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Development of Salbutamol Sulphate fast disintegrating sublingual tablets with enhanced bioavailability and improved clinical efficacy for potential treatment of asthma

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ABSTRACT

Salbutamol Sulphate (SS) as a model bronchodilator drug undergoes first pass metabolism in liver, which has an oral bioavailability of only 50% of the administrated dose. Thus, the aim of this study was to attain rapid absorption and improved bioavailability, with subsequent immediate rapid onset of pharmacological effect. This work introduces a new design of SS fast disintegrating sublingual tablets (FDSTs) using a full factorial design (2^3) with three independent variables: the type of superdisintegrant (Ac-di-sol or Polyplasdone-XL), its concentration (3% or 5%w/w) and the binder type (Avicel PH101 or PEG6000). The formula T7 containing Polyplasdone-XL (5%w/w) with Avicel PH101 (10%w/w) had the least disintegration time (12.83 ± 0.7 s) and the highest dissolution rate (100 ± 2.6%), hence was selected for pharmacokinetic study in human volunteers. T7 showed C_{max} of 19.36 ± 2.64 μg/ml, t_{max} of 1.33 ± 0.24 h; the mean $AUC_{(0-8)}$ was found to be 75.059 ± 7.55 μg h/ml and the $AUC_{(0-\infty)}$ of 90.554 ± 8.027 μg h/ml. The relative bioavailability of T7 was 129.92% when compared to Ventolin® tablets. The clinical evaluation of T7 in fourteen asthmatic patients showed significant difference in forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and peak expiratory flow rate (PEFR) when compared to Ventolin® tablets using ZAN spirometry.

1. Introduction

Asthma is a chronic inflammatory disease of the airways which associated with an exaggerated airway narrowing response to triggers, such as allergens and exercise that leads to symptoms such as wheezing, dyspnea, chest tightness, and coughing. Symptom episodes are generally associated with variable airflow obstruction within the lungs that is usually reversible either spontaneously or with appropriate asthma treatment [1]. In acute asthma attacks, a quick onset of pharmacological effect is mainly desired from drugs for quick relief of bronchoconstriction and symptoms. This can successfully be obtained by injection or inhalers administration, but both methods may not always be convenient for the patient. Injection is painful and not fitting for chronic use [2]. Also, inhaler administration requires that patients should be talented at specific inhalation techniques for each type of inhaler devices, the inappropriate administration can result in decreased drug delivery and potentially reduced efficacy [3]. Consequently, there is rising interest in developing new, non-invasive, consistent and convenient dosage forms where the drug is fast dissolved and immediately absorbed into the systemic circulation [4]. Sublingual drug delivery can recommend a smart alternative route of administration of antiasthmatic drugs. The advantage of the sublingual drug administration is that the drug can be directly absorbed into systemic circulation, bypassing first pass metabolism in liver and enzyme degradation in the gut. Additionally, the thin sublingual mucosa (about 190 μm) and the profusion of blood supply at the sublingual area allow admirable drug penetration/absorption to attain high plasma drug concentration with a quick onset of action [5]. Orally, fast-disintegrating tablets (FDTs) are one of the formulations that have been developed to deliver medications

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sublingually [6]. Different strategies have been implemented in the formulation of FDTs to reduce the tablet disintegration time (DT) which consequently guarantee rapid drug release, dissolution, and delivery [7].

Salbutamol Sulphate (SS) is a bronchodilator broadly used in the treatment of asthma attacks and chronic obstructive pulmonary disease. It is a selective β2 agonist which stimulates β2 receptors on the lung leading to bronchial smooth muscle relaxation. It is well-absorbed orally; nevertheless, it suffers from poor oral bioavailability about 50% due to the first-pass metabolism in the liver [8]. Attributable to the convenience in administration, ease of manufacturing, stability and accurate dosing compared to oral liquids; safety compared to parenteral dosage forms and tamper-proofed compared to capsules, therefore, tablets are the most versatile and popular dosage form (Bastos et al., 2008). Many researchers have developed SS in tablet formulations included: mucoadhesive buccal tablet [8,9], controlled release tablet using natural polymers [10], fast disintegrating tablets [11,12], oral floating tablets [13] and enteric coated tablet [14]. However, the bioavailability and clinical evaluation of SS tablet to test its safety and efficacy in asthmatic patients have not been reported yet in literature.

In the current study, we have developed SS sublingual tablets that bypass the hepatic metabolism thus improve its bioavailability with subsequent enhancement of pharmacological effect especially in acute asthma attacks, overcome swallowing difficulties and improve the patient compliance especially for geriatric and pediatric patients.

2. Materials and methods

2.1. Materials

Salbutamol Sulphate was kindly supplied from (Alexandria Pharmaceutical Company, Egypt). Polyethylene glycol 6000 was purchased from Sigma Chemical Company, St. Louis, USA. Microcrystalline cellulose (Avicel PH101) and mint flavor were supplied by Chemical Industries Development Company (CID), Giza, Egypt. Polyplasdone XL (N-vinyl-2-pyrrolidone) was supplied by Fluka, Germany. Ac-di-sol (Croscarmellose sodium) was from FMC Corporation, Philadelphia, USA. Mannitol and magnesium stearate were purchased from El-Nasr pharmaceutical chemical company, Abu-Zaabal, Cairo, Egypt.

2.2. Experimental design

In this study, a 2^3 full-factorial design was used to optimize tablet formulations. Independent variables include the disentegrant concentration (X1), disentegrant type (X2) and binder type (X3) were selected as independent variables (Table 1). Eight formulations of SS sublingual tablets (T1-T8) were prepared according to the factorial design. Tablet hardness (Y1), disintegration time (Y2) and %SS released after 4 min (Y3) were considered as dependent variables. The statistical analysis of responses was made by Design-Expert®7 Soft-ware (Stat-Ease Inc., Minneapolis, MN, USA).

Table 1
Full factorial design 2^3 used for optimization of sublingual tablet formulations.

Factors (independent variables)	Levels	
X_1: disentegrant concentration	3%	5%
X_2: disentegrant type	Polyplasdone XL	Ac di sol
X3: binder type	Avicel PH101	PEG 6000
Responses (dependent variables)	**Desirability constraints**	
Y_1: Hardness (Kg/cm^2)	In range	
Y_2: Disentegration time (min)	minimize	
Y_3: %SS released after 4 min.	Maximize	

2.3. Pre compression evaluation (evaluation of the powder blends)

Determination of flowability of the eight formulations (T1- T8) would be achieved. Accurately weighed blends were taken into a funnel and allowed to flow freely through the funnel. The height of the funnel was adjusted in a way that tip of the funnel just touched the apex of the heap of powder blends. The diameter of the powder cone was measured and angle of repose was calculated through the following equation [15].

$$\mathrm{Tan}\theta = h/r \quad (1)$$

where h is the height of the heap; r is radius of the base of the heap, θ is angle of repose.

A mass of about 10 gm powder blend of each formulation is carefully introduced in a 100 mL graduated cylinder, then dropped onto a hard surface three times from a height of 2.5 cm at 2 s interval. The tapping was continued until no further change in volume was noticed then bulk and tapped densities were calculated from dividing the mass to the corresponding volume [16].

Hausner's ratio can be calculated mathematically by dividing the tapped density by the bulk density [15].

$$\text{While Carr's index} = (\text{Tapped density} - \text{Bulk density}) \times /(\text{Tapped density}) \times 100 \quad (2)$$

[17].

2.4. Sublingual tablet preparation

The eight formulations (T1-T8) were prepared by direct compression technique; the composition of all formulations is shown in Table 2. The ingredients of every formula were passed through 200 mm mesh sieve and retained on 100 mm mesh sieve and mixed using geometrical dilution method to obtain free flowing powder. Then the powder mixture was manually filled and compressed using 7 mm flat rounded punch tablet press (Manesty Single Punch Machine, Liverpool, England) under a fixed pressure ranging from 100 to 500 kg to get 100 mg tablet [18].

2.5. Tablet characterization (post compression evaluation)

The prepared sublingual tablets were subjected to the following quality control tests:

Table 2
Composition of the formulated FDST of Salbutamol Sulphate.

Formula code	T1	T2	T3	T4	T5	T6	T7	T8
Salbutamol Sulphate (SS)	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Avicel PH 101	10	–	10	–	10	–	10	–
PEG6000	–	10	–	10	–	10	–	10
Ac-di-sol	3	3	–	–	5	5	–	–
Polyplasdone XL	–	–	3	3	–	–	5	5
Magnesium stearate	1	1	1	1	1	1	1	1
Aspartam	1	1	1	1	1	1	1	1
Mint flavour	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aerosil 200	2	2	2	2	2	2	2	2
Mannitol up to	100	100	100	100	100	100	100	100

All ingredients added in mg.