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Original Research Article

Formulation and Evaluation of Medicated Chewing Gum Containing Antibacterial Agent.

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Abstract

Nowadays, due to emerging developments in the oral drug delivery systems several newer technologies are come out. Oral route of administration has achieved much more popularity because of its ease in administration. There are various dosage forms those can be administered orally. Out of which, chewing gum is most popular. It is a potentially useful means of administering drugs locally and systemically. In recent years the medicated chewing gum has gained increasing acceptance as a drug delivery system. Chlorhexidine gluconate is antibacterial agent used for management of tooth decay. In mouth, Chlorhexidine gets readily adsorbed to negatively charged area, including mucosa and pellicle coated teeth. Chlorhexidine remains bacteriostatically active also after adsorption. In this formulation chewing gum release the active ingredient into the saliva up to the time as the gum product is masticated. In present work chewing gum formulations were prepared by synthetic gum base and by using different Plasticizers such as Castor oil, Glycerin and dibutyl phthalate. Glycerin batch shows best result than castor oil as well as dibutyl phthalate.

Keywords: Chewing gum, Chlorhexidine, tooth decay, mucosa, bacteriostatically active, mastication.

Introduction

Drug can be administered via different routes of administration to produce a systemic pharmacologic effect. The most common method to administer drug is oral route, in which the drug is swallowed and it enters the systemic circulation. There are various dosage forms those can be administered orally. Out of which, chewing gum is most popular. It is a potentially useful means of administering drugs locally and systemically. Chewing gum has been used for centuries to clean the mouth as well as freshen the breath. The advantage of buccal route is administration has direct access to systemic circulation. This avoids first pass hepatic metabolism and local loss of the drug at site[1,2]. In the present work non toxic synthetic gum base has been used in the formulation of medicated chewing gum (MCG) containing an antimicrobial agent Chlorhexidine gluconate[3].

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Chlorhexidine gluconate is suitable drug to prepare MCG. It is a cationic bisbiguanide with antibacterial activity[4,5]. It has strong affinity for binding to skin and oral mucus membrane. The aim of the work was to avoid hepatic first pass metabolism and to improve systemic absorption and thereby possible reduction in dose. Glycerin, Castor oil and Dibutyl phthalate were used as plasticizer in varying amount. Sucrose coating was given to the chewing gum pieces. Trial runs were performed using plasticizers in combination. When plasticizers were used in combination, it was observed that the gum formulations formed were very sticky.

Experimental

Chlorhexidine gluconate was obtained from Medley Pharmaceuticals, Mumbai as gift sample. Synthetic gum base was procured from Gum Pharma, Nagpur. Glycerin, Castor oil, Dibutyl phthalate, Sucrose, Mannitol was purchased from Research lab, Islampur.

Preparation of medicated chewing gum[3]

All ingredients were weighed accurately as shown in formulation table 1. Molten mass of synthetic gum base was prepared and plasticizer was mixed thoroughly in porcelain dish. The dish was kept on water bath and temperature was maintained at about 35-45^{o} C. Drug Chlorhexidine gluconate was then added to above mass. Corresponding amount of Sucrose and mannitol was added to above mixture with continuous stirring up to 30 min. Finally the adequate amount of flavor was incorporated in the mixture. The mass was poured in to the mould and was allowed to cool at room temperature. The gum pieces were removed.[4, 5]

Coating of MCG was done by liquid coating solution of sucrose. The coating solution was sprayed uniformly. Coating was dried in hot warm air in temperature range 27^{0}C to 38^{0}C. After cooling chewing gum pieces were wrapped properly[3].

Physical evaluation of drug and synthetic gum base

Preliminary studies

FT-IR studies of Chlorhexidine gluconate were performed using FT-IR (Jasco-4100) and spectrum was shown in figure 1. UV studies of Chlorhexidine gluconate were performed using UV-visible spectrophotometer double beam (Jasco-V-630). The chewing gum base was evaluated for color, softening range, solubility studies in different solvent. Stability studies were performed.

Physical evaluation of medicated chewing gum[6,7]

The formulated chewing gum were evaluated for various physicochemical parameters including color, softening point, stickiness, weight variation, plasticity/hardness, Compatibility studies of drug and excipient by FT-IR, percentage drug content and percentage cumulative *in-vitro* drug release.

Results and Discussion

FT-IR Studies of drug

FT-IR study was performed and results are illustrated in Table 2.

UV Spectroscopy

λ–max of Chlorhexidine gluconate was found to be 231 nm in artificial saliva solution having pH 6.4. (Fig. 3)

Physical evaluation of gum base

Color: Color of synthetic gum base is Pale yellow observe visually**.**

Softening point: Softening point of synthetic gum base was observed by heating the base in Petri dish. The temperature at which it starts melting is the softening point of that base. It was found to be 55-60^{0}C.

Solubility studies of synthetic gum base

Table 4: Solubility studies.

Sr. no.	Solvent	Solubility(gm) / 10 ml
1	Alcohol	Up to 2 gm
2	Chloroform	Up to 17 gm
3	Acetone	Soluble
4	Water	Insoluble
5	Artificial saliva	0.01 gm
6	Diethyl ether	Up to 1.2 gm
7	Phosphate buffer	0.01 gm

As the gum has showed very negligible solubility in artificial saliva and phosphate buffer, it can be concluded that the procured synthetic gum base was the best for use as base for medicated chewing gum preparation.

Physical evaluation of medicated chewing gum

The formulated medicated chewing gum was evaluated physically for following parameters and are mentioned in Table 5.

Color: The color of MCG formulation was observed visually and all the batches were light brown in color which in acceptable limit.

Boiling point: Boiling point of drug was found to be 133^{0}C which is in standard range of 132^{0}C to 136^{0}C.

Stickiness: The formulated medicated chewing gum was placed on plain surface. A mass of 250 gm was hammered on it up to 10 min. the frequency of hammering was about 30/min. None of the batch stuck to hammer or surface.

Weight variation: Chewing gum from each batch were individually weighed on analytical balance, the average weight and standard deviation were calculated which was found in acceptable limit.[3]

Plasticity/hardness: Hardness of chewing gum was determined by Monsanto hardness tester and the average hardness and standard deviation were reported.[3]

Percentage drug content: % drug content of formulated chewing gum was determined by weighing 1000 mg chewing gum equivalent to 10 mg Chlorhexidine gluconate and transferring into volumetric flask. About 60 ml of artificial saliva was added, sonicated for 10 min, then shaken by mechanical means for 30 min and volume was adjusted to 100 ml with the same solvent. Again it was sonicated and filtered. Percentage drug content was determined spectrophotometrically at 231 nm. Same procedure was repeated for three times.

***In vitro* dissolution studies[8]**

In order to study the *in vitro* dissolution pattern from chewing gums, it was necessary to design an apparatus, which could give same impact of mastication on MCG. This was necessary in order to mimic the human mastication. After an extensive literature survey and discussion with guide it was decided to modify the disintegration test apparatus and fabricate suitable chewing gum apparatus. Release measurements were performed using Lab fabricated medicated chewing gum test apparatus at 50 rpm. In each flask a 900 ml of artificial saliva pH 6.4 was filled. The temperature was maintained at 37±0.5°C. At predetermined time intervals (5, 10, 15, 20, 25, 30 and 35 min) absorbance were recorded spectrophotometrically at 231 nm and the percentage of drug released was determined as a function of time[8].

Stability Studies of synthetic gum base

The batch F4 has shown maximum drug content and all acceptable parameters as compared to other batches and also maximum percentage cumulative drug release, stability studies were performed the optimized batch F4. In the stability studies, stability of gum was checked by keeping formulation at different atmospheric conditions viz. at $40^0 \pm 2^0$C / 75% RH ± 5% RH for one month in stability chamber.[3]

Conclusion

The present work was aimed to develop the medicated chewing gum as drug delivery system for Chlorhexidine gluconate with fast onset of action and to avoid first pass metabolism. Chewing gum formulations were prepared using synthetic gum base and different plasticizers such as castor oil, glycerin and dibutyl phthalate in varying concentration. MCG formulations were evaluated for different parameters like stickiness, weight variation, percent drug content and *in vitro* drug release test were performed. *In-vitro* release test was performed using Lab fabricated medicated chewing gum apparatus. The disintegration test apparatus was modified in such a way that the formulation was pressed continuously like mastication process. From the *in vitro* drug release data it was concluded that drug release from the medicated chewing gum was satisfactory. Percent drug release of all formulation batches is in between 46.49% to 96.45 %. Batch F4 containing glycerin as plasticizer was found to be the best formulation in all respect.

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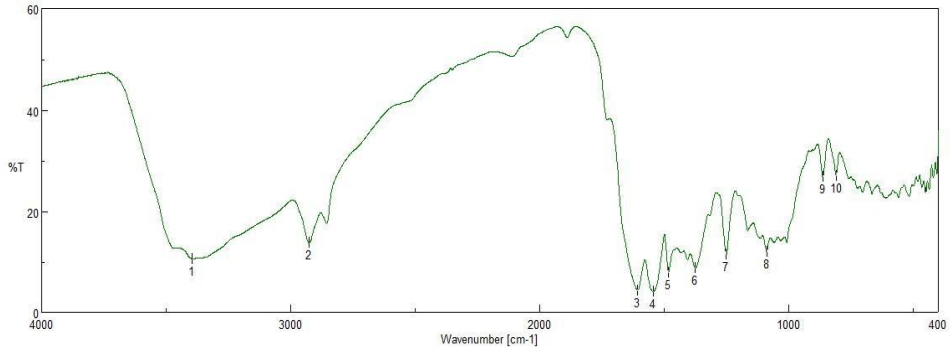

Fig.1: FT-IR spectra of pure drug.

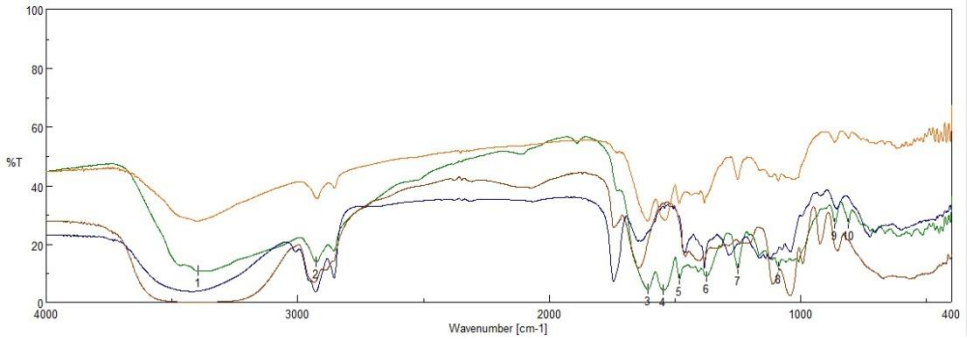

Fig. 2: Compatibility studies of drug and polymer by FT-IR.

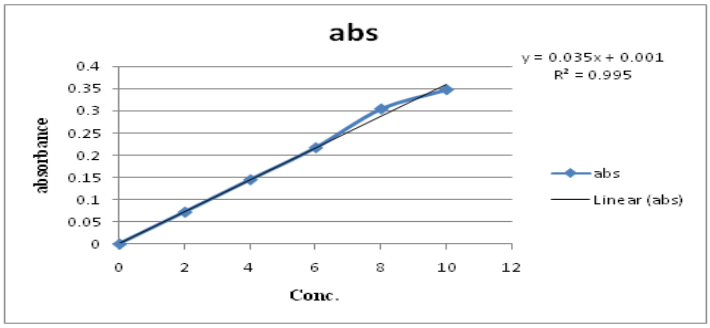

Fig. 3: Calibration curve of Chlorhexidine gluconate.

Fig. 4: Lab fabricated medicated chewing gum apparatus with S.S Die and punch.

Table 1: Formulation table.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Gum Base	550	550	550	550	550	550	550	550	550
Chlorhexidine gluconate	10	10	10	10	10	10	10	10	10
Castor oil	100	150	200	-	-	-	-	-	-
Glycerin	-	-	-	100	150	200	-	-	-
Dibutyl phthalate	-	-	-	-	-	-	100	150	200
Sucrose	65	65	65	65	65	65	65	65	65
Flavor	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
Mannitol	275	225	175	275	225	175	275	225	175

Table 2: FT-IR spectral analysis with and their functional group.

Peak no.	Wavenumber [cm1]	Functional Groups
1	3396.99	N-H Str vibrations in amines
2	2926.45	C-H Str In alkane
3	1607.38	N-H bend in amine
4	1545.67	N-O asymmetric stretch.
5	1482.99	C=C str vibration in aromatic comp
6	1375	deformation alkane
7	1250.61	C-C Str in alkane
8	1088.62	C-N str in amine
9	863.953	C-H Deformation in aromatic compound
10	809.956	C-Cl Str

Table 3: Calibration curve absorbance.

conc.	Abs
0	0
2	0.0717
4	0.1445
6	0.2165
8	0.3036
10	0.3468

Table 5: Physical evaluation of medicated chewing gum**.**

Sr. no	Batch	Stickiness	Color	Weight variation (mg)	Hardness Kg/cm^2	% drug content
1	F1	Non sticky	Light Brown	1000±0.014	2±0.1	84.36 %
2	F2	Non sticky	Light Brown	1000±0.009	2.5±0.1	90.96 %
3	F3	Non sticky	Light Brown	1000±0.017	2.5±0.1	84.93 %
4	F4	Non sticky	Light Brown	1000±0.015	2.5±0.2	93.07 %
5	F5	Non sticky	Light Brown	1000±0.054	2±0.15	88.31 %
6	F6	Non sticky	Light Brown	1000±0.006	2.5±0.1	89.47 %
7	F7	Non sticky	Light Brown	1000±0.005	2±0.12	89.17 %
8	F8	Non sticky	Light Brown	1000±0.007	2.5±0.1	91.76 %
9	F9	Non sticky	Light Brown	1000±0.005	2.5±0.1	85.43%

Table 6: Cumulative % drug release.

Sr. no.	Time (min)	Cumulative % drug release								
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	5	4.14	3.96	25.94	16.38	19.36	11.31	4.11	18.54	2.957
3	10	26.25	32.06	39.31	36.41	39.42	61.66	24.96	22.34	46.77
4	15	31.5	51.48	55.62	63.79	64.36	59.22	32.68	24.86	67.80
5	20	37.92	55.54	72.72	74.90	72.23	64.56	34.94	29.80	71.51
6	25	45.48	62.56	75.31	80.40	75.31	66.03	36.72	36.97	74.39
7	30	52.17	69.94	77.86	91.36	77.81	70.25	48.08	45.15	77.40
8	35	60.09	71.97	79.97	96.45	79.71	86.09	54.95	46.49	81.00

Table 7: Stability studies of optimized batch F4.

Sr. no.	Properties	Observation
1	Color (Initial)	Pale yellow
2	Color (After one month)	Pale yellow
3	Softening point (Initial)	55^0C - 60^0C
4	Softening point (After one month)	55^0C -60^0C
5	% drug content	91%