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Development, In-*Vitro* Evaluation and Physical Characterization of Medicated Chewing Gum: Chlorohexidine Gluconate

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Abstract

Absorption of drugs through the oral cavity was noted as early as 1847 by Sobrero, the discoverer of nitroglycerin, and systemic studies of oral cavity absorption were first reported by Walton and Lacey in 1935. As a site for drug delivery, the oral cavity offers many advantages over other routes of drug administration. The mucosal lining of the oral cavity are readily accessible. During the chewing process, most of the medications contained within the gum product are released into the saliva and are either absorbed through the buccal mucosa or swallowed and absorbed through the gastrointestinal tract. Delivery systems containing actives for oral administration now include various chewing gum formulations. Chewing gums permit release of the active ingredient over time as the gum product is masticated, or chewed. The action of saliva on the gum further facilitates release of the active, as well as its subsequent absorption by the mucous membranes lining the mouth, throat, larynx and esophagus.

Keywords: buccal mucosa, Chewing gums, gastrointestinal tract, masticated, or chewed

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Introduction

Previously, chewing gum was mainly considered a confectionery product, however, fluoride chewing gum and especially nicotine chewing gum which was launched in the 1970s, paved the way for a more general acceptance of chewing gum as a drug delivery system. Inclusion of medical chewing gum in the European Pharmacopoeia (under medicated chewing gum) in 1998 has further contributed to full acceptance. It takes time for a new drug delivery system to establish itself on the market and gain acceptance by both professionals and patients. Chewing gum is believed to manifest its position as a convenient and advantageous drug delivery system. In addition to offering clinical benefits, chewing gum is attractive as it is a discrete and efficient drug delivery system as well as MCG provides patient a conventional mean of taking their medication. [1-3]

The objective of the work is to use of synthetic gum-base which is the non-toxic in the formulation of MCG. Simultaneously, it is also planned to identify the key formulation

parameters affecting the behaviour of MCG. The drug used in this work is an antimicrobial agent. The buccal route of administration has the important advantage of direct access to systemic circulation. This advantage overcomes the first pass hepatic metabolism and local loss of the drug at sight. Chlorhexidine gluconate is the suitable drug for local effect because it strongly binds to oral mucosa and secretes with saliva means continues local oral effect. This model drug is selected for study in order to reduce hepatic first pass metabolism and to improve systemic bioavailability and also possible reduction in dose. Chlorhexidine has a bitter taste so the formulations are repaired in order to mask the taste.

Materials and Methods

Chlorhexidine gluconate from Indoco remedies ltd, Mumbai, Sorbitol, Di-butyl phthalate, Glycerin from Research lab, Mumbai, Talc, Sucrose from Liben pharma, Akola, Synthetic gum base and Peppermint flavor from Candico, Nagpur. UV-visible spectrophotometer double beam, Milton ray, Disintegration test apparatus**,** Electro lab, pH meter (Hanna industries), Hot air oven, Dessicater Thistle apparatus Monsanto hardness tester Kumar industries FT-IR (Jasca).

***Preparation of Medicated Chewing Gum*:** Each gradient weighed accurately. Synthetic gum base and wax was melted to this molten mass ,previously weighed quantity of plasticizer was added and then mixed thoroughly, the melting carried out in a porcelain dish at about 35-45^{0}C on steam bath. This mixture allowed to cool at temperature of 15-20^0 C then the physical homogenous mixture of Chlorhexidine gluconate , talc and sucrose was added with continuous stirring so that to ensure even distribution of drug. Then add flavor and color at the end of mixing. Then the mass was allow to cool at room temperature on steel plate ,the mass was rolled evenly and cut into the pieces of uniform size and weighed pieces are removed and wrapped properly [4-7].

*Physical evaluation of synthetic gum base***:** The results of various test carried out for studying the properties of synthetic gum base and formulations are reported on the basis of their color, softening characters, relative humidity, moisture absorption, solubility studies in different solvents.

Physical Evaluation of Medicated Chewing Gum: All the formulations were visually inspected and hardness of chewing gum was measured by Monsanto type hardness tester.

Weight variation: Weight variation of all formulations was done by method described in experimental work.

Evaluation of MCG: Physical evaluation: All formulations prepared by above procedure were physically evaluated for following parameters, Appearance, Color, Stickiness, Hardness / Plasticity, Weight variation, Drug Content

*Hardness / Plasticity***:** Due to absence of any reported method, it was decided to use the Monsanto type hardness tester for determination of hardness / plasticity of all MCG formulations.

*Weight variation***:** weight of the ten chewing gum is taken in a one batch then average weight is calculated from that standard deviation is calculated.

In-vitro drug release: All the formulation was studied for *in-vitro* drug release and the cumulative % of drug release was calculated. *In-vitro* release of drug was done by method described in experimental work [8, 9, 10, and 11].

Stickiness: The MCG placed on the plain surface, mass of 250 gm Teflon hammer collide on it for period of ten minute. The frequency of hammering was about 30 / minute. After 10 minutes, sticking of mass to the hammered surface was observed and reported.

Stability studies of synthetic gum base: 10 gm of synthetic gum base was stored in bottle at 50° C for 30 days. After 30 days the gum was examined for natural ageing and physical nature.

Table: 1 Different formulations and their ratios of ingredients

SR.NO.	INGREDIENTS	FA	FB	FC	FD	FE	FF
1	Chlorhexidine gluconate	10	10	10	10	10	10
2	Gum base	500	500	500	500	500	500
3	Sucrose	360	410	380	380	360	380
4	Sorbitol	15	15	5	5	5	5
5	Wax	30	-	-	-	-	-
6	Talc	40	40	40	40	40	40
7	Dibutyl phthalate	30	20	-	-	-	-
8	Castor oil	-	-	50	35	-	-
9	Glecerine	-	-	-	-	75	50
10	Color and flavor	15	15	15	15	15	15

Table 2:

Physico Chemical Properties Of Synthetic Gum Base After stabilities studies

S. No.	Properties	Observations
1	Color (before ageing)	off white - light yellow
3	Color (after ageing)	off white - light yellow
4	Softening range (before ageing)	85 -90 ^{0} C
5	Softening range (before ageing)	85 -90 ^{0} C

Table 3:

Physical characteristic of formulations

S. No.	Formulation	Color	Appearance	Stickiness	Pressure required to press gum (kg/cm²)
1	A	Dark red	Soft	Nil	1.4
2	B	Light red	Soft	Nil	1.6
3	C	Dark red	Soft	Negligible	1.7
4	D	Light red	Hard	Nil	2.7
5	E	Red	Hard	Nil	2.5
6	F	Light red	Soft	Negligible	2.1

Table 4:

Content Uniformity of Various Formulations

S. no	Formulation	% Purity
1	A	96.70
2	B	97.25
3	C	94.50
4	D	92.86
5	E	93.95
6	F	95.60

Result and Discussion

Boiling point: The boiling point of the Chlorhexidine gluconate was found to be in the range of 136^0 C. Standard value was found to be 132^0 C-140^0 C. It means the drug used is a pure one.

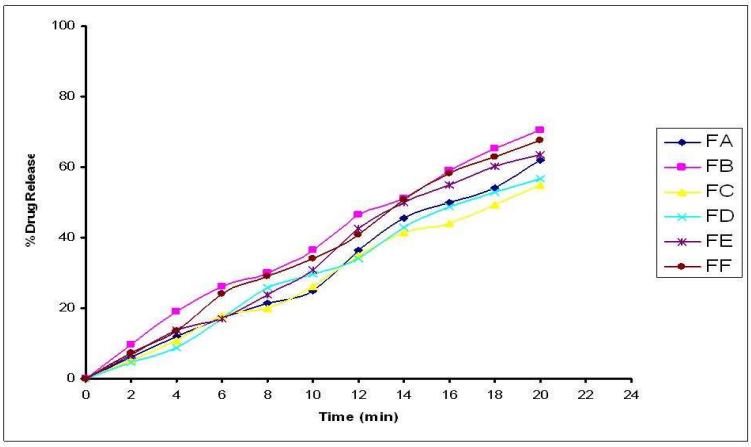
Identification test: The λ max for Chlorhexidine gluconate was found to be 254 nm in the medium in the phosphate buffer having pH 6.8

Infrared spectroscopy: The IR values of chlorhexidine gluconate show the peak at following values which are characteristics of drug.

3264 cm^{-1}, 3288 cm^{-1} , 3295 cm^{-1}, 3325 cm^{-1}, 3361 cm^{-1}, 3466 cm^{-1}, 3496 cm^{-1} shows N-H stretching vibration in amines. 1050 cm^{-1}, 1097 cm^{-1} shows C-N stretching in amines. 855 cm^{-1}, 921 cm^{-1}, 1050 cm^{-1}, 1097 cm^{-1}, 1278 cm^{-1} shows C-C stretching in alkane. 2932 cm^{-1} shows C-H stretching in alkane. 1421 cm^{-1} shows deformation alkane. 1486 cm^{-1} shows C=C shows

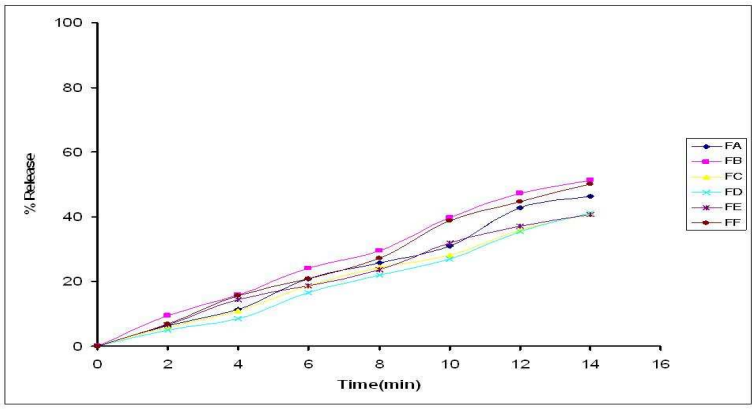
stretching vibration in aromatic compound. 701 cm^{-1},735 cm^{-1},794 cm^{-1},855 cm^{-1} shows C-H deformation in aromatic compound.

Graph 1:



In-vitro drug release of various formulations

Graph 2:



%CDR in saliva from various formulations

*Physicochemical properties of synthetic gum***:** Softening range of synthetic gum base is suitable for formulation of medicated chewing gum.

*Moisture absorption studies of synthetic gum***:** Synthetic gum base absorbs very less % of moisture means gum base is stable during shelf life.

Solubility studies of synthetic gum: Solubility study of synthetic gum shows the sample of gum shows 1% solubility in alcohol. The solubility in alcohol was 17.4%. The percentage of solubility in Chloroform and Diethyl ether was respectively 1.941 % and 1.931 %. As the synthetic gum shows very minor amount soluble in phosphate buffer this value was as negligible so that taken in account so that synthetic gum was to be found to be best suited as chewing gum base in the formulation of MCGs. The synthetic gum shows insoluble nature in which gain boost for use in MCGs and confirms the insoluble nature of gum base. Stickiness of the all formulations was found negligible and hardness was found within the limit. Weight variations of all formulations were also found satisfactory. Drug content uniformity was between 93 to 96% that is within the normal range. Weight variations were also within the normal range.

In-vitro drug release: From the study it was found that drug release of all formulations after 15 minute were more than 55 %. These findings proposed a longer oral presence of chlorhexidine in oral cavity. The graph shows the comparative drug study of all formulations in 20 minute. From the above study it was found that formulation "B" shows better release than other formulation. It concluded that formulation "B "was selected as best batch and carried out for his stability study.
Drug release in saliva: From study it was found that drug release from all formulation after 14 minute was more than 40 %. In this study the drug release was depends upon the chewing frequency of the volunteer. **:** From the study it was found that formulation "B" which we select as a best batch shows better release than other formulation in 14 minute.

*Stability studies of synthetic gum base**:*** The stability study of synthetic gum base confirms the stability of gum during the process of ageing. There was no change in physical appearance and colour of stored sample of synthetic gum base. There was no change in the softening point of gum which confirms stability of synthetic gum base.

Conclusion

Results of *in-vitro* release profile indicated that formulation "B" was the most promising formulation as the extent and steady release of drug from formulation was high as compare to other formulations. Infra-red spectroscopy shows the characteristics of the drug. Stability study conducted on medicated chewing gum for best formulation "B" under stress conditions for one month. Medicated chewing gum were evaluated for physical parameter as *in-vitro* release after stability study, shows no significant changes were found in the parameters studied thus it could be concluded that formulation was fairly stable. A modified *in-vitro* drug release apparatus has been fabricated by modification of the IP disintegration test apparatus. Various Gum formulations with different composition were used to demonstrate the versatility of the chewing apparatus during study. When the *in-vitro* and *in-vitro* drug release results were compared, the drug release patterns *in-vitro* were fairly steady as compared to *in-vitro* and also less amount of drug has been released in equivalent time *in vivo* salivary drug release case. The vitro clinching apparatus needs bit further modifications for steady and relatively similar drug release match up to vivo drug release pattern.

It can be concluded that in concentration of 50% synthetic gum base give promising results with the water soluble drug Chlorhexidine gluconate for steady drug release coupled with adequate release properties from medicated chewing gum. Some of the promising agents may incorporate in medicated chewing gum for improving the drug release from medicated chewing gum. The dissolution curves for the release of chlorhexidine gluconate from the medicated chewing gum formulations are showed a satisfactory release rate. An explanation for this can be proposed by examining the drug release profiles of the gums. Synthetic gum formulations are similar marketed medicated chewing gum in appearance. Since synthetic gum base has 50 % gum base used to formulate MCG compared to market medicated chewing gum this should provide a more pleasant mouth feel and it was expected that this would result in a steady and controlled release of drug.

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