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FORMULATION OF MEDICATED CHEWING GUM OF ONDANSETRON HYDROCHLORIDE AND ITS PHARMACOKINETIC EVALUATIONS

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ABSTRACT

An attempt has been made to formulate new chewing gum device for ondansetron hydrochloride in the form of tablet. The new drug delivery system was obtained, at room temperature, by direct compression using conventional pharmaceutical equipment. The resulting chewing gum tablets comprise a gum core combined with fillers, antioxidants, coloring agent and plasticizers, which provide smooth appearance and flexibility during storage and chewing. Drug release from a dosage form is the critical step in drug absorption and bioavailability, thus an experimental work has been designed to evaluate the efficiency of this kind of therapeutic system by verifying its capability to release the drug dose and by assessing the delivery of ondansetron hydrochloride for by-passing the hepatic first pass effect. Simple diffusion into the medium causes the release of only a small percentage of the drug contained in the medicated chewing gum, while the delivery of the major part of the dose occurs during mastication. In the present study, an attempt has been made to formulate the chewing gum of ondansetron hydrochloride. Different formulations of chewing gum with varying concentration of plasticizers like glycerol and castor oil were formulated. Better consistency of formulation and faster release of drug in saliva was obtained with glycerol F (III), and Castor oil F (II) but castor oil shows optimum result against glycerol combination, which is formulation II. Urinary excretion profile showed that within the short span of time 1.5 h drug was excreted. Buccal absorption test showed that 85% of drug absorbed within 15 min when available to the buccal mucosa at pH 5.5. Hence, ondansetron hydrochloride chewing gum can be considered as a better formulation for the buccal drug delivery system, in which drug is absorbed buccally and reaches the systemic circulation via jugular vein.

INTRODUCTION:

Chewing gum is considered as a convenient "vehicle" or a "delivery system" to administer the drug, that can improve health and nutrition, it has potential as an "alternative drug delivery system"[1]. The European Pharmacopoeia defines medicated chewing gum as ''solid, single-dose preparations with a base consisting mainly of gum that are intended to be chewed but not swallowed''[2]. They can be used as therapeutically for the local treatment of diseases related to buccal mucosa or for systemic treatment after the drug absorption. In addition to the generally higher permeability of the oral mucosa, several other factors enhance mucosal tissue penetration and absorption: age, salivary lubrication, chronic inflammation, infections, physical damage (such as from cheek biting, rough dental fillings and chemical irritants) and dentures.

The release rate of the active medicament, from a chewing gum, is determined by the physico-chemical characteristics of the drug, the composition and manufacturing process of the formulation, and by the patient chewing performances[3, 4]. Patient chewing performance means, people shows different chewing time, chewing frequency and chewing intensity, moreover patients with xerostomia or oromucosal diseases may experience chewing altering their chewing performances[5,6]. For all these reasons the drug released from a chewing gum may show large inter-individual variations. That is most important part of our research work. The drug absorbed from mucosal surface of the buccal area, which is directly goes to superior vanacava and by-passing the hepatic first pass effect so chewing gum is a convenient drug delivery system[7]. The main absorption mechanism is passive diffusion of the un-ionized form of the drug.

The need for and value of *in-vitro* drug release testing is well established for a range of dosage forms, however, standard dissolution apparatus is not suitable for monitoring release of drug from chewing gums as the action of chewing is essential, by providing a renewable surface for drug release after chew action. The release of substances from chewing gums during mastication can be studied by employing a panel of tasters and chew-out studies. During the mastication process, the medication contained within the gum product should be released into the saliva and is either absorbed though the oral mucosa or swallowed and absorbed though the gastrointestinal tract. The chewed gum can then be removed and analyzed for the residual drug substance while pharmacokinetics can be determined from blood samples.

In the present work, ondansetron hydrochloride drug is used, which is a new class of anti-emetic prototype, it blocks the depolarizing action of 5-HT though 5-HT3 receptors on vogal afferents in the GIT as well as in NTS and CTZ (4). It blocks emetogenic impulses at both their peripheral origin and their central relay. Oral ondansetron hydrochloride reduces vomiting and facilitates oral rehydration in children with acute gastroenteritis. The main drawback of conventional dose of ondansetron hydrochloride is its oral bioavailability, which is about 60% with peak plasma concentrations 1.5 hour after an oral dose. The elimination half-life is 3-3.5 hour. The drug undergoes extensive

hepatic metabolization by the cytochrome P450 enzyme system, that it causes hepatic first pass effect. To check its hepatic first pass effect we were prepared medicated chewing gum of ondansetron hydrochloride[9, 10].

The approach of this study was to design a chewing gum where the complete release of the drug dose from the formulation can be detected from an organoleptic change of the gum (in this case, the loss of a color) independently of the different chewing times and chewing frequency of the patients. Here, synthetic polymer is used as a base for chewing gum with different plasticizer, sweetener , colorants, fillers etc. for that we have to study some evaluation parameters like, release of drug in saliva, urinary excretion profile of drug, buccal absorption test. The main aim of this study is to reduce the vomiting frequency by enhancing its bioavailability and to by-pass its hepatic first pass metabolism.

MATERIALS AND METHOD:

Materials: Ondansetron Hydrochloride was a gift sample, provided by GlaxoSmithKline, Ahmedabad. Polyvinyl pyrrolidone used as a synthetic elastomer. Glycerol, Castor oil were used as a plasticizer with a varying concentration[11]. Dextrose as sweetener, Peppermint as a flavoring agent and Calcium carbonate was used as filler[12].

Method: Formulation of medicated chewing gum of Ondansetron Hydrochloride:- Ondansetron hydrochloride was used as a medicated agent. In the chewing gum formulation varying concentration of plasticizers like castor oil and glycerin were used. Peppermint oil was used as flavoring agent. Weight of each piece of the chewing gum is approximately 400 mg [13, 14]. The medicated chewing gum was prepared by direct compression method[15] (Table 1).

Table 1: Formula of ondansetron hydrochloride medicated chewing gum with different concentration of plasticizers

Ingredients	Glycerol			Castor oil		
	I	II	III	I	II	III
Polyvinylpyrrolidine	300	300	300	300	300	300
Ondansetron Hcl	05	05	05	05	05	05
Plasticizer	16	20	24	16	20	24
Bees wax	29	29	29	29	29	29
Dextrose	23	23	23	23	23	23
Peppermint	04	04	04	04	04	04
Filler cal carbonate	24	24	24	24	24	24
Antioxidant	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%

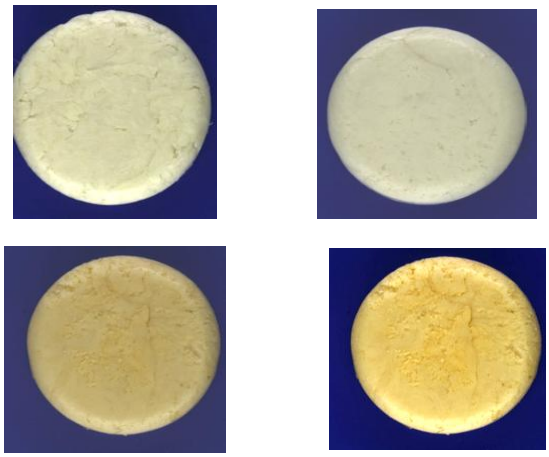

Fig 1: Photographs of Ondansetron hydrochloride chewing gum prepared by direct compression method

Evaluation parameters of medicated chewing gum:

(a) Release of drug in saliva: The drug release process from medicated chewing gum is quite different compared to a conventional oral drug delivery system, in fact; in this case, not only the dosage form but also the chewing activity of the patient may influence drug delivery. Gums are not intended to dissolve/disintegrate by themselves but a mechanical treatment of the dosage form is required to cause the drug to be delivered. For these reasons, the European Pharmacopoeia guidelines suggest the employment of a specific apparatus for gum formulations which simulates human chewing behaviour.

To overcome all these difficulties, alternative solutions have been proposed[19, 20,21] the most accessible and obvious approach is to ask to a panel volunteers to chew the drug delivery device for a certain period of time and to assess the remaining quantity of active substance in the residual gum. In this way, the gums are really chewed and the formulation is subjected not only to the mechanical stresses of an artificial machine but also it undergoes all the phenomena involved in this process (increase of salivary secretion, saliva pH variation, swallowing and absorption by the oral mucosa, etc.) which can strongly influence the performance of the dosage form and the amount and rate of drug release.

Optimized formulation with good consistency was selected for the release of drug in saliva. Four human volunteers were selected (two male and two female). Volunteers were instructed to rinse their mouth with distilled water and allowed to chewing the medicated ondansetron hydrochloride chewing gum for 15 minutes, so that its maximum release has to be taken. Sample of saliva was taken after the 5 minutes and then intervals were 2, 4, 6, 8, 10, 12, 14, 15 min. The saliva sample was made diluted in the phosphate buffer pH 6.6 and absorbance was analyzed at 305 nm by UV spectrophotometric method against reagent blank[22].

(b) Dissolution test of residual medicated chewing gum: In the current experiment, Gums have been tested by a panel of volunteers to verify the drug release process from the drug delivery system. Each person chewed one sample of the tableted gum for different time periods (1, 5, 10, 15 min). The residual gums have been cut into small pieces, frozen and then ground till obtaining a fine powder. The residual drug content has been determined by UV detection using the dissolution test apparatus (U.S.P. dissolution test apparatus, 100 rpm and at 37°C). The amount of drug released during mastication is calculated by subtracting the amount of residual active ingredient present in the gum from the total content[23].

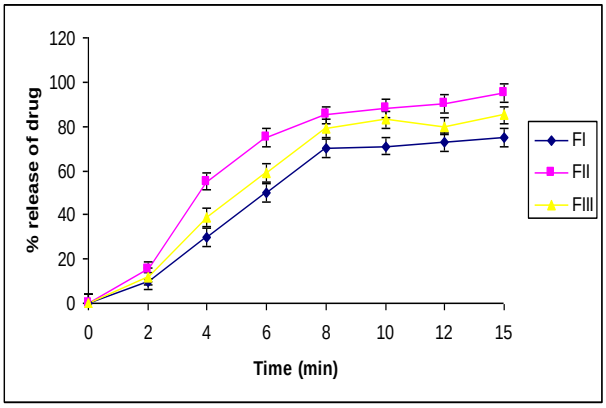

Fig. 2: *In-vitro* release of ondansetron hydrochloride from gum formulations in artificial saliva at 37°C

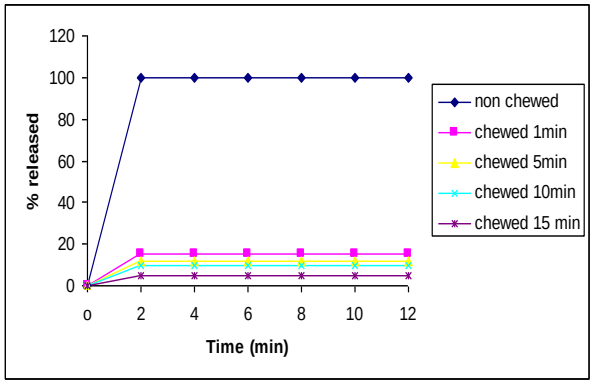

Fig. 3: *In-vitro* release of Ondansetron hydrochloride from gum formulations in artificial saliva at 37°C. The chewing gums containing different plasticizer like castor oil (5, 10, 20 mg) were studied using a dissolution apparatus

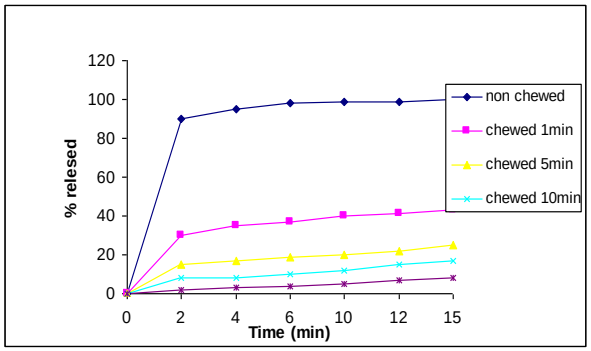

Fig. 4: Ondansetron hydrochloride with castor oil plasticizer of Formulation II (F II), releaseprofiles from the residual gums after different chewing times (average value ± S. D., *n* = 6)

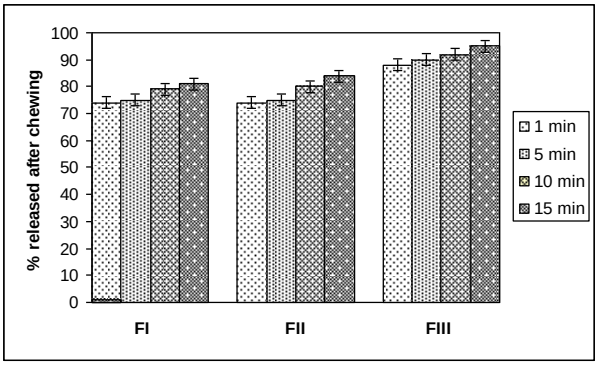

Fig. 5: Ondansetron hydrochloride with glycerol plasticizer of Formulation II (F II), release profiles from the residual gums after different chewing times (average value± S. D., *n* = 6)

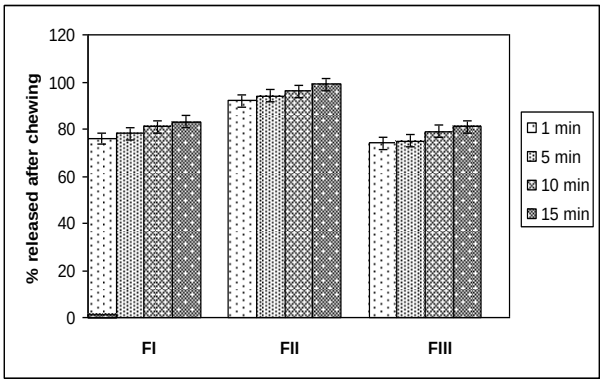

Fig. 6: Percentage of drug released as a function of chewing time from ondansetron hydrochloride containing castor oil (average value ± S. D., *n* = 6)

(c) Urinary excretion profile of medicated chewing gum: Four healthy human volunteer were selected for the study of formulations (FII and FIII). Volunteers were strictly instructed that they should not take any medicine in the last 48 hour. They were fasted overnight, and emptied their bladder in the volumetric flask. Sample collection started from blank of zero hour urine. Then sample collection was done on the 15 min, 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 24 hour intervals after administration of medicated chewing gum. The volunteers were asked to drink water at regular intervals of 30 min. and absorbance was analyzed at 305 nm by UV spectrophotometric method against blank reagent.

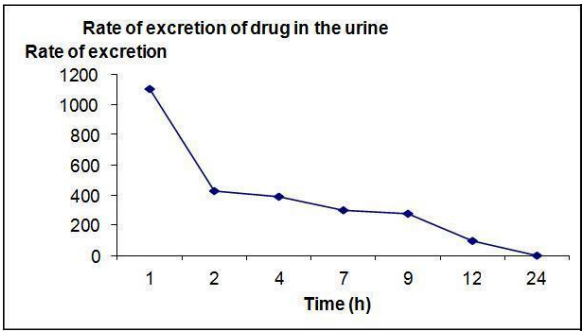

Fig. 7: Rate of excretion of ondansetron hydrochloride in the urine of F (II) containing castor oil as plasticizer

(d) Buccal absorption test[24]**:** It was done by introducing 25 ml of drug solution of concentration about 5 mg / ml at different pH value of 1.2, 5, 6, 6.5, 7, 7.5, 7.8, 8, in the oral cavity of human volunteer who swirled it for 15 min and then expelled out. The expelled saliva was analyzed at 305 nm by UV spectrophotometric method against blank reagent.

Table 2: Buccal Absorption test at different pH of Formulation II (F-II) containing castor oil as plasticizer

pH of buffer solution	% drug absorbed
5.0	70.73±0.60
5.5	85.33±0.13
6.0	68.67±0.15
6.5	65.54±0.35
7.8	64.44±0.60
8.0	53.63±0.63

RESULT AND DISCUSSION:

In the present study, an attempt has been made to formulate chewing gum of ondansetron hydrochloride. To obtain ondansetron chewing gum, powder blends have been prepared with the varying concentrations of plasticizers of glycerol and castor oil, were tried to formulate chewing gum containig 1.25% w/w of ondansetron hydrochloride each. It is designed to form the tablet core by direct compression using conventional pharmaceutical equipment. Different formulations have been prepared and tested with the aim to provide chewing gums with good organoleptic and technological properties. A pleasant mouth feeling and good chewing property is a prerequisite to develop this dosage form that means long-lasting taste, an optimal chewing volume, and antiadherent properties to the teeth, from a pharmaceutical view point, the ability to guarantee a fast and complete drug release. A model composition (%) of the different formulations with varying concentration of plasticizers was reported in (Table 1).

The gum-base is a mixture of products containing different percentages of gum to balance the chewing gum hardness and texture. Co-adjuvant excipients (Polyvinylpyrrolidine, plasticizer, bees wax, filler, calcium carbonate and antioxidant) were added to the mixture to optimize the compression process. Sweeteners and flavours were used to obtain a final pleasant taste. Preferably high intensity and non carcinogenic sweeteners were selected. Dextrose is the main component of the external layers. It is able to provide a sweet taste and antiadherent properties at the same time. Chewing gums were produced by progressively filling the die of a single-punch tableting machine with the weighed amount of the different mixtures and then compressed (Fig. 1). Formulations were found to be having uniformity in the content of the drug as 5 mg in all formulations. Percentage drug released as a function of time was plotted. Better consistency of formulation and faster

release of drug in saliva was obtained with glycerol F (III), and Castor oil F (II) but castor oil shows optimum result against glycerol combination, which is formulation II (Fig. 3, 4). The dissolution test was performed on the ondansetron hydrochloride chewing gum (non-chewed portion) and on its residuals chewed for 1, 5, 10, 15 min. (Fig. 5 and 6). The dissolution test confirms that this method is optimal to determine the drug content remained in the dosage form after chewing, in fact, the active substance, remained in the gums, can be easily measured once the gum cuds are finely ground and placed in the dissolution medium. It is evident that the whole drug content is released after few minutes from the beginning of the test as a confirmation that the drug did not form linkage with the gum-base neither during the compression process nor during chewing. The release profiles, obtained after different chewing times, are a proof of the functionality and efficiency of this dosage form (we verify that for many drugs the whole drug dose is delivered completely during mastication). In fact, already after a short chewing time (1 minute), ondansetron is released completely and the amount still present in the residual.

These results proved that the dosage form was a good administration system. It was able to guarantee a fast and complete drug release after a relatively brief chewing time, according to the therapeutic requirements. The total amount, contained in the dosage form, is delivered after the lowest mastication time (1 min) and no significant increase of drug recovery from the gum cuds are detected by increasing mastication time. As the comparison point of view the gum formulations contained castor oil as plasticizers provide better against glycerol. By subtracting the amount of the drug content in the gum cuds to the initial total content, the drug released during the chewing action has been computed for each chew-out time. Ondansetron chewing gum containing varying concentration of plasticizers helped in maintenance of integrity drug delivery system after few minutes of mastication (Fig. 5, 6). Almost the 85% of the drugs dose is delivered after a mastication time of 10 min, which can be considered the mean chewing time of a gum. No significant differences can be evidenced among this quantity and those obtained after 10-15 minute chewing; it means that the therapeutic product is readily available for absorption.

The data reported are very reproducible as confirmed by their low standard deviation values; this suggests that drug release from chewing gum is independent from the chewing efficiency offering a large applicability of this dosage form. From our tests, three factors which can influence the release performance of a medicated chewing gum are the chewing time and the drug physico-chemical properties and concentration of plasticizers. The percentage of drug released as a function of mastication time from chewing gum containing glycerol as a plasticizer was also determined (Fig. 5). It is

evident that the percentage of the actives delivered increases progressively as a function of the chewing time. In any case, the data evidence that in 15 minute of chewing the active is delivered in a high amount becoming available for absorption. While for the formulations containing castor oil (Fig. 6) shows an almost release of the actives has been achieved in a very short mastication time (10 min.). This different behaviour could be explained by considering the varying concentration of the active principles and plasticizers. The drug release rate seems dependent upon water solubility and nature and concentration of plasticizer.

Urinary excretion profile showed that within short span of time 2 hour, drug was excreted bypassing the first pass effect of the drug (Fig. 7). Very less amount is remained to be available for the body. Because buccal cavity pH vary with food intake behaviour so, that delivery system is pH dependent, hence buccal absorption vary by varying pH of buccal cavity. Buccal absorption test showed that 85% of drug absorbed within 15 min when available to the buccal mucosa at pH 5.5 (Table 2). Result also showed that most of the drug is readily available for absorption without going hepatic first pass metabolism. Hence this system is perfect for the buccal delivery of ondansetron hydrochloride.

CONCLUSION:

From the above studies, it was concluded that polyvinyl pyrrolidone is a synthetic gum base used in chewing gum preparations. It shows better compatibility and it is easily available and cheap. After the chewing of ondansetron hydrochloride chewing gum formulation for 15 min., some drug was buccally absorbed. Some amount was analyzed from expelled saliva and remained amount was in the formulation, in the residual form. It is clear that 80-85% of the drug was buccally absorbed, 10-15% was analyzed from expelled saliva, 5-8% of drug remained in the preparation in the residual form because of the binding of lipid soluble drug to the synthetic gum base.

Hence, ondansetron hydrochloride chewing gum with castor oil plasticizer can be considered as a better formulation for buccal drug delivery system in which drug is absorbed buccally and reaches circulation via jugular vein. Only a small portion of drug is carried with saliva in gastrointestinal tract that is in dissolved and dispersed form, hence can be absorbed easily. Finally, chewing gum as a buccal drug delivery can be considered as faster and novel drug delivery system for drug to avoid first pass effect, reduce risk of over dosing, easy administration and faster action.

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