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Obtaining fast dissolving disintegrating tablets with different doses of melatonin

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ABSTRACT

Fast dissolving disintegrating tablets (FDDTs) containing different dosages of melatonin have been manufactured for administration to a specific target population: pediatric patients, having potential difficulties taking other oral forms. The lower dosages (3 and 5 mg) are intended for epileptic children, migraine prevention, neurodevelopmental disability, sleep disorders and blindness. Dosages of 10 and 60 mg are intended for Duchenne muscular dystrophy. Two FDDT groups have been designed, one which has excipients for direct compression and others having direct compression and effervescent excipients. Tablets have been produced having disintegration times of less than 25 s and with friability and hardness values that require no special storage or packaging conditions.

1. Introduction

FDDTs are uncovered tablets intended for fast disintegration in the oral cavity prior to being swallowed. According to the definition by the Royal Spanish Pharmacopoeia (RFE), these tablets should disintegrate, when tested, in less than 3 min. This disintegration testing should be conducted at temperatures ranging between 35 and 39 °C, simulating the temperature of the oral cavity.

Another requirement which these pharmaceutical forms must comply with is that of appropriate mechanical resistance, both for handling as well as for secondary packaging and storage purposes. The tablets must also have ideal organoleptic characteristics.

These tablets may be used by individuals having difficulties swallowing, thereby facilitating administration, having been received very positively by patients (Grace, 2006). In some cases, these tablet forms may improve active substance absorption, offering increased bioavailability as compared to other pharmaceutical traditional forms (tablets and capsules), offering oropharyngeal as well as gastrointestinal absorption (Chatap et al., 2007). The active substance portion that is absorbed in this method is not subject to the first pass effect, and thus, higher plasma concentrations of these substances may be achieved.

On a technological level, various processes may be applied in the manufacturingof orodispersible tablets. In selecting excipients, rapid dissolution in water, sweet flavor, low viscosity (to improve palatability) and high compressibility are considered. Sugars are commonly used, due to their pleasant taste and successful masking of other flavors, while also being very soluble in water, dissolving quickly in saliva (Bogner and Wilkosz, 2009). Manufacturing techniques are quite varied. In addition to classical tablet manufacturing methods, the use of freeze–drying techniques have also proven highly effective, resulting in the so-called FLAS tablets (Guiseppina et al., 2006).

In this study, the classic direct compression method has been used. Conventional tablets obtained via this technique are characterized by a hardness that permits handling and transport resistance. However, they do not offer fast disintegration in the oral cavity (Mizumoto et al., 2003). Therefore, formulations have been created in order to improve disintegration times without affecting the high active substance concentrations, while also offering appropriate degrees of hardness so as to permit primary and secondary packaging and traditional storage methods (30.4–44.4 N).

The active substance used in the manufacturing of these tablets is melatonin, a hormone derived from 5-hidroxytryptamine which is secreted primarily in the 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 (Flórez and Armijo, 2008).

Melatonin production begins with the uptake of the amino acid tryptophan, the majority of which is converted into serotonin.

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Acetylation and subsequent *O*-methylation processes result in melatonin (Axelrod, 1974).

Approximately 90% of the melatonin is metabolized and degraded in an initial step taking place in the liver, via 6-hydroxylation of the indole ring and in a second step occurring in the kidneys (Kveder and McIsaac, 1961). All of the hormone's metabolites are excreted in urine, and this excretion is parallel to the circadian rhythms of the hormone. Only 1% is eliminated in urine without suffering any transformation.

Of the numerous potential functions of melatonin, those described in this study in regards to the different pharmaceutical forms are of special interest (Cousin et al., 1995; Khanjari et al., 2000). The 3 and 5 mg dosages are intended for use in children treated with valproic acid, as these dosages are found to improve attention, memory and language (Madhur et al., 2004) while decreasing seizure frequency and intensity of crises (Fauteck et al., 1999). Melatonin is also used as a prophylactic for migraine prevention (Miano et al., 2008; Viswanathan, 2001), sleep disorders, children with neurodevelopmental disabilities, jet lag (Wassmer and Whitehouse, 2006) and in blind children (Cavallo et al., 2002). In the case of the 10 and 60 mg dosages, the melatonin acts to alleviate the damaging effect (in children suffering from Duchenne muscular dystrophy) of the hyperoxidative erythrocyte state (Chahbouni et al., 2011; Ruiz and Muñoz, 2013).

2. Materials and methods

2.1. Materials

To the formulation of fast dissolving disintegrating tablets were employed:

Melatonin was purchased from Methapharmaceutical IND S.L. (Spain).

Mannitol, polyvinylpyrrolidone (crospovidone), lactose, magnesium stearate, anhydrous coloidal silica, tartaric acid, sodium bicarbonate. All supplied by Fagron Ibérica S.A.U. (Spain).

Distilled water.

2.2. Methods

In order to ensure that the melatonin responds to official medication provision requirements, a physical–chemical characterization has been carried out via:

Desiccation of the active substance in an oven J.P. SELECTA, S.A. (Spain).

Determination of pH with a CRISON GLP-type pH-meter (Germany).

Verification of the endothermic or exothermic areas of the melatonin via differential scanning calorimetry (DSC) using a Mettler Toledo DSC1 apparatus (USA).

The melatonin evaluation is conducted via UV–vis spectrophotometry with the 8500 UV/VIS spectrophotometer, Dyn Co. (Denmark). The validity of this method is assessed by determining its precision, safety and accuracy.

For the manufacturing of the orodispersible melatonin tablets: the Specac pellet press is used (Atlas Series^{TM} (Germany)), the manual 15 t press and 5 and 10 mm diameter pellet dies.

The galenic trials conducted on the orodispersible tablets, in accordance with those in the Royal Spanish Pharmacopoeia, include (RFE, 2012):

I Uniformity of mass using a precision balance such as the A&D Instruments LTD, GR-202. Some 20 tablets are randomly selected, determining their average mass. The RFE describes the general acceptance criteria, indicating the maximum acceptable deviation based on tablet weight.

II Friability: With a Roche friability tester such as the ERWEKA GmbH (Germany). Randomly selecting 20 tablets and determining their average mass. The RFE describes the general acceptance criteria, indicating the maximum acceptable deviation based on tablet weight. This test is intended to determine tablet mass lost due to abrasion, under defined conditions. This loss, expressed in percentage, is the friability.

III For hardness testing, a hardness tester such as the ERWEKA TBH 20 (Germany) is used. It is used to assess resistance to breakage, and is a test which provides indications, not only of tablet's mechanical stability, but also of decomposition and subsequent dissolution as well as the release of principle actives. When conducting the test, a diametrical, progressive and increasing force is exerted on the tablet until it breaks. The test is conducted on 10 tablets.

IV Disintegration: This test is used to determine the ability of the tablets to disintegrate in a liquid medium over a determined period of time. In order for the orodispersible tablets to comply with the disintegration times indicated in the RFE, disintegration should occur in less than 3 min. For this test, the ERWEKA GmbH (Germany) device is used.

V Dissolution testing: This test is of considerable importance in tablet quality control, as dissolution of the principle active tends to be the limiting factor for its absorption. This test is described in most pharmacopoeias, utilizing different devices. In this study, the Sotax AT7 Smart (Germany) device was used.

3. Results and discussion

3.1. Analysis of the formulations

Our objective is to manufacture small-sized tablets; therefore, two pellet die sizes (5 and 10 mm diameter) were to be used. First, production was undertaken with the smaller-sized dies. A high adherence to the compression chamber was observed, even upon modification of pressures, compression times and lubricating excipients. Thus, it was decided to use the 10 mm diameter pellet die, manufacturing the formulations described in Tables 1 and 2.

Table 1
Fast dissolving disintegrating tablets obtained by direct compression, with classics disintegrations.

Formulation	Melatonin (%)	Mannitol (%)	Polyvinylpyrrolidone (%)	Magnesium stearate (%)	Silicio coloidal anhydre (%)
1	2	66.67	28	2	1.33
2	3.33	66.67	26.67	2	1.33
3	6.67	63.33	26.67	2	1.33
4	40	44.67	13.33	1.33	0.66