Bulletin of Faculty of Pharmacy, Cairo University xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Bulletin of Faculty of Pharmacy, Cairo University

journal homepage: www.sciencedirect.com

Original Article

Formulation design and optimization of novel fast dissolving tablet of chlorpheniramine maleate by using lyophilization techniques ☆

Vivek Dave *, Renu Bala Yadav, Richa Ahuja, Sachdev Yadav

Department of Pharmacy, Banasthali University, Banasthali, Rajasthan, India

ARTICLE INFO

Article history:
Received 25 July 2016
Received in revised form 25 November 2016
Accepted 3 December 2016
Available online xxxx

Keywords:
Chlorpheniramine maleate
Lyophilization
Experiment design
Gelatin
PVP K30
Full factorial design

ABSTRACT

Fast dissolving tablets (FDTs) have received more interest in the pharmaceutical industry for those categories of drug which show slow dissolution and less oral bioavailability. Nowadays various technologies have been developed for FDTs with improved patient compliance and convenience. FDTs tablets provide an advantage particularly for the pediatric and geriatric patients who have difficulty in swallowing and also for that who are travelling for a long and suffers from lack of water availability. Lyophilization (freeze-drying) is a process in which water is sublimated from the product after freezing at a specific temperature and pressure. Lyophilization technique is used in order to improve the dissolution of the given substance and improve the oral bioavailability of the drugs with poor solubility and high permeability. In this work, chlorpheniramine maleate FDTs was formulated by lyophilization method. The prepared tablets were subjected to various evaluation such as hardness (2.4–2.9 kg/cm^2), friability (0.68–0.79%), disintegration time (10–19 s), drug content (95.32–99.09%), water absorption ratio (31–53%), wetting time (64–106 s) and *in-vitro* drug release shown in 5 min (96.04–99.92%). FTIR studies showed that there is no interaction between drug and polymer. Stability studies showed that there is no change in drug content within three and six months. Results revealed that fast dissolving tablets of chlorpheniramine maleate prepared by lyophilization method result in rapid dissolution.

1. Introduction

Fast dissolving tablets are tablets which disintegrate and dissolve rapidly in saliva within seconds even if water is not available. From all drug delivery technology, oral route is the best route for taking therapeutic agents. The reasons behind this are accurate dosing, self medication, avoidance of pain, patient compliance, low cost. According to European pharmacopoeia, fast dissolving tablets are those which disintegrate on tongue before swallowing and it should disperse in less than 3 min [1–7]. Dosage forms such as tablets and capsules are being utilized most commonly but dysphasia and difficulty in swallowing are their drawbacks. To overcome these problems, mouth dissolving tablets have developed which are known as novel solid dosage forms and come under novel drug delivery system. Chlorpheniramine maleate (CPM) is used as drug which is incorporated in these fast dissolving tablets prepared by lyophilization techniques method. Chlorpheniramine maleate is an antihistaminic agent which helps in relieving symptoms of allergy, hay fever, cold rashes, watery eyes, itchy eyes, cough, runny nose, sneezing and also it is used in itching of chicken pox. Chlorpheniramine maleate blocks a natural substance known as histamine which is made by our body during an allergic reaction. It also blocks acetylcholine and helps in drying of some body fluids. It also helps in relieving symptoms such as watery eyes, runny nose etc. FDTs are quickly soluble in water, well absorbed and thus dissolves within seconds and good absorbed. Thus, FDT acts like a tablet which dissolves as well as being absorbed very fast. Chlorpheniramine maleate shows first-pass metabolism and its metabolites are desmethyl and di-diesmethylchlorpheamine which decreases its bioavailability. But fast dissolving tablets avoid first pass metabolism and enhance bioavailability of drug. Thus these tablets undergo rapid dissolution within seconds and faster action within minutes. There are various techniques for formulating fast dissolving tablets such as lyophilization, direct compression, tablet molding, sublimation, and lyophilization techniques etc. Elderly people experiences deterioration of their physiological and physical abilities. As per European pharmacopoeia, "Fast dissolving tablets are uncoated tablets placed in the mouth resulting in their dispersion rapidly before being swallowed".

Peer review under responsibility of Faculty of Pharmacy, Cairo University.
* Corresponding author at: Department of Pharmacy, Banasthali University, Banasthali, Rajasthan 304022, India.
E-mail address: vivekdave1984@gmail.com (V. Dave).

http://dx.doi.org/10.1016/j.bfopcu.2016.12.001
1110-0931/

Please cite this article in press as: V. Dave et al., Formulation design and optimization of novel fast dissolving tablet of chlorpheniramine maleate by using lyophilization techniques, Bulletin Facult Pharmacy Cairo Univ (2016), http://dx.doi.org/10.1016/j.bfopcu.2016.12.001

Hence in the present study, fast dissolving tablets of chlorpheniramine maleate were prepared by lyophilization techniques method and superdisintegrants such as croscarmellose sodium, crospovidone have been utilized for faster disintegration. The advantages of these tablets are patient compliance, increased bioavailability, rapid onset of action, convenience in administration, good mouth feel etc. [4–6].

2. Materials and methods

2.1. Materials & components

CPM was obtained from MP biomedicals, Mumbai, India, PEG 6000 and PEG 4000 were obtained from HiMedia Pvt. Ltd., Mumbai, India, mannitol was obtained from Central Drug House Pvt. Ltd., Mumbai, India, and microcrystalline cellulose, gelatin & PVP K30 were obtained from Merck, India. All other reagents and chemicals used were of analytical grade.

2.2. Formulation method of FDTs by lyophilization techniques

In this study, FDTs containing Gelatin and Microcrystalline cellulose were prepared by lyophilization techniques method according to the formulae given in Table 1. To prepare different batches, all ingredients (except gelatin and glycine) according to the formula were accurately weighed and passed through 60 and 100 mesh sieve and mixed geometrically. Gelatin was soaked in water, and hydrated gelatin was stirred onto a magnetic stirrer until a clear phase was obtained, an equal proportion of glycine and given amount of mannitol was added to prevent shrinking of gelatin during manufacturing. An accurately weighed amount of Chlorpheniramine maleate (500 mg) was dispersed in the prepared aqueous solution and stirred on magnetic stirrer to obtained a continuous homogenous phase that result in dose of 50 mg Chlorpheniramine maleate FDTs when it was molded to 1 × 10 poly vinyl chloride (PVC) blister pack with a diameter of 13 mm and a depth of 3 mm. These fillings were kept to the deep freezer condition at −20 °C for 24 h. The pre freeze tablet mixtures were placed in lyophilizer (Labconco corporation 8811, 18 lt.) with a condenser temperature of −87 °C (provided by auto cut system) and a pressure of 0.133–0.187 mbar.

The best formulated FDTs were collected and forward to next stage which involved the addition disintegration accelerators namely, PEG 4000, PEG 6000 and Tween 80 to achieved a FDT with good tablet properties [3,11].

2.3. Design of experiment (DOE) for FDTs of Chlorpheniramine maleate by lyophilization method

In this study, an experimental design matrix was formed with 2 factors, 3 level, and 9 runs to optimized the influence of variable by using Statistica V.10 software (StatSoft, Inc. USA). In this matrix design independent variable such as (A) percent of gelatin conc. and (B) percent of PVP K30 conc. were selected and their impact on formulation was predicted. All these dependent variable is summarized in Table 2. On the behalf of this design set goals, 10 FDT formulation were prepared and characterized for *in-vitro* drug release (R1), disintegration time (R2), water absorption ratio (R3), and wetting time (R4) which were taken as a dependent variable (response parameters) [2].

Table 2
Variables and their constraints in Box-Behnken design.

Variables	Constraints	
	Lower limit	Upper limit
Independent variables		
(A) = Percent of gelatin conc.	0.25	0.75
(B) = Percent of PVP K 30	0.50	1.00
Dependent variables	**Goals**	
(R1) = *In-vitro* drug release	Maximize	
(R2) = Disintegration time	Minimize	
(R3) = Water absorption ratio	Optimize	
(R4) = Wetting Time	Minimize	

2.4. Measurement of tablet tensile strength and friability

The ability to withstand mechanical shock of handling in manufacturing, packaging and shipping is measured in terms of tensile strength or crushing load and friability. The crushing load for FDTs of various batches was determined by compressing the tablets in diametric direction using a Pfizer tablet hardness tester (Cadmach, India). The friability of tablets was determined using Roche friabilator USP test apparatus (Electrolab, Mumbai). Randomly six FDTs were chosen from each batch and their initial weight was determined Table 3. The FDTs were placed in friabilator and rotated at 25 rpm for 4 min. They were then removed, dusted and their final weight was determined [14–16,19–23]. The formula for calculating friability is given as Eq. (1):

$$F = \frac{W_i - W_f}{W_i} \times 100 \quad (1)$$

where W_i is initial weight and W_f is the final weight of the tablets.

2.5. Weight variation and tablet thickness

Twenty tablets were randomly taken from each batch and the weight of their average weight was determined. Then individual tablet was taken and its weight was calculated. That individual weight was compared with average weight. The weights were measured using weighing balance [18]. Twenty tablets were randomly selected from formulations and thickness was measured individually by screw gauge. The results were expressed in millimeters Table 3.

Table 1
Formulation table of Chlorpheniramine maleate by lyophilization method.

Ingredients	Formulations									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Chlorpheniramine maleate(mg)	50	50	50	50	50	50	50	50	50	50
Gelatin (mg)	–	–	0.25	0.5	0.75	0.75	0.75	0.75	0.5	0.25
Mannitol (mg)	97.25	97.25	95.75	94.25	96	94.75	93.75	96	93.5	93.25
Glycine (mg)	8.75	8.75	8.75	8.75	8.75	8.75	8.75	8.75	8.75	8.75
Microcrystalline cellulose(mg)	90	92	90	92	90	90	90	90	92	92
PVPK30 (mg)	–	–	0.5	0.5	0.5	0.75	1	0.5	0.5	0.75
PEG6000 (mg)	3	1	3	2	1	2	1	1	_	_
PEG4000 (mg)	_	_	1	2	3	3	4	2	4	4
Tween 80(%w/v)	1	1	0.75	_	0.75	0.75	0.75	1	0.75	1
Total (mg)	250	250	250	250	250	250	250	250	250	250

Please cite this article in press as: V. Dave et al., Formulation design and optimization of novel fast dissolving tablet of chlorpheniramine maleate by using lyophilization techniques, Bulletin Facult Pharmacy Cairo Univ (2016), http://dx.doi.org/10.1016/j.bfopcu.2016.12.001