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ORIGINAL ARTICLE

Formulation development and evaluation of medicated chewing gum of anti-emetic drug

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Ex-vivo buccal permeation study;
Statistical analysis for quality

Abstract *Context:* Medicated chewing gum (MCG) of Domperidone Maleate (DM) was developed by direct compression method with the goal to achieve quick onset of action and to improve patient compliance. *Objective:* Formulation development of MCG of DM and optimization of the formulation by screening of different excipients. *Material and methods:* MCG containing DM was prepared by screening different concentrations of sweeteners, flavouring agents, softening agents, lubricants and anti-adherents by changing one variable at a time. Performance evaluation was carried out by evaluating size, shape, thickness, taste, scanning electron microscopy, texture analysis, in vivo drug release study, ex vivo buccal permeation study and by studying statistical analysis for quality. *Results and discussion:* The statistical analysis showed significant improvement in organoleptic properties such as chewable mass, product taste, product consistency, product softness, total flavour lasting time and pharmaceutical properties like micromeritic properties after incorporation of appropriate excipients in an optimum amount in final optimized MCG formulation. In vivo drug release study showed 97% DM release whereas ex vivo buccal permeation study through goat buccal mucosa exhibited 11.27% DM permeation within 15 min indicating its potential for increasing bioavailability by decreasing time of onset. The optimized formulation showed good surface properties and the peak load required for drug release was found to be acceptable for crumbling action. *Conclusion:* The developed formulation of medicated chewing gum can be a better alternative to mouth dissolving and conventional tablet formulation. It may be proved as a promising approach to improve the bioavailability as well as to improve patient compliance.
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1. Introduction

Nausea and vomiting are the most commonly occurring symptoms in majority of pathophysiological conditions such as motion, cancer, pregnancy, and postoperative conditions. Nausea refers to feeling of impending vomiting. Vomiting

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refers to forceful expulsion of contents of the stomach and the proximal small intestine (Pleuvry, 2006).

Antiemetic drugs are used to prevent or suppress vomiting. They act by blocking several receptors located in vomiting centres such as H_1 histaminic, dopamine D_2, 5-HT_3 receptor, muscarinic, and neurokinin1(NK_1) receptor. Drugs such as Anticholinergics, H_1-antihistamines, Neuroleptics, 5-HT_3 antagonists act by penetrating blood brain barrier which leads to sedation. Prokinetic drugs such as metoclopramide and domperidone maleate act as dopamine D_2 blockers. Their antiemetic activity is due to antagonism of D_2 receptors in Chemoreceptor Trigger Zone (CTZ) which is located outside of the blood brain barrier so they do not cause side effects related to brain and hence do not cause disturbance in regular activities such as driving, and office work. It is reported that metoclopramide has more side effects as compared to Domperidone maleate (Tripathi, 2003).

Domperidone Maleate (DM) has very low oral bioavailability (15%) owing to its extensive metabolism in liver and gut wall (Tripathi, 2003). It is available in the form of tablets, capsules, suspensions, injections, sustained release capsules, etc. But these formulations have several disadvantages such as difficulty in swallowing tablets or capsules which also requires water. Besides these, suspension does not possess pleasant taste and dose accuracy. Patients suffering from trypanophobia experience difficulty in medication by needle. In addition, drug if given by oral route, undergoes first pass metabolism that decreases bioavailability of DM. Formulations of DM investigated by various researchers are coevaporates (Nagarsenker et al., 2000), fast dissolving tablet (Bhatt and Trivedi, 2012), orodispersible tablet (Islam et al., 2011), etc.

Chewing gum is a pleasure that almost everyone enjoys. Chewing gum usually consists of a gum core, which may or may not be coated. Medicated chewing gums are defined by the European Pharmacopoeia and the guidelines for pharmaceutical dosage forms issued in 1991 by the Committee for Medicinal Products for Human Use (CPMP) as 'solid single dose preparations with a base consisting mainly of gum that are intended to be chewed but not to be swallowed, providing a slow steady release of the medicine contained' (European Pharmacopoeia, 2010). Chewing gum has also being exploited for the drug delivery and many times referred as mobile drug delivery system (Ingole et al., 2012). Medicated chewing gum (MCG) gives local (treatment of oral disease) as well as systemic action (buccal absorption or by swallowing saliva). MCG helps to increase patient compliance by fast onset of action and by improved bioavailability of drug as some amount of drug is absorbed through the buccal mucosa. It can also be administered without water (Jacobsen et al., 2004; Chaudhary and Shahiwala, 2010; Chaudhary and Shahiwala, 2012). MCG has been exploited for various drugs such as cetirizine (Stojanov and Larsen, 2012; Swamy et al., 2012), dextromethorphan hydrobromide (Swamy et al., 2012), dimenhydrinate hydrochloride (Mehta and Trivedi, 2011), nicotine (Morjaria et al., 2004; Cherukuri et al., 2000), antacids (Zyck et al., 2003), miconazole (Pedersen and Rassing, 1990), aspirin (Woodford and Lesko, 1981), caffeine (Tyrpin et al., 2002), antimicrobial decapeptide (Dong et al., 2005), ondansetron hydrochloride (Nagaich et al., 2010), and nystatin (Andersen et al., 1990).

The aim of present research work was to formulate medicated chewing gum of DM to fasten the onset of action and to improve the bioavailability so as to get the quick relief from nausea and vomiting with greater patient compliance.

2. Methods

2.1. Materials

DM was received as gift sample from Vasudha Pharma Chemical Limited (Hyderabad, India). Health In Gum® (HIG PWD 02) was received as gift sample from Cafosa (Barcelona, Spain). All other ingredients and solvents used were of analytical or pharmaceutical grade.

2.2. Drug excipients compatibility study

2.2.1. Fourier Transform Infrared Study (FTIR)

The drug-excipient compatibility study was carried out by FTIR. FTIR spectra of the (a) pure drug, (b) gum base and (c) mixture of drug:excipients (1:99) were recorded. The samples were prepared by weighing and homogenously dispersing with dried KBr in a mortar and pestle, and compressing the powder under vacuum with a compression force using round flat face punch for three minutes to produce a pellet compacts. The sample was placed in the IR light path using a FTIR Instrument (NICHOLET 6700, Thermo Scientific, USA). Spectra were recorded in the wavelength region of 4000–400 cm^{-1}. The peaks were observed for any types of interaction between the drug and excipients (Dixit, 2013).

2.3. Formulation development of MCG

The technique of screening of one excipient at a time was adopted. The whole process of the formulation development is given in Fig. 1.

2.4. Pre-compression study

Flow properties of gum base and drug: excipient mixtures were determined by measurement of angle of repose, bulk density, tapped density, compressibility index (CI) and hausner's ratio.

2.5. Preparation of medicated chewing gum

Medicated chewing gums were prepared by direct compression method. In this method, the flavour was added in accurately weighed DM with continuous mixing in a mortar for 15 min. Flavoured drug was screened through 30# sieve (0.600 mm) followed by addition of accurately weighed and 30# pre-sifted gum base, anti-adherent and sweeteners and blended for 10 min. 30# pre-sifted lubricant was precisely added and blended for 10 min. Finally, the prepared blend of formulation was compressed on a tablet compression machine (Rimek Mini Press-II, Karnavati Engineering) (Rao et al., 2011).

2.6. Screening of excipients by human volunteers

MCGs were evaluated for several organoleptic properties such as chewability, flavour lasting time, sweetness, and softness in a panel of healthy human volunteers ($n = 6$). The permission for conducting these studies was obtained from Institutional

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