, statistical analysis showed (*P <0.05)* significant difference in the release profile of both dosage forms. Figure 6 shows the results of melatonin film and melatonin conventional tablets, during the first 5 minutes total 100% of melatonin released from oral films while only about 33% of melatonin was released from conventional (*P <0.05)*. this is an indication of oral films as fast disintegrating dosage form.

Conclusion

Melatonin films were successfully formulated using 45% combination of water-soluble polymers (HPMC K15 and NACMC), development of melatonin film is an alternative route for immediate action. Hypromellose and sodium carboxymethyl cellulose were both good film former with acceptable thickness and mechanical strength which led to faster disintegration time and releasing of melatonin from the dosage form when compared with a novel fast dissolving tablet.

Funding

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kathpalia H, Gupte A, An introduction to fast dissolving oral thin film drug delivery systems a review. Current Drug Delivery 2013; 10:667–84.
2. Siddiqui M, Garg G, Sharma PK. A short review on a novel approach in oral fast dissolving drug delivery system and their patents. Adv Biol Res 2011; 5:291–303.
3. Bala R, Pawar P, Khanna S, Arora S. Orally dissolving strips a new approach to oral drug delivery system. Int J Pharm Investing 2013; 3:67 –76. 10.4103/2230-973X.114897.
4. Karki S, Kim H, Na SJ, Shin D, Jo K, Lee J. Thin films as an emerging platform for drug delivery. Asian J Pharm Sci 2016; 11:559–74. https://doi.org/10.1016/j.ajps.2016.05.004
5. Reiter RJ, Tan DX, Fuentes-broto I. Melatonin a multitasking molecule. Pro Brain Res 2010; 181:127-51.https://doi.org/10.1016/S0079-6123(08)81008-4
6. Byeony back K. Melatonin synthesis in rice seedlings in vivo is enhanced at high temperatures and under dark conditions due to increased serotonin n□acetyltransferase and n□acetylserotonin methyltransferase activities. J Pin Res 2014; 56(2):189–95. https://doi.org/10.1111/jpi.12111
7. Tordjman S, Chokron S, Delorme R, Charrier A, Bellissant E, Jaafari N, et al. Melatonin pharmacology functions and therapeutic benefits. Curr Neuro pharm 2017; 15(3):434–43.
8. Patel DM, Dabhi DV. Development and characterization of oral dissolving film for promethazine hcl. Inter J Pharm Sci and Res 2014; 5(11):4728. 10.13040/IJPSR.0975-8232.5(11).4728-40.
9. Ghorwade VI, Patil AJ, Hullale AS. Fast dissolving films a novel approach for the delivery of montelukast sodium. Int J Pharm Pharm Sci 2012; 4(2):228–32.
10. Ghodake PP, Karande KM, Osmani RA, Bhosale RR, Harkare BR, Kale BB. Mouth dissolving films innovative vehicle for oral drug delivery. Polymer 2013; 9:20.
11. Rani KC, Parfati N, Aryani NL, Winantari AN, Fitriani EW, Pradana AT, et al. Development evaluation and molecular docking of oral dissolving film of atenolol. Pharmaceutics 2021; 13(10):1727. https://doi.org/10.3390/pharmaceutics13101727
12. Londhe VY, Umalkar KB. Formulation development and evaluation of fast dissolving film of telmisartan. Ind J Pharm Sci 2012; 74:122 –6. 10.4103/0250-474X.10384
13. Irfan M, Rabel S, Bukhtar Q, Qadir MI, Jabeen F, Khan A. Orally disintegrating films a modern expansion in drug delivery system. Saudi Pharm J 2016; 24:537–46. https://doi.org/10.1016/j.jsps.2015.02.024
14. Yir-erong B, Bayor MT, Ayensu I, Gbedema SY, Boateng JS. Oral thin films as a remedy for noncompliance in pediatric and geriatric patients. Ther Deliv 2019; 10:443–64. https://doi.org/10.4155/tde-2019-0032

15. Nalluri BN, Sravani B, Anusha VS, Sribramhini R, Maheswari KM. Development and evaluation of mouth dissolving films of sumatriptan succinate for better therapeutic efficacy. J Appl Pharm Sci 2013; 3:161–6. 10.7324/JAPS.2013.3828.
16. Mahaparale MA, Shivnikar SS, Pawar KV, Prashant N. Fast dissolving oral films an innovative drug delivery system. I J RR Pas 2012; 2(3):482–96.
17. Kathpalia H, Sule B, Gupte A. Development and evaluation of orally disintegrating film of tramadol hydrochloride. Asi J B Pharm Sci 2013; 3(24):27–32.
18. Pezik E, Gulsun T, Sahin S, Vural I. Development and characterization of pullulan-based orally disintegrating films containing amlodipine besylate. Eur J Pharm Sci 2021; 156:105597. https://doi.org/10.1016/j.ejps.2020.105597
19. Muhammed RA, Omer HK. Formulation and evaluation of fast dissolving oral film of imipramine. Poly Tech J 2020; 10(1):182–8. https://doi.org/10.25156/ptj.v10n1y2020.
20. Al-ghabban FM, Al-ani IH, Hassan SF, Salan N. Formulation of prifinium bromide and prifinium bromide-diclofenac sodium combination as orodispersible tablets. Int J Pharm Pharm Sci 2013; 5:652–9.
21. Centkowska K, lawrecka E, Sznitowska M. Technology of orodispersible polymer films with micronized loratadine influence of different drug loadings on film properties. Pharmaceutics 2020; 12:250. https://doi.org/10.3390/pharmaceutics12030250
22. Hussain A, Latif S, Abbas N, Irfan M, Arshad MS, Bukhari NI. Hydroxypropyl cellulose based orally disintegrating films of promethazine hcl for the treatment of motion sickness. Tro J Pharm Res 2018; 17(6):991–6. doi: 10.4314/tjpr.v17i6.2
23. Sabar MH. Formulation and in-vitro evaluation of fast dissolving film containing amlodipine besylate solid dispersion. Int J Pharm Pharm Sci 2013; 5(4):419–28.
24. Sharma R, Kamboj G, Singh G, Rana V. Development of aprepitant loaded orally disintegrating films for enhanced pharmacokinetic performance. Eur J Pharm Sci 2016; 84:55–69. https://doi.org/10.1016/j.ejps.2016.01.006.