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Design and Development of Orodispersible Tablets of Promethazine Theoclate Using Coprocessed Superdisintegrants and Subliming Materials

A.J. Chacko[1], Sajan Jose[1*], Neeba Babu[1], Lucille and Marlyn Michelle[1]

[1*]Dept. of Pharmaceutical Sciences, M.G. University,
Cheruvandoor campus, Kottayam, Kerala, India.

ABSTRACT

The objective of the study was to develop a traveller friendly orodispersible tablet of promethazine theoclate by direct compression using superdisintegrant combinations and subliming materials. The poor aqueous solubility of Promethazine theoclate makes its absorption as dissolution rate-limited and thus delay onset of action. In this work an attempt was made to develop a novel drug delivery system for Promethazine theoclate by simple and cost effective direct compression technique. Formulations were developed using superdisintegrants (crosspovidone, CP and sodium starch glycolate, SSG) and co-processed superdisinetgrants (CP:SSG 3:1, CP:SSG 1:1, CP:SSG 1:3) in different concentrations. After examining the flow properties of the powder blends, it was subjected to tablet compression. Prepared tablets were evaluated for organoleptic properties, thickness, hardness, friability, disintegration time, wetting time, water absorption ratio, weight variation, percentage drug content, in-vitro dispersion time, uniformity of dispersion and in-vitro dissolution studies. Based on the results, formulation containing CP: SSG 3:1 at a concentration 5% was found to be promising and selected as the optimized formulation. A similar formulation was prepared by sublimation technique and compared with the optimized formulation. This comparative evaluation revealed that direct compression method is a better alternative to sublimation method. It was concluded that dissolution rate of PT can be enhanced to a great extent by direct compression technique with the addition of novel co-processed superdisintegrants which give immediate relief from emesis.

Keywords: Promethazine Theoclate, Orodispersible tablets, Direct compression, Sublimation, coprocessed superdisintegrant.

INTRODUCTION

Oral ingestion remains to be the perfect route for administration of therapeutic agents despite of the tremendous advancements in drug delivery (Banker, 1986).Two widely faced challenges in oral drug delivery are dysphagia and delivery of unpalatable drugs (Bhandari *et al.,* 2008). Therefore to improve the compliance and quality of life of mainly pediatric and geriatric patients, emphasis is laid on the development of novel drug delivery systems. One such approach is orally fast disintegrating tablets, which do not require water to aid swallowing (Chatap *et al.,* 2007). These orodisperse tablets are synonymous with fast dissolve, rapid dissolve, fast melts, quick disintegrating, melt in mouth tablets, porous tablets, and freeze dried wafers (Chatap *et al.*, 2007; Dobetti, 2001; Bandari *et al.*, 2008; Pfister and Ghosh, 2005; Sharma, 2008; Satpathy, 2007). When such tablets are placed in the oral cavity, saliva quickly penetrates into the pores to cause rapid tablet disintegration without any chewing by patients. Skillful taste masking hides the bitterness and will result in a superior product (Brown, 2003).

Recently we confirmed that orodisperse tablets can be prepared by conventional techniques like lyophilization, molding, spray drying, sublimation, direct compression and disintegrant addition (Dobetti, 2001; Bandari, 2008; Sharma, 2008; Kundu and Sahoo, 2008; Kuchekar and Arumugam, 2001; Gohel and Jogani, 2005; Patel, 2006). However to eliminate expensive sophisticated techniques, we investigated a cheap convenient method of preparing orodisperse tablets using coprocessed superdisintegrant combinations. We choose

***Corrosponding author**
Sajan Jose
Email id: sajanjose@hotmail.com

crosspovidone and sodium starch glycolate as superdisintegrants.

The aim of the present study was to develop and evaluate orodisperse tablet of promethazine theoclate exploring the functionality of coprocessed superdisintegrants. The optimization of the formulations was followed by the comparative evaluation of the optimized formulation with the formulation prepared by sublimation. Promethazine theoclate is a histamine H_1 receptor antagonist with the greatest effectiveness in motion sickness and vestibular disturbances. Rapid onset of action is of prime importance in patients with nausea and motion sickness (Indian Pharmacopoeia, 1996; Tripathi, 1985). So the patient would be benefited by the proposed drug delivery system.

MATERIALS AND METHODS

Promethazine theoclate was obtained as gift sample from Mehta Pharmaceutical Industries, Mumbai, Microcrystalline cellulose and Sodium starch glycolate were obtained as gift samples from Sance Laboratories Pvt Ltd, Palai, Crospovidone was obtained as gift sample from Microlabs, Bangalore, Mannitol, Magnesium stearate, Colloidal silicon dioxide, Talc, Sodium saccharin and Vanillin were purchased from Nice chemicals, Kochi. Other reagents were of analytical grade.

Fabrication of orodispersible tablets (Banker and Anderson, 1986; Sharma, 2008; Gohel *et al.,* 2007; Mohapatra, 2008; Wells *et al.,* 2002; Kumar *et al.,* 2009)

Coprocessed superdisintegrants are initially prepared in the ratios 1:3, 1:1 and 3:1. After evaluating the flow properties of pure and coprocessed superdisintegrants, powder blends of promethazine theoclate were prepared by varying concentrations of pure and coprocessed superdisintegrants were prepared. These powder blends were evaluated for their flow properties and followed by tablet compression by direct compression technique using Cadmach tableting machine equipped with round flat punch of 8mm diameter. Compositions of different batches of tablets prepared are shown in Table 1 and Table 2. Orodispersible tablets of promethazine theoclate are also prepared by sublimation technique using camphor which is shown in Table 3.

Evaluation of tablets

The prepared tablets were evaluated for thickness (Banker and Anderson, 1986), weight variation (United State Pharmacopoeia, 2000) and drug content uniformity test (Mohapatra *et al.,* 2008) was conducted.

Hardness and Friability (Banker and Anderson, 1986)

Hardness was measured using Pfizer hardness tester with ten tablets. Friability of twenty tablets was determined by Roche Friabilator rotated at 25rpm for 4 minutes.

Wetting time and Water absorption ratio (Mohapatra *et al.,* 2008; Bandari, 2008)

Wetting time and water absorption ratio was measured by placing a tablet on a piece of tissue paper folded twice in a small culture dish containing 6 ml of phosphate buffer pH 6.8 and water respectively. The time required for water to reach the upper surface of the tablet was noted as the wetting time.

In vitro disintegration test (Indian Pharmacopoeia, 1996; Sharma, 2008)

The disintegration time was measured using disintegration test apparatus. One tablet was placed in each tube of the basket. This basket was immersed in water bath at 37 ± 2^0 C. The time required for complete disintegration was recorded with standard deviation.

Test for dispersion (Mohapatra, 2008; Indian Pharmacopoeia, 1996)

In vitro dispersion time was measured by dropping a tablet into 10ml of phosphate buffer pH 6.8 in a beaker at 37±0.5ºC. Time required for complete dispersion of the tablet was recorded.

Dissolution study (United States Pharmacopoeia, 2000; Sharma and Gupta, 2008)

In vitro dissolution study was performed using USP dissolution apparatus Type 2 (Paddle type) at 100rpm using 900 ml phosphate buffer pH 6.8 as the dissolution medium at 37±0.5ºC. Aliquots of dissolution medium were withdrawn and the absorbances of filtered solutions were determined by UV Spectrophotometer at 211.0nm. Six trials were performed for each batch and average percentage drug release with standard deviation was calculated and recorded.

RESULTS AND DISCUSSION

The prepared tablets of all the formulations possessed good mechanical strength with sufficient hardness in the range of 3.5±0.0817 kg/**c**m^2 to 4.2±0.0983 kg/**c**m^2 and the friability value ranged from 0.62% to 0.84% which was found to be within the limit (i.e. maximum 1%). All the prepared formulations disintegrated in less than 3 minutes indicating the efficacy of both superdisintegrants and coprocessed superdisintegrants. The *in vitro* disintegration time for all tablet formulations ranged from 12±2.2509 seconds to 151±17.7050 seconds. Among the formulations, F9 was found to have the minimum disintegration time of 12±2.2509 seconds. Hence coprocessing resulted in the formation of quickly disintegrating tablets.

The average wetting time for all formulations were in the range of 21±1.5063 seconds to 159±7.7825 seconds. The minimum and maximum wetting time was observed for F9 and F4 respectively. Water absorption ratios for all formulations were in the range of 44.14±3.5533% to 123.65±3.3515%. The percentage drug content of all formulations was found to be between 94.5 to 106.3% of Promethazine theoclate which are within the acceptable limits. All the tablets passed weight

variation test as the percentage weight variation was much within the pharmacopoeial limits of 7.5%. The *in vitro* dispersion time for all formulations was found to be decreasing with increasing disintegrant concentration. Formulation F9 was found to be promising and displayed an *in vitro* dispersion time of 23 seconds which facilitates their faster dispersion in the mouth.

The cumulative percentage of promethazine theoclate released as a function of time from formulations F1 to F15 ranged between 85.18±2.8504 % and 98.29±2.6531 % at 12 minutes. Dissolution for the control batch with no disintegrants (F16) was very slow with only 62.68±1.7252 % released in 3 minutes and about 76.2±1.0062 % in 12 minutes. The rapid drug dissolution was observed in F9 (CP: SSG 3:1 5%) which released 98.29±2.6531 % at the end of 12 minutes. The rapid drug dissolution might be due to easy break down of particles due to the presence of superdisintegrants and coprocessed superdisintegrants and dissolution of drug into the medium. F9 formulation showed good dissolution efficiency and rapid dissolution.

Rapid disintegration with tablets having higher levels of superdisintegrants might be one of the probable causes for their faster dissolution. Another reason could be that in the presence of disintegrants, the matrix might have distorted resulting in higher surface area, allowing the superdisintegrants to readily pick up water and thereby rendering rapid rate of dissolution.

Formulation F9 having co processed superdisintegrants CP: SSG 3:1 in the concentration of 5% was selected as the optimized formulation. F9 tablets displayed better disintegration time of 12 seconds, wetting time of 21 seconds, water absorption ratio of 119%, *in vitro* dispersion time of 23 seconds compared to the control formulation.

Comparison of results of evaluation of tablets prepared by sublimation technique and optimized batch

The use of subliming agent results in tablets with increased friability and minimized wetting time, disintegration time and invitro dispersion time. This is attributed to the faster uptake of water by capillary action due to the porous structure formed, thus facilitating the disintegrant to bring about faster disintegration. Eventhough the *in vitro* dissolution profile indicated faster release from formulation F17; it was proved that there was no significant difference between the dissolution profiles of formulation F17 and F9. It is concluded that simply by direct compression technique, orodispersible tablets of promethazine theoclate can be successfully prepared.

CONCLUSION

We developed mouth dissolving tablets of promethazine theoclate using coprocessed superdisintegrant combination by direct compression technique. F9 tablets which displayed minimum disintegration time and wetting time was selected as the optimized batch. The optimized formulation and the formulation prepared by sublimation showed similar dissolution profile. Hence this technique proves to be an effective alternative approach to use of more expensive and sophisticated techniques in the formulation of orodisperse tablets.

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