Evaluation of Orally Disintegrating Tablet Formulations in The Treatment of Oral Mucositis

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Abstract

Aim: Orally disintegrating tablets (ODT) are widely used dosage forms with high patient compliance, which preferred in the treatment of many diseases currently. In this study we aimed to develop an orally disintegrating tablet formulation can be preferred in the treatment of oral mucositis, which often occurs after chemotherapy during cancer treatment.

Methods: Lidocaine hydrochloride, which is a local anesthetic substance, was used as active pharmaceutical ingredient to obtain ODT formulation for the treatment of oral mucositis. ODTs were prepared by direct compression technique and crospovidone was used as super-dispersant

Results: The method developed for lidocaine determination was validated. Characterization of powder mixtures conducted; angle repose was found to be as 25.780°±0.810, flow time was 4.180±0.772 s, compressibility index was 9.591±0.774% and Hausner's ratio was calculated as 1.106±0.014. The uniformity of weight and content for the ODT formulation was 493.705±3.583 g, 78.890±2.546 mg, respectively. The tablets had a diameter of 12.031 ±0.015 mm while thickness was 4.420 ±0.021 mm. The hardness was calculated as 28.701±1.123 N, while percent friability value was 0.760%. Disintegration time of the tablets were 31.551±0.354 s, and approximately 90% of the prepared formulation dissolved in around 20 minutes according to dissolution testing.

Conclusions: The prepared formulation was evaluated through powder and tablet controls; it was found to comply with the limits specified in the European Pharmacopoeia. The developed ODT formulation for the treatment of oral mucositis, is planned to be evaluated through in vivo tests to complete the assessment of the formulation.

Keywords: *Orally disintegrating tablets, Evaluation methods, Lidocaine hydrochloride*

1. Introduction

When taken orally, the tablets disintegrate rapidly before swallowing. ODT is defined in the European Pharmacopoeia as "uncoated tablets which are placed in the mouth and quickly disintegrate before swallowing". The U.S. Food and Drug Administration defines ODT formulations as solid drugs containing active ingredients that disintegrate quickly, usually within a few seconds inside the mouth. These dosage forms are also called as fast-dissolving, orodispersible tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelt saccording to different sources[1].

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ODTs should be swallowed quickly without the need for water and should not leave any residue in the mouth. ODTs should be prepared in a way that leaves a pleasant aftertaste, especially for bitter-tasting active substances.

They must be durable for use during and after production. In addition, it should not be sensitive to environmental factors such as humidity and temperature. ODTs must be manufacturable by standard production and packaging methods and the cost of production must be low. In addition to these properties, ODTs are expected to be bioequivalent to conventional market preparations where drug absorption occurs in the post-gastric route. Depending on the physicochemical properties of the active substance contained in ODTs, the drug is absorbed at different levels along the pregastric tract. This may have an impact on the pharmacokinetic profile and bioavailability of ODT. Differences in the pharmacokinetic profile of ODTs due to high drug levels in the blood and systemic exposure are a result of the lack of first-pass effect of ODTs due to pregastric absorption. This has an impact on the safety and efficacy of ODTs[2-3].

In addition, the solubility of the active ingredient in the ODT formulation is highly effective in the disintegration time of the tablets, depending on the particle size. The aim in the development of ODT is that the drug has a systemic effect rather than a local effect. For this reason, active substances with systemic effects are used. In addition, some of the active ingredient is absorbed in the mouth, as the tablet is disintegrated by the salivary fluid. Therefore, it is very important that the active ingredient used for formulation is in non-ionized form. Choosing the appropriate dispersing agent and water-soluble excipients is very important in the creation of ODTs. This improves the porous structure of the tablet and allows rapid absorption of water into the tablet matrix. As a result, it allows the tablets to disintegrate quickly.

ODT tablets contain excipients such as superdispersant, diluent, lubricant, permeability enhancer, sweetener and aromatizer. In the selection of these excipients, rapid dispersion, not adversely affecting the validity of other excipients and the stability of the finished product, and a melting point between 30 and 35 degrees Celsius are taken into account. The pleasant taste in the mouth of ODT formulations is an important factor that makes the patient more responsive to using the drug. The properties and proportions of the excipients in the composition of the formulation affect the taste of the tablets in the mouth. The excipients used in the formation of ODT should hide the bad taste of the drug, leave a smooth and pleasant taste without leaving any residue in the mouth, and should not be affected by factors such as humidity and temperature[4]. Dispersants, taste masking polymers, diluents, lubricants, sweeteners, aromatizers, preservatives, binders and flocculating agents are frequently used in ADT formulations[5-7]. Superdispersants are excipients that change the disintegration time and dissolution of the tablet with high dispersion efficiency at low concentrations. When used in high doses, superdispersants can affect the mouthfeel, hardness and friability of the tablet. To be a good superdispersant, tablets require rapid dispensing, a pleasant mouthfeel, small particle size and high fluidity. In addition, it should be of a quality to increase the flow properties of the powder mixture[8].

Lidocaine hydrochloride, which is one of the local anesthetics with average potency and duration of action, has a 1% solution in 0.9% sodium chloride at a pH of 6.5–7 and is freely soluble in water. It can be described as a reliable agent. Prepared solutions should be stored away from light. It does not harm the tissues even at 8% concentration. It is three times more potent and 1.5 times more toxic than procaine. 0.5%, 1%, 1.5% and 2% solutions are available for peripheral nerve blocks and peridural block applications. In spinal anesthesia applications lasting 30-60 minutes, 7.5% glucose and 5% lidocaine solution can also be used[9-10]. Various damages occur in the mouth and pharynx of cancer patients due to chemotherapy treatment. This is called oral mucositis. Hoarseness and sore throat are also among the main symptoms[11]. The incidence of oral mucositis is 85-95% in patients receiving high-dose chemotherapy for hematopoietic stem cell transplantation, and 98% in patients with head and neck cancer who receive chemotherapy together with radiation. Oral mucositis, a four-phase process recommended by the World Health Organization, is classified into the initial inflammatory or vascular phase (Stage I), epithelial phase (Stage II), ulcerative or bacteriological phase (Stage III), and healing phase (Stage IV)[12]. It occurs one week after chemotherapy and usually resolves after 21 days. However, during periods of mucositis, dehydration, malnutrition, anorexia, cachexia, and daily life functions and nutrition of the patients are adversely affected. This causes pain, difficulty chewing, swallowing, and slurred speech. The use of opioid analgesics due to pain and the transition to total parenteral nutrition due to nutritional problems are due to mucositis. In addition, oral mucositis causes infections, which increases the spread of opportunistic infections, increases sepsis deaths and hospital stays, increasing the cost of treatment. In addition, this may result in skipping or reducing the dose of therapy administered to the patient until the mucositis resolves. The above-mentioned adverse effects of mucositis significantly reduce the quality of life of patients, while at the same time causing problems in responding to treatment and the development of life-threatening conditions. A gel, ointment, or ODT is applied for this side effect or other oral mucositis issues.

In this study, it was aimed to develop ODT formulations containing lidocaine hydrochloride as a model drug and to evaluate them with in vitro characterization tests.

2. Materials and methods

2.1. Determination of Lidocaine Hydrochloride

The chromatographic conditions of the high pressure liquid chromatography (HPLC) method to be used for the determination of lidocaine hydrochloride are shown in Table 1. In order to obtain the calibration line of lidocaine hydrochloride, a stock solution of 100 µg/mL concentration was prepared in a mixture of Water:Acetonitrile (50:50, v/v), which is the mobile phase in the quantification method. Based on this solution, standard solutions were prepared at eight different concentrations (5-40 µg/mL), 6 for each concentration, with appropriate dilutions. After quantification, the regression analysis with concentration versus peak areas data yielded the calibration line and the correct equation to be used in other analyses. The validity of the analytical method was demonstrated by evaluating the parameters of linearity, accuracy, precision, limit of detectability/observability (LOD), and limit of detectability (LOQ).

Table 1

The HPLC chromatographic conditions used for the determination of the active ingredient

Device	Shimadzu, LC-2030C Prominence
Stationary phase	VP-ODS C-18 column
Mobile phase	Water:Acetonitrile (50:50, w/w), pH 2.5
Temperature conditions	40 ± 2 °C
Flow rate	1 mL/min
Injection volume	20 µL
Monitoring wavelength	240 nm

Table 2

Prepared ODT formulation unit formula

Composition	mg/tablet
Lidocaine hydrochloride	80
Avicel pH 1*2	150
Mannitol	150
Crospovidone	50
PVP K30	60
Aerosil	5
Talc	5
Total amount	500

2.2. ODT Formulation and Preparation Method

ODT formulation is given in Table 2. Direct compression method was preferred for the preparation of the tablet formulation. For this purpose, all formulation content (Lidocaine HCl, Avicel PH 102, mannitol, crospovidone, PVP-K30) except the lubricants (Aerosil and talc) were weighed and mixed homogenously. Aerosil and talc were finally added to the mixture and mixed for another 5 min. and tablets were pressed with a single punch tablet machine.

2.3. Evaluation of Powder Properties Before Compression

In order to evaluate the powder properties of the prepared ODT formulation powder mixture, the angle of repose, flow time, compressibility index and Hausner's ratio values were calculated and evaluated according to the European Pharmacopoeia[13].

2.4. Evaluation of ODT Controls

The parameters of weight and content uniformity, diameter, thickness, hardness, disintegration time, dissolution tests were evaluated on the ODT formulation prepared using the direct compression method.

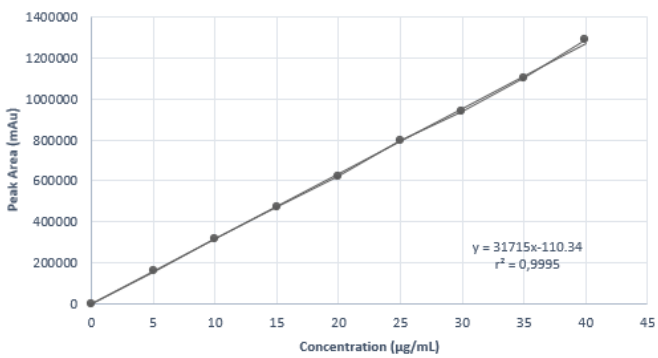
2.5. Results and Discussion

2.5.1. Determination of Lidocaine Hydrochloride

The resulting calibration line and equation are shown in Figure 1. The validity of the analytical method was proved by evaluating the linearity (R:0.9995), accuracy (% Relative error <2%), precision (Coefficient of variation <2%), Limit of Detectability (LOD) (0.440 µg/mL) and Limit of Determinability (LOQ) (1.280 µg/mL) parameters.

Figure 1

Lidocaine HCl calibration curve and equation



2.5.2. Results of Powder Properties Before Compression

Powder properties were carried out to determine the flow properties of the powder mixture prepared for lidocaine HCl ODT formulation. The results of the powder properties for lidocaine HCl ODT formulation are shown in Table 3.

Table 3

Results of powder control tests for lidocaine HCl ODT formulation

Powder Controls	Results (X±SD)
Flow time (s, n=10)	4.180±0.772
Angle of repose (n=10; °)	25.780±0.810
Compressibility index (n=6; %)	9.591±0.774
Hausner ratio (n=6)	1.106±0.014

X=Average; SD=Standart deviation

2.5.3. Results of ODT Controls

An example digital photograph of ODT containing lidocaine HCl is given in Figure 2. In vitro control findings of the prepared ODT formulation are given in Table 4. The dissolution test on lidocaine HCl ODT formulation was performed in pH 6.8 phosphate buffer medium (n=6) and the dissolution test profiles are shown in Figure 3.

Figure 2

Lidocaine HCl-containing ODT formulation digital photograph

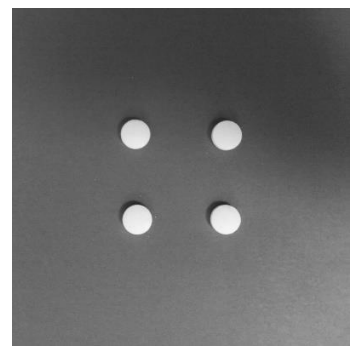
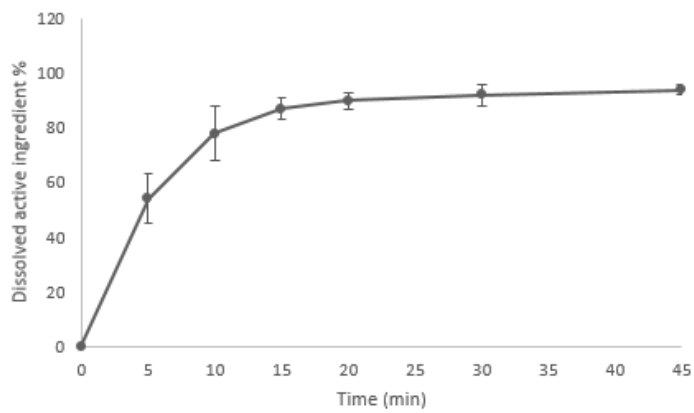


Figure 3

Lidocaine HCl ODT formulation dissolution profile



3. Results

Direct compression is faster, simpler and easier compared to other techniques used in the preparation of tablets, such as wet and dry granulation. For direct compression, the compressibility and flow properties of the powder mixture must be suitable. Poor powder flow properties are an important parameter that deteriorates the quality characteristics of the prepared tablet, including content uniformity. Therefore, before the ODT formulation was prepared, necessary controls were first performed on the powder mixture prepared for the formulation. These checks reveal the powder flow properties and allow for a preliminary assessment prior to tablet pressing[14]. Angle repose, flow time, compressibility index and Hausner's ratio values were calculated on the powder mixture forming the ODT formulation and evaluated according to the European Pharmacopoeia. When the findings obtained were evaluated (Table 3); angle repose was found to be 25.780°±0.810, flow time 4.180±0.772

s, compressibility index 9.591±0.774% and Hausner's ratio 1.106±0.014. According to the European Pharmacopoeia when the angle repose degree is within the range of 25-30°, the powder mixture is described as exhibiting ''excellent flow''; additionally the compressibility index and Hausner's ratio are defined as 1-10% and 1-1.1115, respectively, for a powder mixture to be categorized as demonstrating "excellent flow" [15-16]. Furthermore, a repeatable flow time of less than 10 s was achieved and all these findings were found compatible within the limits specified in the European Pharmacopoeia[16].

In order to develope ODT formulation in vitro experiments have been performed. These tests included content and weight uniformity, diameter, thickness, hardness, disintegration time and dissolution tests. The results obtained (Table 4) indicated that the uniformity of weight for the ODT formulation was 493.705 (±3.583 g) and the calculated % deviation value did not exceed the 5% limit[17]. The uniformity of content for the prepared tablet (Table 4) was determined as 78.890 mg (+2.546 mg)[18]. For the prepared formulation, the tablets had a diameter of 12.031 ±0.015 mm and a thickness of 4.420 ±0.021 mm (Table 4).

Table 4

In vitro control findings for lidocaine HCl ODT formulation

Disintegration time (s, n=6)	31.551±0.354
Uniformity of weight (mg, n=20)	493.705±3.583
Uniformity of content (mg, n=6)	78.890±2.546
Friability (%)	0.760
Hardness (N, n=10)	28.701±1.123
Diameter (mm, n=20)	12.031±0.015
Thickness (mm, n=20)	4.420±0.021

When the results were examined in terms of SS data it was shown that the diameter and thickness were found to be appropriate. Even though the diameter and thickness of the tablets are not registered in the pharmacopoeia, keeping the size of the prepared tablets consistent is important[19]. Furthermore, the hardness of the formulation prepared by direct compression method, reached approximately 28.701 ± 1.123 N. For ODTs, it is recommended that the hardness should be below 50 N to allow for faster disintegration in the mouth. Prepared formulation had shown compatible results within the literature in terms of hardness. Friability is defined as measurement of the mechanical strength of a tablet. High values of friability is undesirable condition as it may lead to the tablet not maintaining its integrity during transportation, packaging, or handling[1]. For the prepared ODT formulation, the % friability value was calculated as 0.760 (Table 4). The friability test results for the tablets were evaluated according to the European Pharmacopoeia (<1%) and were found compatible with pharmacopeial limits[20]. It has been reported in the European Pharmacopoeia that orally dispersible tablets should "disintegrate in less than 3 minutes". Disintegration time was determined as 31.550±0.354 s (Table 4). The disintegration time of the formulation is within the appropriate limits specified by the European Pharmacopoeia[21]. In vitro dissolution testing is low cost and fast experiment widely used in drug development studies to demonstrate drug quality and predict in vivo performance[22-23]. According to dissolution results, approximately 90% of the prepared formulation dissolved in around 20 minutes. Sink conditions were ensured in dissolution studies.

The ODT formulation containing lidocaine hydrochloride was prepared using the direct compression method with the use of crospovidone as superdispersant. When the prepared formulation was evaluated through powder and tablet controls, it was found to comply with the limits specified in the European Pharmacopoeia. The developed formulation, which is considered an important and effective step providing the advantages of ODT tablets in the treatment of oral mucositis, is planned to be evaluated through in vivo tests to complete the assessment of the formulation. This formulation preparation represents a significant milestone in offering an alternative product to the formulations in the Turkish Pharmaceutical Market.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Çukurova University Medical Ethics Committee with the decision no. 80-31 dated 31.08.2018.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Author contributions

Study design: ED, DO, TÇ; Materials: ED, DO, TÇ; Data analysis and evaluation: ED, DO, TÇ; Literature search: ED, DO, TÇ; Manuscript writing: ED, DO, TÇ; Data interpretation and compilation: ED, DO, TÇ.

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