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Development and evaluation of terbutaline sulfate orally disintegrating tablets by direct compression and freeze drying methods

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ABSTRACT

Asthma is a chronic respiratory condition characterized by attacks of spasm in the bronchi of the lungs, causing difficulty in breathing. Oral and inhalation routes are generally used for the treatment of asthma. Terbutaline sulfate (TBS), is a widely used bronchodilator for the treatment of asthma, is available in formulations in the market. However, there is no commercially available orally disintegrating tablets (ODTs) containing TBS. Therefore, this study was aimed to develop and characterize TBS-containing ODTs. ODTs were prepared using freeze-drying technique and direct compression using ready-to-use ODT excipients Ludiflash® and Parteck ODT®. Quality controls and permeability study across Caco-2 cells were performed. ODTs prepared by direct compression were disintegrated within 3 min, and freeze-dried ODT in 11 s. Acceptance value for content uniformity was 13.2% for freeze-dried ODTs, and about 22% for direct compressed ODTs. In vitro dissolution test showed that commercial tablet and all ODTs fulfilled the tolerance limit recommended in TBS conventional tablet monograph of USP. Results of the permeability studies demonstrated that TBS can be classified as a well absorbed compound. All these results indicate that to improve patient compliance, ODT approach for TBS can be used to improve patient compliance and also for rapid onset of action.

1. Introduction

The oral administration is the most commonly accepted route due to its ease of administration, convenience, safety and most importantly patient compliance [1]. Several new technologies such as preparation of orally disintegrating tablets (ODTs) for oral drug delivery have recently been available to improve patient compliance [2]. In the literature, various names are available for ODTs such as rapidly disintegrating, fast disintegrating, fast dispersing, rapid dissolving, fast dissolve/dissolving, rapid melting, fast melting, orodispersible tablets [3–9]. ODTs are defined as "The products are designed to disintegrate or dissolve rapidly on contact with saliva, thus eliminating the need to chew the tablet, swallow an intact tablet or take the tablet with liquids" in Food & Drug Administration [10]. ODTs offer the advantages of both solids and liquids such as quick disintegration and dissolution due to maximize its pore structure, no residue in mouth, administration without the need of water, provides pleasant taste, enables high drug loading, convenience and accuracy of dosing, simple production, small packaging [11]. Thus, they are preferred to conventional tablets especially for geriatric, pediatric, paralyzed and psychiatric patients [12,13] who have difficulty in swallowing. Various methods (e.g. freeze drying, moulding, direct compression technologies, granulation, spray drying, cotton candy, phase transition, three-dimensional printing, and mass extrusion methods) are used for the preparation of ODTs. With freeze drying method, improved solubility, accuracy of dosing, applicability for extremely low-dose strengths and bulk powder with poor flow characteristics, and with direct compression method, low cost, just enough conventional equipment, less processing steps can also be implemented. Besides, high doses of drugs which are sensitive to heat and moisture could be prepared by freeze drying method [14].

Asthma, a chronic disease involving the airways in the lungs, is very common in both industrialized and developing countries, and can be seen at any age [15]. It is characterized by attacks of spasm in the bronchi of the lungs, causing difficulty in breathing [16]. Therefore, the quality of life of asthma patients is very low. In 2014, 334 million people worldwide were reported to be asthmatic [17]. It is estimated that this number will rise to 400 million by 2025 due to urbanization [18]. Oral and inhalation routes are generally used for the treatment of asthma. Medications used in the treatment of asthma are divided into two general groups: quick-relief medications (such as albuterol,

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levalbuterol, pirbuterol or ipratropium), and long-term control medications (such as salmeterol and formoterol inhaler, cromolyn or nedocromil inhaler; montelukast tablets or granules; theophylline tablets, solution, sustained release tablets) [19].

Terbutaline sulfate (TBS), a class II drug (low solubility and high permeability) according to Biopharmaceutics Classification System (BCS) [20], is a widely used selective β-adrenergic agonist bronchodilator for the treatment of asthma, chronic obstructive pulmonary disease and bronchitis [21]. TBS is variably absorbed from the gastrointestinal tract, and approximately 60% of the absorbed drug undergoes first-pass metabolism in the gut wall and the liver [22]. The oral bioavailability of TBS is low (about 9.5–30%) due to stereoselective absorption and hepatic first pass metabolism. The peak plasma concentration is reached within 1–4 h after oral administration [23,24]. It has a low plasma protein binding (14–25%), however, it is bound to erythrocytes (equilibrium ratio is about 2.0–2.6) [25]. Its volume of distribution is about 1.6 L/kg at steady state. In the literature, a terminal half-life of 2–5 h is given for TBS after intravenous, subcutaneous and oral administration [25].

Commercially, TBS is available in formulations (e.g. conventional and controlled release tablets, syrups) for oral intake, inhalation and injection in the market. However, there is no commercially available ODTs containing TBS to our knowledge. In the literature, there are only two studies in regard to TBS ODT formulations. One of these studies, ODT formulations containing TBS were prepared by wet granulation method using sublimable ingredients [26]. In the other study, TBS fast dissolving tablets were prepared by the direct compression method using superdisintegrants (Explotab, Ac-Di-Sol and Polyplasdone XL) [27]. Therefore, the purpose of this study was to develop and characterize TBS containing ODTs prepared using direct compression and freeze-drying techniques to provide rapid onset of action in asthmatic patients. Ready-to-use ODT excipients (e.g. Ludiflash® and Parteck ODT®) were used for the preparation of ODTs by direct compression method. TBS containing ODT was also prepared using freeze drying technique. Content uniformity, diameter and thickness, hardness, friability, water absorption, disintegration time, and dissolution tests were used as the quality control parameters for these developed ODTs. Also, permeabilities of raw TBS and developed ODTs were determined across Caco-2 cell monolayers. Commercially available conventional TBS tablets were used as the reference in our study.

2. Materials and methods

2.1. Materials

TBS was obtained from Melody Healthcare Pvt. Ltd. (India). Ludiflash® and Parteck ODT® were purchased from BASF (Germany) and Merck (Germany), respectively. Magnesium stearate and mannitol were purchased from E. Merck (Germany), sodium alginate, simethicone, gelatin, hydroxypropyl methyl cellulose (Pharmacoat® 603), Pluronic F68 and PEG 4000 from Sigma, St. Louis (USA). Strawberry flavor was kindly provided by Mustafa Nevzat İlaç Sanayi A.Ş.

Commercially available Bricanyl® tablet (2.5 mg; AstraZeneca, Turkey) was obtained from Turkish market, and used as the reference in dissolution and permeability studies. Caco-2 cells (human colon carcinoma cell line) were purchased from ATCC (USA).

Dulbecco's Modified Eagle's Medium (DMEM), Hank's balanced salt solution (HBSS), fetal bovine serum (FBS) were all purchased from Biochrom AG (Germany), Penicillin-Streptomycin solution from Life Technologies, Inc. (USA), and Thincerts™ cell culture inserts (0.4 μm) from Grenier Bio-one (Germany). All other chemicals were of analytical grade.

2.2. Methods

2.2.1. Preparation of ODT formulations

2.2.1.1. Selection of excipients. The ODT formulations were prepared using two different types of ready-to-use direct compression excipients (Ludiflash® and Parteck ODT®), strawberry flavor as a taste masking agent, and magnesium stearate as a lubricant.

Freeze-dried ODT formulation was prepared using gelatin (as a matrix former), mannitol (as a filler), sodium alginate (as a viscosity modifier), PEG 4000 (as a disintegration accelerator), Pluronic F68 (as a surfactant), hydroxypropyl methyl cellulose (as a cellulosic binder), and simethicone (as an anti-foaming agent).

2.2.1.2. Terbutaline sulfate containing ODTs by direct compression method. Homogeneous physical mixture of TBS with Ludiflash® (or Parteck ODT®) was prepared by progressive mixing for 5 min in a roller mixer (mixture A). Strawberry flavor and magnesium stearate were blended in the same way (mixture B). After then, mixture A was added on mixture B, and then mixed progressively for a further 5 min. Physical properties of each powder mixtures were determined by means of flow time, angle of repose, bulk/tapped volume and density, moisture content.

The ODTs (400 mg) with Ludiflash® (TBS-DC-ODT-L) or Parteck ODT® (TBS-DC-ODT-P) were compressed by direct compression method using Erweka AR 400 (Germany). Quality control tests were performed on each ODTs.

2.2.1.3. Terbutaline sulfate containing ODT by freeze-drying method. After swelling of gelatin in pre-heated distilled water (40–50 °C) for 30 min, other excipients were added one by one, and then mixed thoroughly by a magnetic stirrer. TBS was added at last, and mixed until a homogenous solution was obtained. The final solution was distributed into round shaped blisters and frozen overnight at −20 °C, and then lyophilized at −55 °C and 0.44 mbar by using Heto Power Dry PL3000 (Denmark) [28].

The excipients of commercial TBS-tablet are lactose monohydrate, corn starch, PVP-K30, microcrystalline cellulose, magnesium stearate. Compositions of the prepared ODT formulations were given in Table 1.

2.2.2. Characterization of ODT formulations

2.2.2.1. Determination of physical properties of the powder mixtures

2.2.2.1.1. Bulk/tapped volume and density. A tap density powder tester (Aymes Company, Turkey) was used to determine the bulk/tapped volume and density of each powder mixture. For this purpose, 50 g of powder mixture (TBS-DC-ODT-L or TBS-DC-ODT-P) was filled

Table 1
Composition of TBS containing formulations.

Formulation	Ingredients	Amounts (mg)/Tablet
TBS-DC-ODT- L	[a]Mannitol	349
	[a]Crospovidone	20
	[a]Polyvinyl acetate (Kollicoat® SR 30 D)	20
	Magnesium strearate	4
	Strawberry flavour	2
TBS-DC-ODT-P	[b]Mannitol	369
	[b]Croscarmellose sodium	20
	Magnesium strearate	4
	Strawberry flavour	2
TBS-FD-ODT	Gelatin	20
	Mannitol	100
	Sodium alginate	0.5
	PEG 4000	9
	Pluronic F68	7
	HPMC	0.1
	Simethicone	0.5

[a] Excipient content of Ludiflash®.
[b] Excipient content of Parteck ODT®.