FORMULATION AND EVALUATION OF DIPHENHYDRAMINE MEDICATED CHEWING GUM

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Abstract

The release of a drug from chewing gum is dependent upon its water solubility. Water soluble substances are released rapidly and completely from chewing gum and methods are available which retard their release from chewing gum to provide an extended release profile. An attempt has been made to formulate new chewing gum device for Diphenhydramine in the form of tablet. 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 Diphenhydramine for by passing the hepatic first pass effect. 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 P (IV), 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 80% of drug absorbed within 10 min when available to the buccal mucosa at pH 5.5.

Key words: *Diphenhydramine, Medicated chewing gums, local disinfectant, mouth diseases.*

INTRODUCTION

The dosage form or delivery system is critical to the success of a pharmaceutical product. Today chewing gum is gaining new consideration as drug delivery system it provides additional patient benefits and compliance, new competitive advantages from technological and marketing view point. Medicated chewing gums are solid, single dose preparations that have to be chewed and not swallowed chewing gums contain one or more active ingredients that are released by chewing. A medicated chewing gum is intended to be chewed for a certain period of time, required to deliver the dose, after which the remaining mass is discarded during the chewing process, the drug contained in the gum product is released from the mass into the saliva and it could be absorbed through the oral mucosa or swallowed reaching the stomach for gastro intestinal absorption [1]. Thus, two absorption pathways are possible to introduce the active into the systemic circulation, giving rise to a systemic effect.

Drug absorbed directly, via the buccal membrane, avoids metabolism in the gastrointestinal tract and the first pass effect of the liver. it might therefore be possible to administer a reduced dose in chewing gum compared to other oral delivery systems. Alternatively, drug released from medicated chewing gum which is not absorbed through the oral cavity membranes, will be swallowed and reach the stomach in a diluted or very dispersed form, thus being very easily available with a consequent fast onset of action. The other advantages and applications of this delivery system are easy to understand: the therapeutic system has not to be swallowed and this increases patient compliance, especially for children or patients with swallowing disorders, moreover, the product is discreet: it can be taken anywhere and at any time and it does not require liquids to be swallowed [2].

Recently, chewing gums produced by direct compression have been proposed. According to this conventional tablet compression technology, these chewing gums can include higher levels of active ingredients than traditional extruded gums, low temperature protects sensitive bioactive and phytochemical components, moreover lower moisture content also improves shelf life of active molecules. However, the most common drawback in direct compression of the gum base is its sticking effect to the punches of the tableting equipment. This effect is due to the adhesive nature of the gum, the main component of the formulation for this reason, the procedure is difficult and needs slower production speed and cooling operations to prevent a tableting machine

damage. The tableting tools are kept at temperatures below18ºC, it should be noted that the temperature should not be so low as to interfere with the handling of the medicated gums and the tableting process [3]. Thus, the temperature should be above 10–12 ºC.

In the present work, Many H1 antihistamines have been conventionally added to antitussive/ expectorant formulation. They afford relief in cough due to their sedative and anticholinergic actons, but lack selectivity for the cough centre. They have no expectorant action, may even reduce secretions by anticholinergic action. They afford protection of motion sickness for 4-6 hours, but produce sedation and dryness of mouth.

MATERIALS AND METHOD

Diphenhydramine was a gift sample, provided by Indoco remidies ltd, Mumbai. Polyvinyl pyrrolidone used as a synthetic elastomer gift samples, Bliss chemicals & pharmaceuticals India Ltd. (Thane). Glycerol, Castor oil were used as a plasticizer with a varying concentration. Dextrose as sweetener, Peppermint as a flavoring agent and Calcium carbonate was used as filler purchased from Central drug house Ltd, Delhi.

Formulation of Medicated Chewing Gum of Diphenhydramine

Diphenhydramine 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 [4]. Weight of each piece of the chewing gum is approximately 250 mg. The medicated chewing gum was prepared by direct compression method (Table 1).

Table-1 Formula of Diphenhydramine medicated chewing gum with different concentration of plasticizers

Ingredients	Glycerol				Castor oil			
	I	II	III	IV	I	II	III	IV
Polyvinyl Pyrrolidine	200	200	200	200	200	200	200	200
Diphenhydramine	05	05	05	05	05	05	05	05
Plasticizer	15	21	26	30	15	21	26	30
Dextrose	24	24	24	24	24	24	24	24
Bess wax	22	22	22	22	22	22	22	22
Peppermint	05	05	05	05	05	05	05	05
Filler Calcium carbonate	24	24	24	24	24	24	24	24
Antioxidant	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%

EVALUATION PARAMETERS OF MEDICATED CHEWING GUM

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 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 or disintegrate by themselves but a mechanical treatment of the dosage form is required to cause the drug to be delivered [5]. To overcome all these difficulties, alternative solutions have been proposed 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 Diphenhydramine chewing gum for 10 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 min. The saliva sample was made diluted in the phosphate buffer pH 6.6 and absorbance was analyzed at 258 nm by UV spectrophotometric method against reagent blank.

Dissolution Test of Residual Medicated Chewing Gum

In these experiments, chewing gums have been tested by a panel of volunteers to verify the drug release process from the drug delivery system [6]. Each person chewed one sample of the tableted gum for different time periods (1, 5, 10 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. 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.

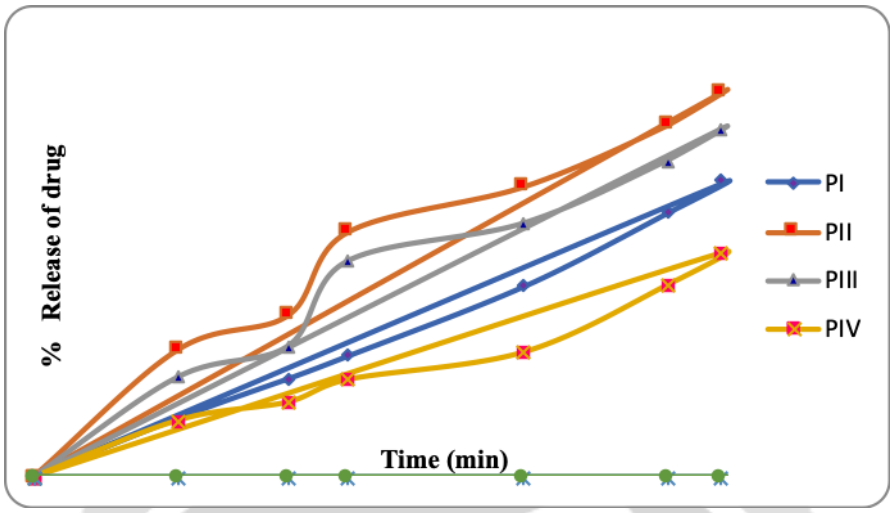

Figure-1 *In-vitro* release of Diphenhydramine from gum formulations in artificial saliva at 37°C

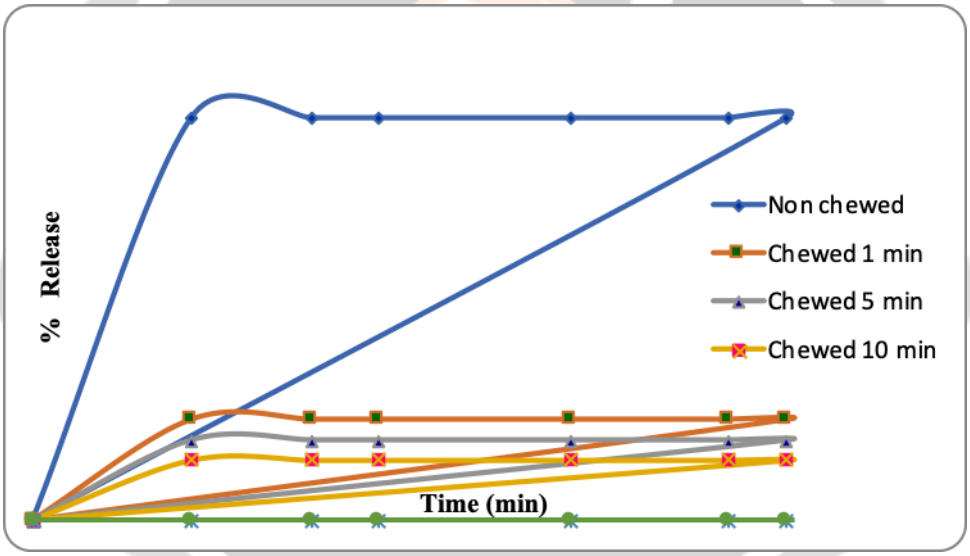

Figure-2 *In-vitro* release of Diphenhydramine from gum formulations in artificial saliva at 37°C. The chewing gums containing different plasticizer like castor oil (5, 10 mg) were studied using a dissolution apparatus

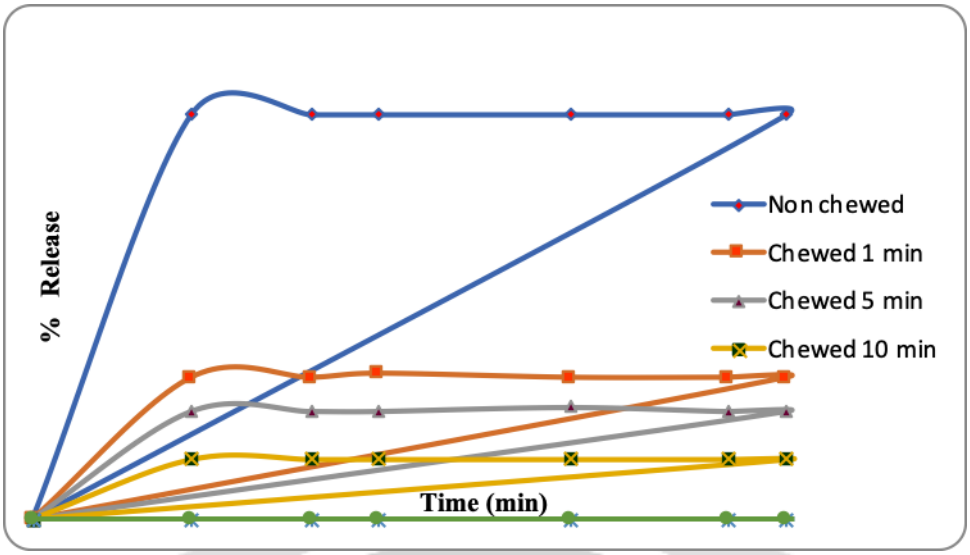

Figure-3 Diphenhydramine with castor oil plasticizer of Formulation II (P II), release profiles from the residual gums after different chewing times (average value ± S. D., *n* = 6)

Urinary Excretion Profile of Medicated Chewing Gum

Four healthy human volunteers were selected for the study of formulations (FII and FIV). Volunteers were strictly instructed that they should not take any medicine in the last 48 hours. They were fasted overnight, and emptied their bladder in the volumetric flask. Sample collection started from blank of zero-hour urine [7]. 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 258 nm by UV spectrophotometric method against blank reagent.

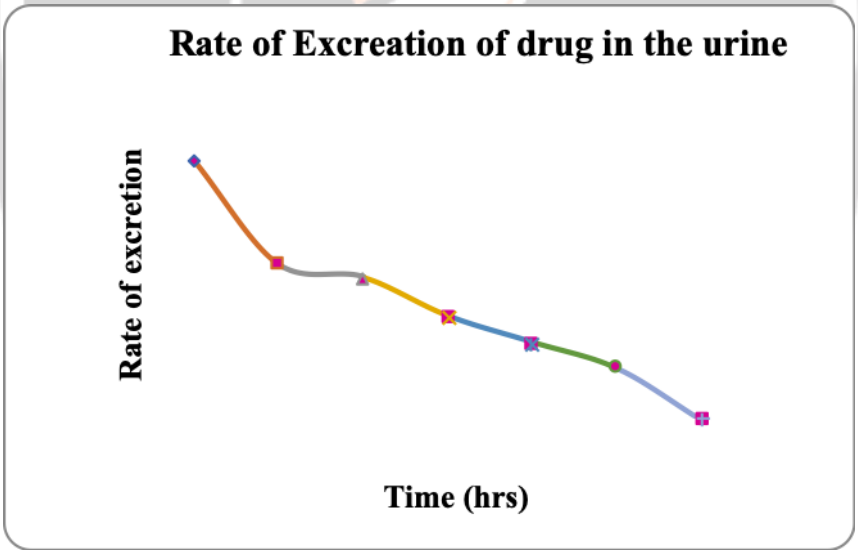

Figure-4 Rate of excretion of Diphenhydramine in the urine of P (II) containing castor oil as plasticizer

Buccal Absorption Test

It was done by introducing 25 ml of drug solution of concentration about 5 mg / ml at different pH value of 5.0, 6.5, 7.0 and 7.5, in the oral cavity of human volunteer who swirled it for 10 min and then expelled out [8]. The expelled saliva was analyzed at 258 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

SI.No.	pH of buffer solution	% drug absorbed
1	5.0	80.34 ± 0.16
2	6.5	67.25 ± 0.12

3	7.0	68.85 ± 0.15
4	7.5	65.68 ± 0.52

RESULT AND DISCUSSION

In the present study, has been made to formulate chewing gum of Diphenhydramine. To obtain Diphenhydramine chewing gum, powder blends have been prepared with the varying concentrations of plasticizers of glycerol and castor oil, were tried to formulate chewing gum containing 1.25% w/w of Diphenhydramine each. It is designed to form the tablet core by direct compression technique [9]. 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 as shown Table 1.

The gum-base is a mixture of products containing different percentages of gum to balance the chewing gum hardness and texture. The adjuvant excipients (Poly vinyl pyrrolidine, plasticizer, bees wax, filler, calcium carbonate and antioxidant) were added to the mixture to optimize the compression process. Sweeteners and flavors were used to obtain a final pleasant taste [10]. 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. 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 (IV), and Castor oil F (II) but castor oil shows optimum result against glycerol combination, which is formulation II as shown in Fig.2 and 3. The dissolution test was performed on the Diphenhydramine chewing gum (non-chewed portion) and on its residuals chewed for 1, 5, 10 min. 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 [11]. 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 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. In fact, already after a short chewing time (1 minute), it 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 chewed out time. It chewing gum containing varying concentration of plasticizers helped in maintenance of integrity drug delivery system after few minutes of mastication. Almost the 80% of the drugs dose is delivered after a mastication time of 10 min, which can be considered the mean chewing time of a gum [12]. No significant differences can be evidenced among this quantity and those obtained after 5-10minute 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 physic 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. 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 10 minutes of chewing the active is delivered in a high amount becoming available for absorption [13]. While for the formulations containing castor oil. shows an almost release of the actives has been achieved in a very short mastication time (10 min.). This different behavior 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. Very less amount is remained to be available for the body. Because buccal cavity pH varies with food intake behavior so, that delivery system is pH dependent, hence buccal absorption vary by varying pH of buccal cavity. Buccal absorption test showed that 80% of drug absorbed within 10 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 Diphenhydramine.

CONCLUSION

Finally, 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 Diphenhydramine chewing gum formulation for 10 min some drug was buccally absorbed. It is clear that 70-80% of the drug was buccally absorbed, 5-10% was analyzed from expelled saliva, 5-7% of drug remained in the preparation in the residual form because of the binding of lipid soluble drug to the synthetic gum base. Hence, Diphenhydramine 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. 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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