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Formulation and evaluation of medicated chewing gums containing Methyl Prednisolone IP

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Abstract: The medicated chewing gum containing methyl prednisolone IP may be an excellent formulation to treat oral ulcer caused by the consumption of chewing tobacco. The developed medicated chewing gums had drug content of 82.5% and it maintained its properties as per the prescribed standards. The medicated chewing gum had better drug release profile in comparison with conventional tablets of methyl prednisolone IP.T he developed medicated chewing gums were stable during the period of stability study. The medicated chewing gums may be a better formulation to treat similar oral ulcers.
Key words: Medicated chewing gums, methyl prednisolone, in vitro, oral ulcers.

Introduction and Experimental

The first commercial gum was produced in 1848 by John Curtis and his brother in Maine, USA and consisted of pure spurce resin, although the brothers later modified the formulations to include paraffin and flavours. The first chewing gum patent was granted on 28th December 1869, to William finely semple, a dentist from Mount Vernon, Ohio. This product, consisting of liquorice and rubber dissolved in alcohol and naphtha, was initially intended to be used as a dentifrice. The chewing gum is potentially useful means of administering drugs either locally to, or systemically via, the oral cavity.[1, 2, 3]

The consumption of chewing tobacco in India is very common and always on the rise in spite of statutory warnings. Several cases related to oral ulcer due to the usage of chewing tobacco are reported on daily basis. The need for better drug delivery tool to treat such a common ailment may be a necessity under these circumstances. The medicated chewing gum may be an excellent possibility to incorporate various molecules to treat such oral ulcer. According to European Pharmacopoeia, 4th 2002, 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. The medicated chewing gum s are the solid, single dose preparations that have to be chewed and not swallowed; chewing gums contain one or more ingredients that are released during chewing. The medicated chewing gum s are formulated to release the majority of their active ingredient after 20-30 minutes, but factors such as intensity of chewing and quantity of saliva produced will influence this release and the absorption from the buccal cavity[4].

During the chewing process, the drug contained in the gum product is released from the mass into saliva and it could be absorbed through the oral mucosa or swallowed reaching the stomach for gastro-intestinal absorption. Thus, two absorption pathways are possible to introduce the active ingredients into the systemic circulation, giving rise to a systemic effect. Drug absorbed directly, via the buccal membrane, avoids metabolism in the gastro-intestinal tract and the first past effect of the liver, it might therefore be possible to administer a reduced dose in chewing gum compared to other oral delivery systems[5,6].

Formulation of medicated chewing gums mainly comprises of active ingredient and gum base. The taste of active ingredient must be with in the acceptable limits. The particle size of the active ingredient should be kept below approximately 100 µm to avoid unpleasant gritty feeling during chewing. Low dose active ingredients are the prime candidates for the formulation of medicated chewing gums. E.g: Nicotine, Dimenhydrinate, Anti-emetics etc. Gum base forms up to 40% of the gum and is complex mixture, Apart from these major ingredients, elastomers, fillers, plastisizers, colours, sweetners, preservatives etc form the part of gum base[7].

Two types of manufacturing processes are available for the production of chewing gums ie. melting method or conventional production process and direct compression process.Each process do carry its own merits and demerits. Recently, free flowing directly compressible co-processed gum materials such as pharmagum developed by SPI pharma and health in gum developed by CAFOSA , have become available in the market. Chemically, it is a mixture of polyols (sorbitol/xylitol/mannitol) and of sugar with gum, plasticizers and anticaking agents[5].

The medicated chewing gum s are evaluated for their in-drug release profile, which is different from conventional technique applied for 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. Various other methods. have been developed by researchers to evaluate chewing gum characters and apparatus are fabricated which will mimic normal mastication process[8,9,10]. The official modified dissolution apparatus for assessing drug release from medicated chewing gum, as per European pharmacopoeia, is depicted in Figure 1.

Figure 1. Schematic diagram of chewing chamber of In-vitro chewing apparatus

Oral formulations of Methyl Prednisolone IP was widely prescribed by the physicians to treat oral ulcers caused by the usage of chewing tobacco. Methyl Prednisolone IP is presently available as tablets, gargles, gels etc. To overcome the deficiencies of existing formulations and improve the effectiveness of treatment with better patient compliance Methyl Prednisolone IP may be formulated as medicated chewing gum. This formulation may show improved dosage form related properties and therapeutic efficacy than the existing formulations.

Materials

The pure drug methyl prednisolone for the investigation was purchased from M/s Yarrow chemicals, Mumbai.Gum base was provided by Pops food products, Bangalore as free sample. Peppermint oil was used as flavouring agent and amaranth was the coloring agent. All the chemicals and solvents used for the study were of analytical grade.

Formulation of chewing gums of Methyl Prednisolone IP (MCG)

The MCG was prepared using the conventional production process or melting method with required modifications. The gum base was heated in a china dish on a water bath until it melts (70ºC). The drug was dissolved in glycerine and added to the molten gum base and stirred thoroughly until uniform. Flavours are

added last. Then the mixture was cooled, rolled, cut into pieces to produce sticks, later they are packed in aluminium foil and stored under controlled temperature and humidity conditions[3,4,6].

General appearance and physical parameters

Organoleptic properties such as appearance, colour and odour were evaluated for the developed MCG's. Gums from each batch were randomly selected and colour was visually compared and odour was checked[11].

Drug content estimation

Drug content was estimated by using 40 ml of simulated saliva in a mortar and crushed with the pestle for about 30 minutes. From the medium 5ml of the sample was withdrawn and absorbance was taken at 246nm after suitable dilutions[12].

In-vitro drug release studies[5,]

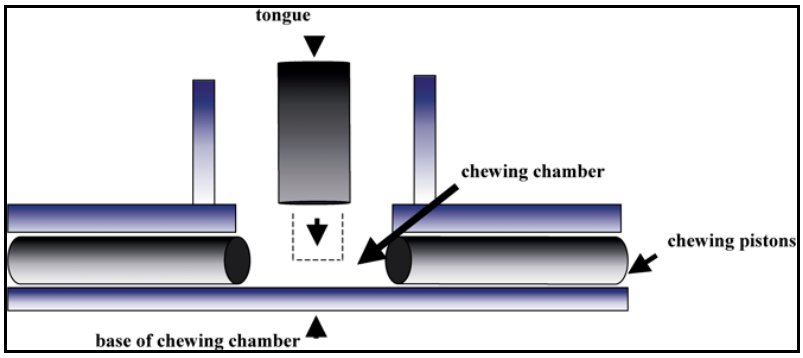

Figure 2. Apparatus for In-vitro drug release study

In-vitro drug release studies for developed MCG was performed by special equipment which will mimic the normal mastication process of humans (Figure 2). This is basically a manually operated machine. A 250ml beaker was positioned on the hollowed out thermocol base mounted on a tension spring which gives a upward thrust while working. The base of the beaker acts as lower jaw and a die punch acts as an upper jaw. The armature shaft is connected with a pulley with a handle. When this pulley is rotated manually it results the upper punch to move down and punch the bottom of the beaker which act as lower jaw. Thus chewing gum placed in the beaker is punched with the medium which mimics the normal mastication process. About 40ml of dissolution medium used, i.e., simulated saliva of pH 6.8. Punching frequency used here is 40-60 strokes/min for 30 minutes. About 1 mL of sample was withdrawn at every 5 minutes interval. After suitable dilutions drug release was determined spectrophotometrically at 246 nm after filtration and suitable dilution. An effort was made to study the effect of various frequencies of chew strokes (i.e., 30, 40, 50 and 60 strokes) on drug release of prepared MCG [5, 8, 12].

In-vitro dissolution studies for Methyl Prednisolone IP tablet

In-vitro dissolution study of Methyl Prednisolone IP tablet was carried out using USP Type II apparatus (Paddle type) at 100 rpm. In this study PBS of pH 6.8(900 ml) was used as the dissolution medium and the temperature was maintained at 37± 0.5ºC. The amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at 246 nm[12].

Stability studies of developed MCG

Accelerated stability studies of developed Methyl Prednisolone IP chewing gums were carried out as per ICH Q1A (R2) guidelines with necessary modification.Chewing gums were packed in separate aluminium foil and stored at 40 ± 2º C/75± 5% RH for 45 days. The samples were evaluated for physical appearance, colour, odour and drug content[13, 14].

Results and Discussion

Preformulation studies were carried out to assess the melting point and the compatibility of drug with its excipients. The melting point was determined as 243ºC, which complies the IP 1996.The Loss on drying of Methyl Prednisolone IP was determined as described in IP, the result obtained was 0.8% for Methyl Prednisolone IP. In order to investigate the possible interaction between drug and excipients, FT-IR studies were carried out. After spectral comparison, it was confirmed that no incompatibility reaction took place between drug and excipients[11].

Figure 3. Formulated medicated chewing gums of Methyl Prednisolone IP

The visual inspection confirmed the colour and texture of the developed formulations. The colour of the developed chewing gum of Methyl prednisolone IP was found to be light red as the colouring agent used in the formulation was amaranth (Figure 3). The developed MCG was found to be soft based on the hardness test carried out. The optimum concentration of glycerine may be helpful in maintaining the softness of the formulation. The odour of the formulation was found to be minty as the flavouring agent used was peppermint oil. The average drug content was found to be 82.5%. The good drug content showed the success of formulation and methodology employed for the development of formulation.

The percentage drug release at a chewing frequency of 30 strokes/ min was 24.5% at the end of 5 minutes. At 15 minutes, it was found to be 42.06%, and at the end of 30 minutes the amount of drug release reached up to 65.35%. After the completion of 30 minutes, nearly 35% of drug was found to be unreleased from the formulation. When the chewing frequency was increased to 40 strokes per minute, at the end of 5 minutes the amount of drug released was found to increase marginally, i.e., 25.6%. At the end of 15 minutes the % drug released was found to be 50%. At the end of 30 minute the amount of drug released reached upto 80%. In this case, nearly 20% of drug was unreleased from the developed formulation.

At the chewing frequency of 50 strokes/min, at the end of 5 minutes the % drug release was found to be 47.67%. At the end of 15 minutes the drug release was increased to 71.95%. At the end of 30 minutes the % drug release reached upto 93.77%. The chewing frequency of 60 strokes per minute, at the end of 5 minute the amount of drug release was found to be increased upto 48.9%. At the end of 15 minutes the % drug release reached 72.15%. There was an increase in drug release compared to the data obtained during other chewing frequencies. At the end of 30 minute the drug release was found to be 96.45 %.

As per the in-vitro drug release study under different chewing frequencies,there was a significant increase in the drug release with the increase in chewing frequency. Chewing frequency of lower masticating jaw also plays an important role in the drug release from a chewing gum. The increase in the frequency of chewing or movement of lower masticating jaw to 60 strokes/min showed significant improvement in the drug release. When sample subjected for 60 stroke/min frequency, at the end of 30 minute only less than 4% of drug was found to be unreleased, which high lightens the significance of chewing frequency in case of medicated chewing gums. This investigation showed that the % drug release was increased as the chewing frequency was increased. When the chewing frequency was correlated with percentage drug release, it was evident that with increase in chewing frequency percentage of drug release was improved. Comparisons of data (Figure 4) collected during this investigation comply with the findings of literature[13,14,15]

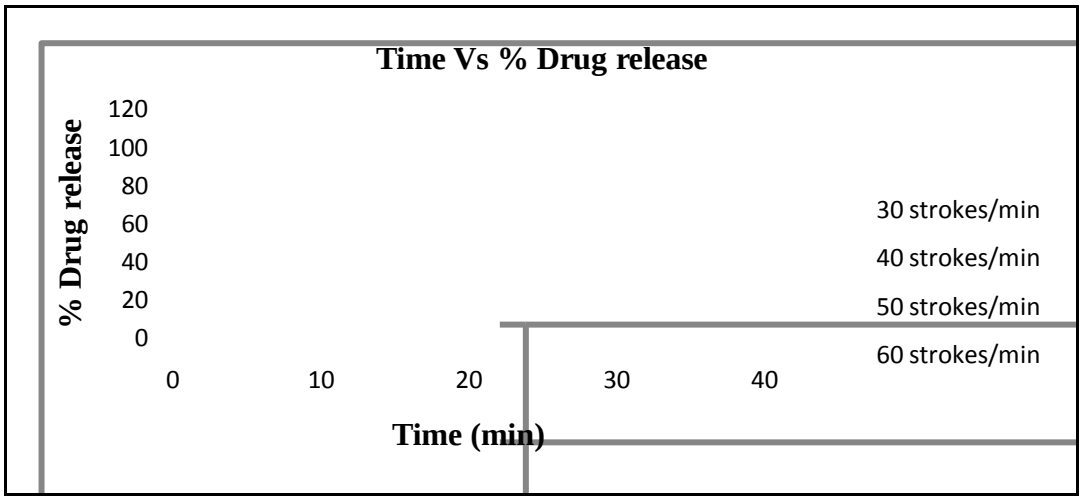

Figure 4.Comparison of drug release from MCG at different stroke frequencies

Table 1. Comparison of % drug release for MCG and conventional tablet

Time (min)	% drug release at different strokes/min				Conventional tablet
	30	40	50	60	
0	0.000	0.000	0.000	0.000	0.000
5	24.5	25.6	47.67	48.9	22.45
10	32.6	31.45	53.0	53.9	30.48
15	42.06	50.0	71.95	72.15	41.93
20	58.52	61.55	83.0	84.5	54.05
25	59.137	71.45	86.57	88.2	57.06
30	65.35	80.0	93.77	96.45	63.71

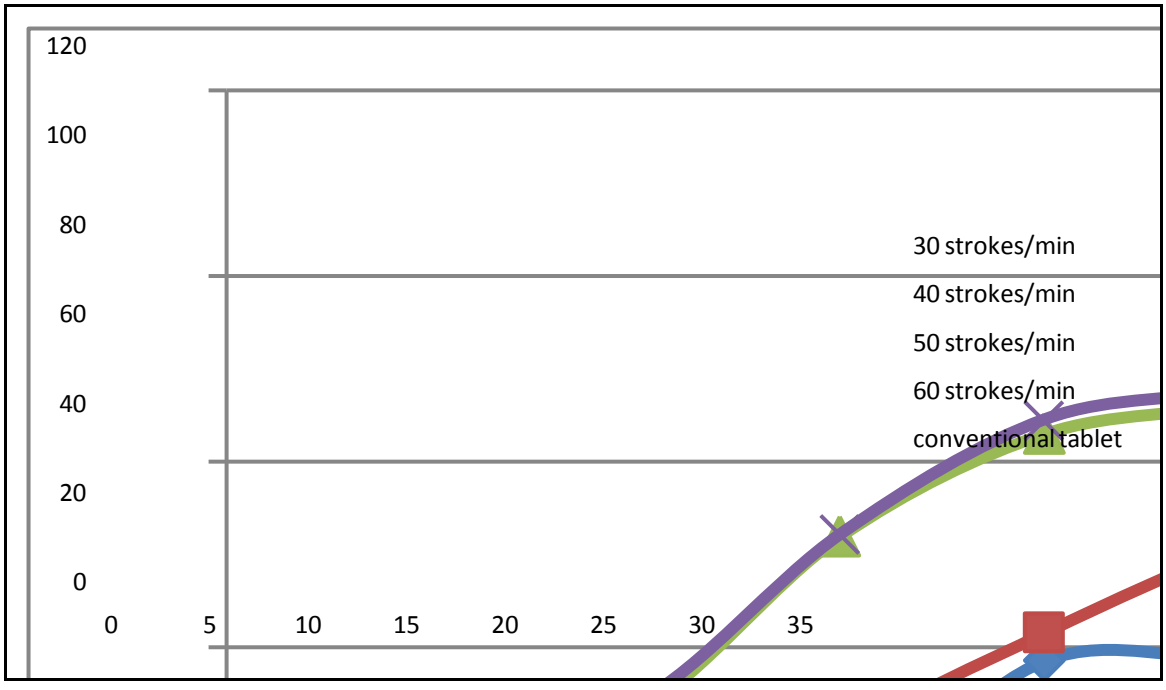

Figure 5. Comparison between formulated MCG and conventional tablets

To substantiate the benefits of formulating Methyl Prednisolone IP as a chewing gum, in-vitro dissolution study of conventional tablets of Methyl Prednisolone IP was carried out and compared against MCG (Table 1 & Figure 5). As per the data, MCG was able to release higher percentage of Methyl Prednisolone IP in comparison to conventional tablet at all the points of sample withdrawal. The maximum percentage of drug release obtained for MCG was 96.45% at 30th minute, which is much higher than the 63.71% recorded for conventional tablet at the same period of sampling. After the completion of study nearly 37% of drug was found to be unreleased from the conventional tablet, whereas only 4% of drug was unreleased from the developed MCG. In fact, even at lower chewing frequency, MCG was showing better release profile than the conventional tablet. Hence it may be suggested that Methyl Prednisolone IP may be formulated as medicated chewing gum for treating oral ulcer caused due to the usage of chewing tobacco.

Every formulation should maintain its physicochemical integrity to deliver its therapeutic goals.There was no significant change was reported with the developed MCG in terms of colour, odour and appearance Medicated chewing gum containing methyl prednisolone was able to maintain its drug content unchanged at 82.5% throughout the period of study. The study results substantiated the possibility of MCG as a stable formulation.

Summary and Conclusion

The developed medicated chewing gums of Methyl Prednisolone IP was soft, light red in colour with minty flavour. The presence of glycerine at optimized concentration provided the softness for the developed medicated chewing gum. The average drug content in the developed medicated chewing gum was found to be 82.5%, which confirmed the success of the formulation and the methodology employed for its development.

The drug release profile for medicated chewing gums may significantly affected by the chewing frequency,hence the percentage drug release of the developed MCG was measured at 30, 40, 50 and 60 strokes/min. The maximum drug release of 96.45% was reported after 30 min of dissolution study at a chewing frequency of 60 strokes/min. Hence it may be confirmed that percentage drug release increases with increase in chewing frequency. For all the chewing frequencies, Methyl Prednisolone IP was showing superior release profile from the developed medicated chewing gum than conventional tablet. The developed medicated chewing of Methyl Prednisolone IP was able to maintain its physical integrity during the entire duration of stability study.

The results obtained from this investigation may strongly suggest the possibilities of formulating medicated chewing gums of Methyl Prednisolone IP for the successful and effective treatment of oral ulcer caused due to the usage of chewing tobacco. Further In-vitro and In-vivo investigations may be recommended on the developed chewing gums of Methyl Prednisolone IP to substantiate its possibility as a better drug delivery tool.

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