

An Account of Modified Release of Melatonin from Compression-coated, Uncoated and Bilayer Tablets

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Abstract

Modified release formulations offer several advantages over conventional systems used in therapeutics. The aim of this work was to extend our previous studies on the chronobiotic hormone melatonin controlled release, by comparing its release from uncoated, compression-coated and bilayer tablets. Each tablet was comprised of melatonin and combinations of the following excipients: ethylcellulose, polyvinylpyrrolidone (PVP, MW:10.000), dextran, low viscosity sodium alginate, Avicel PH 102, lactose monohydrate, iron oxide pigment red 30 and magnesium stearate. The compression-coated tablets consist of the same drug and inner excipients core, but different outer coating shells. As for the bilayer tablets, they incorporate an immediate release layer and a sustained release layer. The dissolution experiments were carried out in a USP XXIII dissolution apparatus for ten hours (the first three hours at pH 1.2 and the rest seven at pH 7.4). The results obtained reveal that the initial release of melatonin is slower from coated tablets than from the respective uncoated. The use of lactose in the outer coating shell, instead of PVP, results in a lower release in the pH 1.2 medium. In the medium with pH 7.4, lactose leads to a faster release than PVP. The increase of dextran concentration in the outer coating shell of the coated tablets delays the drug release at both pHs. In uncoated tablets, most of the formulations show similar release profiles, although the presence of PVP seems to delay the drug release. The release of melatonin from bilayer tablets, is initially faster than from both coated and uncoated tablets.

The present study demonstrates that the assembly of tablets, with and without coatings, results to different controlled release behaviour of the chronobiotic hormone melatonin.

Keywords: Melatonin, Modified release, Coated, Uncoated, Bilayer tablets.

Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine, MT) (Figure 1) is a hormone synthesised by the pineal gland and it has a significant

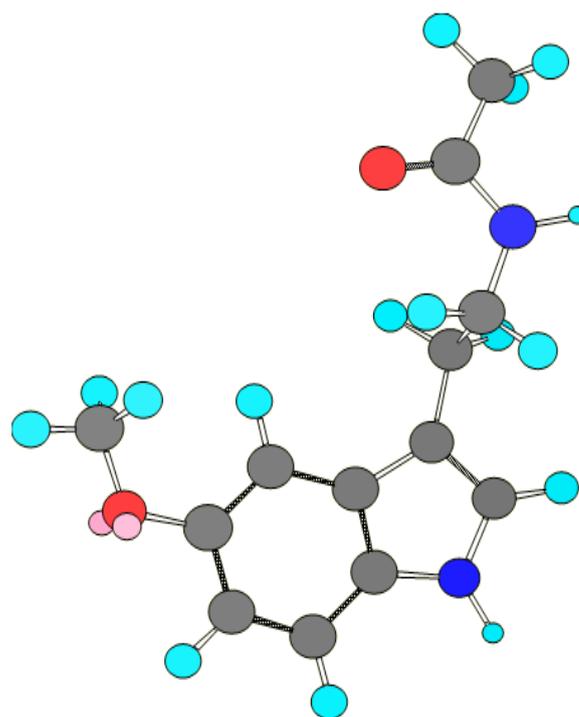


Figure 1: 3-D structure of melatonin

role in the regulation of the circadian biological clock [1,2]. The physiological actions of melatonin in regulating seasonal and circadian rhythms are mediated through G-protein-coupled cell membrane receptors [3].

Sleep is increasingly recognised as important to public health, with sleep insufficiency linked to motor vehicle crashes, industrial disasters, medical and other occupational errors [4]. Insomnia is a symptom of difficulty initiating and maintaining sleep and is associated with daytime consequences. It is the most common sleep disorder with a prevalence of about 10% and can occur as an independent disorder or secondary to other conditions [5,6]. Several different types of medications are effective for treating insomnia. The advantage of MT compared

to other drugs, like benzodiazepines [7], non-benzodiazepines [8] and barbiturates [9], used for treating insomnia, is that it is well tolerated and an effective treatment for a number of sleep disorders related to circadian rhythm disturbances, without toxic side effects and addiction characteristics [10].

Generally, MT may be helpful in the treatment of circadian rhythmic disorders, like sleep syndrome, insomnia, jet lag, seasonal affective disease, shift work syndrome, etc [11]. Melatonin is secreted by the pineal gland in a circadian fashion that rises during the night (over 8 h). Dosage form products which mimic the physiologically produced endogenous elevated levels of MT in plasma concentration during night-time could be clinically advantageous in the treatment of sleep circadian disorders [12].

It was reported that the modified-release MT treatment was more clinically useful to initiate and maintain sleep in elderly insomniacs compared with immediate-release or conventional therapy. Prolonged-release melatonin may improve quality of sleep in older people with minimal side effects [13,14].

During the last decades, a huge number of modified release systems have been developed, as they display several advantages over conventional systems used in therapeutics [15]. Different approaches are employed to deliver the drugs to the patients, such as multilayer, compression coating, bilayer tablets, etc [16]. Compression-coating is an absolute dry coating method that can modify the drug release pattern depending on the excipients used in the coating. The compression coated tablet, or otherwise called tablet-in-tablet design, is a time-controlled drug delivery device, consists of a core tablet and an outer layer, which surrounds the core tablet [17]. Bilayer tablets, consisting of one drug, are suitable for quick/slow release profiles depending on the excipients used, as one layer provides immediate release and the other layer provides sustained release and acts as a maintenance dose [16,18].

The last ten years we have conducted numerous studies on the controlled release of melatonin from solid pharmaceutical formulations. Our findings suggest that the nature and combination of excipients used in MT's formulations have a profound effect on both the onset and maintenance of sleep in patients suffering from insomnia [19,20]. The aim of this work is to extend our previous studies on melatonin modified release, by comparing its release from uncoated, compression-coated and bilayer tablets.

Materials and Methods

Materials

Each tablet was comprised of melatonin and combinations of the following: ethylcellulose, polyvinylpyrrolidone (PVP, MW:10.000), dextran, low viscosity sodium alginate, Avicel PH 102, lactose monohydrate, iron oxide pigment red 30 and magnesium stearate. The compression-coated tablets consist of MT and an inner excipients core, but different outer coating shells. As for the bilayer tablets, they incorporate an immediate release and a sustained release layer.

Formulations of compression-coated, uncoated and bilayer tablets were prepared by direct compression using punch (Maassen, type MP150) and dye (Maassen, dyes of various diameters) instrumentation.

Uncoated tablets: For core tablets three different formulations

were evaluated. F1U consists of PVP, dextran, lactose and ethylcellulose. F2U includes a higher amount of lactose than F1U, PVP is absent, while the content in ethylcellulose remains the same. F3U, compared to F1U, has a higher amount of dextran and lactose and no PVP, whilst, with respect to F2U, a higher amount of dextran, the same amounts of lactose and ethylcellulose and no PVP (Figure 2, appearance of the uncoated tablets).

Compression-Coated tablets: The outer shell was designed to delay the release of melatonin. To achieve this, PVP, ethylcellulose and dextran were used for the preparation of the outer shells of F1C, while in F2C and F3C, PVP was replaced with an equal amount of lactose. Disintegrant sodium alginate was added to the core tablet, in order to facilitate the immediate release of MT (Figure 2, appearance of the compression-coated tablets).



Figure 2: Melatonin compression-coated and uncoated tablet formulations

Bilayer tablets: In bilayer tablets, one layer, consisting of sodium alginate, lactose and Avicel, acts as an immediate release layer. The second layer, consisting of dextran, ethylcellulose and lactose, acts as a sustained-release layer. Magnesium stearate is added in equal amounts in both layers. Figure 3 depicts the bilayer tablet during the dissolution experiment.

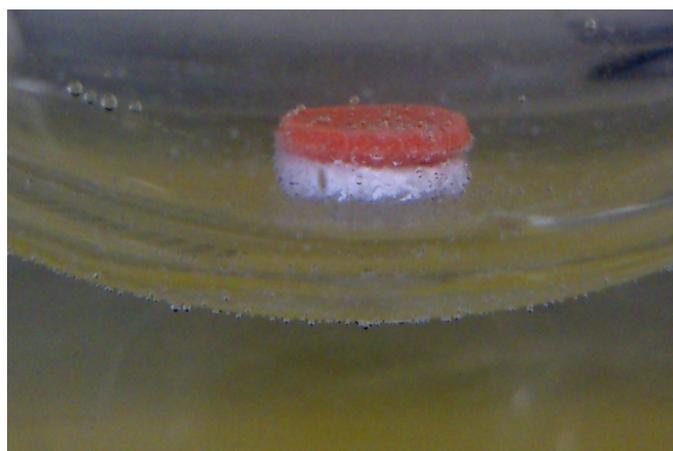


Figure 3: Melatonin bilayer tablet during dissolution

Tablet tensile strength

The hardness tester (Erweka, Type TBH 28) was used to measure tablets crushing strength: the tablet was placed on a flat surface and the load applied along its diameter by a movable platen; the tablets were broken along their diameter in a single fracture into two pieces of similar size and the fracture force recorded (n=3 from each batch). The tensile strength was expressed in terms

of load required for tablet crushing over tablet area (eq. 1) and values between 8-10 ±5% kg/cm² were considered acceptable according to Pharmacopeia specifications.

$$\sigma_x = \frac{2L}{3.14DH} \quad (\text{eq. 1})$$

where, σ_x is the tensile strength, L is the load required for tablet crushing, D is the tablet diameter and H is the tablet height.

Tablet average weight and friability

Average weight and friability were determined on 10 tablets for each batch using respectively an electronic balance and a friabilator (Erweka, type TA3R) at 25 rpm for 4 min. The friability was expressed in terms of weight loss and calculated as percentage of the initial weight; according to Pharmacopeia specifications, friability under 1% was considered acceptable.

Dissolution Experiments

The dissolution experiments were carried out in a USP XXIII dissolution apparatus I at a rotation speed of 50 rpm, in aqueous medium, at 37 ±0.5 °C. For simulating the conditions along the gastrointestinal tract, the release of melatonin was monitored for ten hours, the first three hours at pH 1.2 and the rest seven at pH 7.4. Samples (5 ml) were withdrawn at predetermined time intervals, filtered and analyzed at $\lambda_{\text{max}}=278$ nm using a Perkin-Elmer UV spectrophotometer.

Results and Discussion

The hardness of all the prepared tablets was found to be in the range of 8.81 to 10.08 kg/cm². The weight of all 10 tablet formulations were found to be uniform in the range of 99.4 to 100.8 mg. The friability of all the prepared tablet formulations was found to be in the range of 0.19 to 0.65 %, which complies with official requirement of less than 1%.

The present study is an attempt to compare MT release from melatonin modified release preparations, i.e. uncoated, compression-coated and bilayer tablets. Among these formulations the compression coated tablets, offering a prolonged release with a 2 hour lag time period, could be used to treat sleep maintenance, insomnia and early morning awakening [21]. On the other hand, bilayered tablets consisting of a fast release portion and a slow release portion of MT was developed in order to mimic the circadian rhythm of MT showing a desirable drug release profile with the fast-release fraction giving an initial burst effect followed by a sustained release effect from the slow release fraction [12]. The different release profiles of the melatonin bilayer tablet can be beneficial both in patients' sleep onset but also for sleep maintenance [21].

The dissolution profiles of the formulations F1U, F2U and F3U are presented in Figure 4, for the uncoated tablets, and in Figure 5 for the coated tablets (F1C, F2C and F3C).

Figure 6 depicts the comparison of the dissolution profiles for all uncoated and coated tablets, while Figure 7 represents the comparison of all the above formulations, and the bilayer tablets.

The results obtained reveal that the initial release of melatonin is slower from coated tablets than from the respective uncoated (Figure 6). The use of lactose in the outer coating shell, conversely

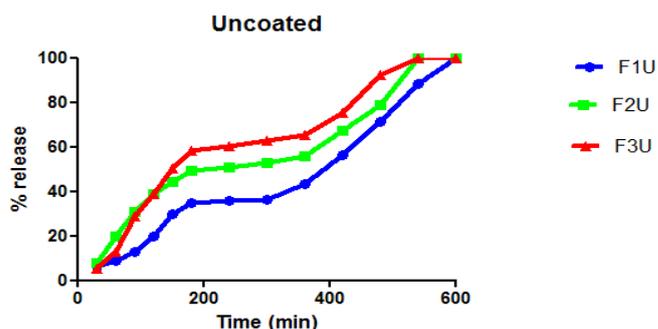


Figure 4: % Drug release vs time of the uncoated formulations F1U, F2U and F3U

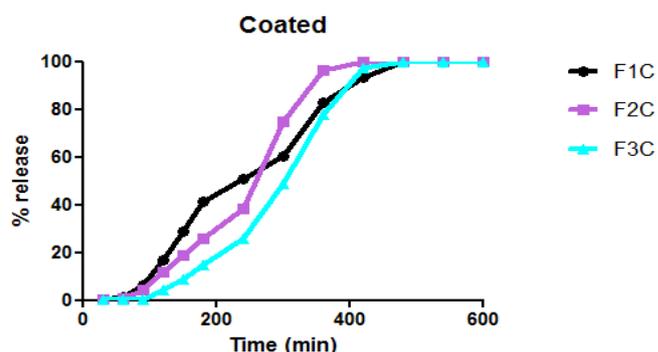


Figure 5: % Drug release vs time of the compression-coated formulations F1C, F2C and F3C

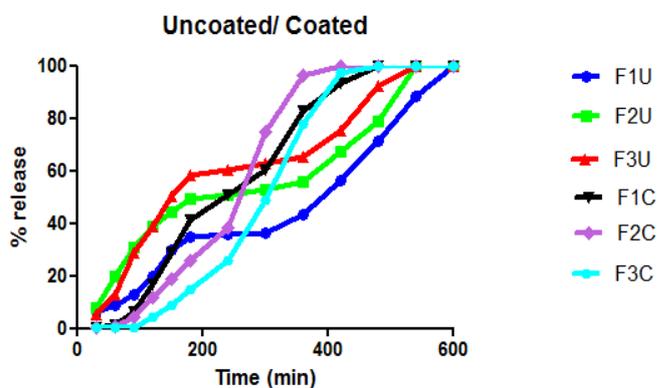


Figure 6: % Drug release vs time of all uncoated and compression-coated formulations

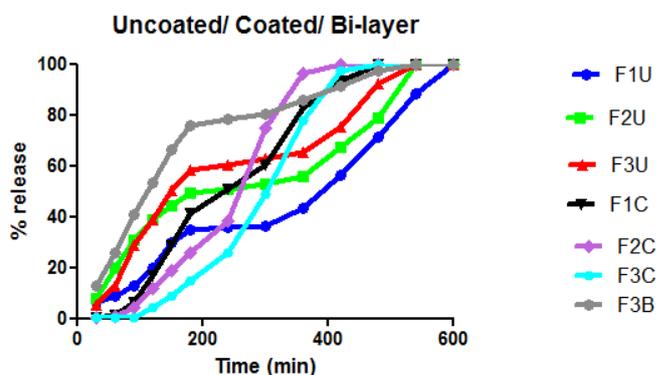


Figure 7: % Drug release vs time of all formulations (uncoated, coated and bilayer tablets)

to PVP, results in a lower release in acidic medium during the first 180 min (Figures 5 and 6). This might be attributed to the fact that at pH 1.2, PVP (I) is converted to the *gem*-diol (C), as shown in Figure 8. The formation of the diol favours the interaction of PVP with the 5-OMe group of MT. This, through H-bonding, enhancement of interaction of PVP with MT results to its more facile release in the acidic environment.

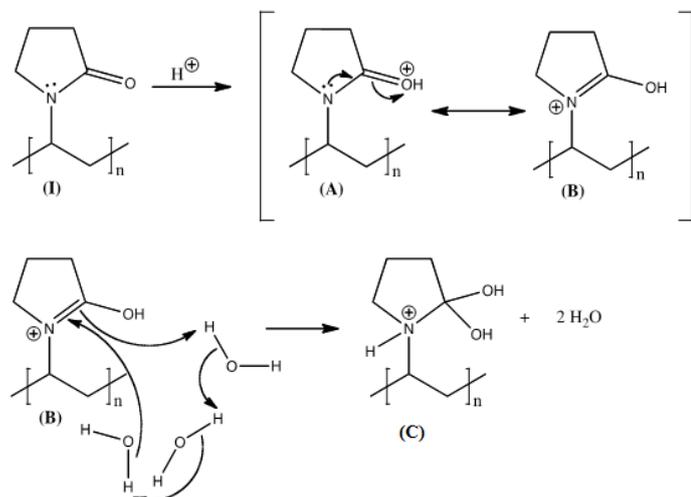


Figure 8: PVP (I) conversion to the *gem*-diol (C)

In the pH 7.4 medium, the presence of lactose leads to a 100 % release at 420 min, whilst PVP sixty minutes later. The increase of dextran concentration in the outer coating shell (F3C) delays the drug release at both pHs (coated tablets, Figure 5). Dextran is a carbohydrate polymer extensively applied in pharmaceutical formulations, particularly as drug conjugate macromolecular carrier or drug delivery system. As a polysaccharide, it improves the stability of the therapeutics enabling also the control of their release. When used as an excipient in a tablet formulation, its gel forming ability enhances the sustained drug release [22].

In uncoated tablets, the formulations with ethylcellulose, dextran and lactose monohydrate in higher concentration (F2U and F3U) have a faster release, compared to F1U, where the content in lactose is considerably lower (10 %) (Figure 4). Lactose is a water-soluble excipient, it increases the hydration rate, resulting in more dissolved drug diffusing out from the matrix. By its

hydrophilic nature, it facilitates gel formation and shortens the penetration time of the dissolution medium into the matrix. Being a soluble substance, it acts as a channeling agent by rapidly dissolving and easily diffusing outward, therefore, decreasing tortuosity and/or increasing the matrix porosity and achieving faster drug release [23].

The release of melatonin from bilayer tablets, with their immediate release layer consisting of lactose monohydrate, sodium alginate and Avicel PH 102, is faster than from both coated and uncoated tablets (Figure 9). There are several advantages reported in the literature regarding the bilayer tablet technology. As stated in the Abebe et al. 2014 article, the same active pharmaceutical ingredient with different release profiles can be delivered as a single bilayer tablet (e.g. drugs with an immediate release and an extended release profile).

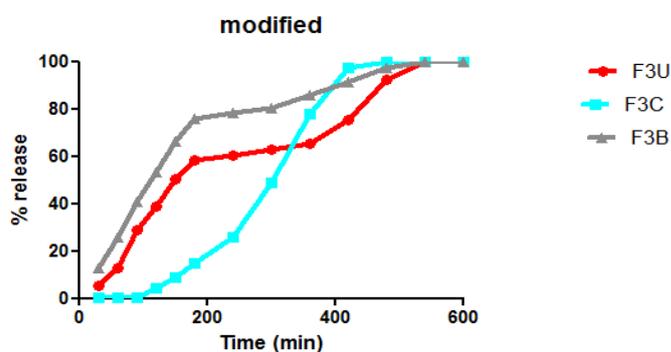


Figure 9: % Drug release vs time of the uncoated formulation F3U, the coated formulation F3C and the bilayer formulation F3B

Conclusions

This study demonstrates that the assembly of the bilayer tablets and the tablets with and without coating, has a profound effect on the modified release profile of melatonin. Information about the oral absorption profile of the above MT formulations will be useful for future *in vivo* studies. Currently, we extend our studies on the hormone using various other formulants of different physicochemical characteristics, which will help to probe further the release mechanisms of MT and develop formulations having a potential for commercial application for persons whose sleep patterns are disturbed.

Table 1: Melatonin Tablet Formulations

Ingredients	Uncoated (%)			Compression-Coated (%)						Bilayer (%)	
	F _{1U}	F _{2U}	F _{3U}	F _{1C}	F _{2C}	F _{3C}		F _{3B}			
Melatonin	1.0	1.0	1.0	1.0	1.0	1.0		1.0			
Dextran	9.5	9.5	11.5	9.5	9.5	11.5		11.5			
PVP (10.000)	10.0	-	-	10.0	-	-		-			
Ethylcellulose (45 cps)	30.0	30.0	28.0	30.0	30.0	30.0		30.0			
Avicel PH 102	6.7	6.7	6.7	6.7	6.7	6.7		6.7			
Lactose monohydrate	17.5	27.5	27.5	17.5	17.5	10.0	17.5	10.0	17.5	10.0	
Sodium alginate	24.3	24.3	24.3	24.3	24.3		24.3		24.3		
Mg stearate	1.0	1.0	1.0	0.5	0.5	0.5	0.5	0.5	0.5	0.5	
Total	100.0	100.0	100.0	100.0	100.0		100.0		100.0		

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