ORIGINAL ARTICLE

Formulation and Evaluation of Chlorhexidine Medicated Chewing Gums by Different Methods

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Abstract

Aim: The aim of this work is development and evaluation of chlorhexidine medicated chewing gums by different methods and to study the influence of different plasticizers and methods on physicochemical parameters and *in vitro* drug release profile. **Materials and Methods:** Chlorhexidine is an antibacterial agent used for management of tooth decay. The formulations are prepared with varying concentrations of plasticizers and synthetic gum base by different methods such as direct compression and melting method. The prepared formulations are evaluated for thickness, hardness, weight variation, friability, stickiness, color, drug content, and drug-excipient interations. *In vitro* drug release was performed by modified dissolution apparatus. **Results and Discussion:** The formulations prepared by direct compression method with castor oil as a plasticizer, i.e., F11 shows good drug release compared to formulations prepared with glycerin. In melting method, as the gum base concentration increases, the *in vitro* drug release is increased. The formulations prepared with both methods show good drug release, but direct compression formulations show high drug release compared to formulations prepared by melting process. **Conclusion:** This study indicates that it is the better choice to prepare medicated chewing gums of chlorhexidine by different methods to improve the patient acceptance.

Key words: Castor oil, glycerin, medicated chewing gums, modified *in vitro* dissolution apparatus, synthetic gum base

INTRODUCTION

The oral route of drug administration is the preferred one because of self-administration and patient acceptability.[1] Nowadays, researchers are concentrating on the development of medicated chewing gums because of its popularity as a novel drug delivery system and are used to treat both local and systemic problems.[2]

Medicated chewing gums are the solid, single-dose preparations that have to be chewed and not to be swallowed, chewing gums contain one or more active ingredients that are released by chewing.[3] The release rate of the active medicament is dependent on physicochemical characteristics of the drug, the composition and method adopted to prepare chewing gum and by the patient chewing process.[4-7] Chewing gum provides new competitive advantages over conventional drug delivery system:[8-15]

- Rapid onset of action
- High bioavailability
- Pleasant taste
- Higher patient compliance (easy and discreet administration without water)
- Instant use
- High acceptance by children
- Less side effects
- Can be spilled out in the case of any adverse drug reaction is noticed.

In this work, chlorhexidine drug is used to prepare chewing gum. It used as an antimicrobial agent to inhibit dental plaque formation in chronic gingivitis. Chlorhexidine is a broad spectrum antimicrobial agent which acts against a wide range of Gram-positive and Gram-negative bacteria, yeasts, dermatophytes and some lipophylic viruses. It acts by binding to negatively charged bacterial cell wall thereby disturbing membrane integrity and affecting its functions. In higher concentrations it acts as a bactericidal agent.

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Received: 20-03-2016
Revised: 12-04-2016
Accepted: 17-04-2016

MATERIALS AND METHODS

Chlorhexidine was received as a gift sample from Smruthi Organics Ltd., (Shloapur, India), Synthetic gum base was received as a gift sample from (GRV Confectionary and Foods Private Ltd., Indore, Madhya Pradesh). Polyvinylpyrrolidone obtained from Bliss Chemical and Pharmaceuticals India Ltd. Thane, Maharashtra, India. All other ingredients are obtained from S.D. Fine Chem. Ltd., Mumbai, Maharashtra, India.

Drug-excipient compatibility studies

Fourier transform infrared (FT-IR) studies

The drug-excipient compatibility study was carried out by FT-IR (Bruker Alpha E Opus), FT-IR spectra of pure drug and optimized formulation were recorded. The baseline correction was done by blank background and 400-4000/cm was used as scanning range.

Analytical method used in the determination of chlorhexidine

The UV spectrophotometry (Systronic 2202, Ahmedabad, Gujarat, India) method was developed for the analysis of chlorhexidine using double beam spectrophotometer.

Determination of λmax

Chlorhexidine was dissolved in required quantity of 6.8 pH phosphate buffer and made to volume 100 ml using 6.8 pH phosphate buffer. The prepared solution was scanned for maximum absorbance using UV double beam spectrophotometer in the range 200-400 nm. The λ_{max} of the drug was found to be 257 nm.

Standard graph for chlorhexidine

About 100 mg of drug was taken and placed in 100 ml of volumetric flask, 6.8 pH phosphate buffer was used to mad the volume to 100 ml, which is equal to 1000 µg/ml, using this stock solution prepare different dilutions from 10 to 60 µg/ml and the absorbance was recorded at 257 nm using UV spectrophotometer.

Preparation of chewing gum by direct compression method

Required quantities of drug, polyvinylpyrrolidone, $CaCo_3$ are taken into mortar and mixed. To this melted, beeswax and plasticizers were added and mixed well. To this mixture remaining ingredients are added and compressed using 12 mm punches by Rotary Tablet Compression Machine (Cadmach, Ahmedabad, India). The formulation chart was shown in Table 1.

Formulation chart

Chlorhexidine medicated chewing gum is prepared by direct compression and melting method, formulae of both methods shown in Table No.1 and Table No.2 respectively.

Preparation of chewing gum by melting method

The chlorhexidine medicated chewing gum is prepared by melting method formulae was shown in Table 2. The required amount of synthetic gum base was taken into the porcelain dish, melted at the temperature of 60-70°C, until it is softened. To this molten base, required quantity of liquid glucose was added and removed from heat. Then all ingredients are added, mixed well and rolled in $caco_3$ powder and then that rolled mass was cut into required size and shape.

Pre-compression study

The blend which is made into chewing gum by direct compression method was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

Evaluation studies

The medicated chewing gums are evaluated for hardness, weight variation, thickness, friability, stickiness, color, drug content, and *in vitro* drug release studies.

Hardness

Due to the absence of any reported method, it was decided to use the Monsanto type hardness tester for determination of hardness of all medicated chewing gum (MCG) formulations. The average values, standard deviation, and relative standard deviation were calculated.

Weight variation

According to specifications weight of 20, chewing gums are taken then average weight is calculated from that standard deviation is calculated.

Drug content

Randomly 10 medicated chewing gums were taken, crushed and amount equivalent 10 mg of chlorhexidine was taken and dissolved in 6.8 pH phosphate buffer, sonicated, filter the solution and record the absorbance using spectrophotometer at 257 nm. Then, drug concentration was measured using standard graph. The measurements were carried out in replicates ($n = 6$).

In vitro drug release studies

After extensive literature survey, disintegration apparatus was slightly modified for this study. The modified apparatus which mimics the human chewing behavior was used to determine the drug release. The MCG placed in 500 ml of 6.8 pH phosphate buffer and samples were collected periodically for each time interval of 5, 10, 15, 20, 25, and 30 min and absorbance was measured at 257 nm. Measurements were carried out in replicates ($n = 6$) and mean ± standard deviation values are recorded.

RESULTS AND DISCUSSIONS

Drug-excipient compatability studies

FT-IR studies

The FT-IR spectrum of pure drug and optimized formulations was shown in Figures 1 and 2. FT-IR spectra results showed that same peaks were observed for pure drug and optimized formulation, and there are no additional peaks are observed.

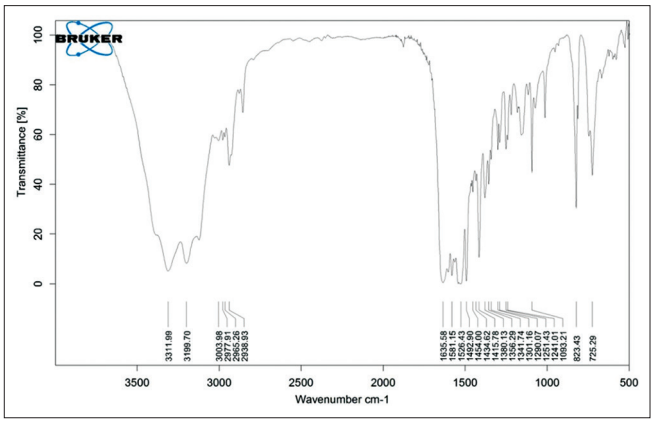

Figure 1: Fourier transform infrared spectra of pure drug

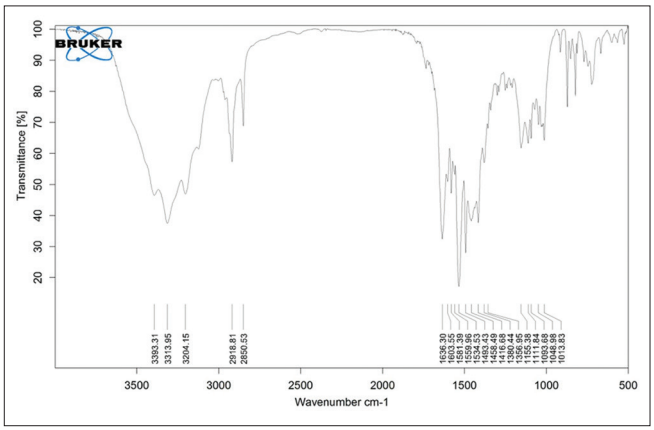

Figure 2: Fourier transform infrared spectra of optimized formulaton

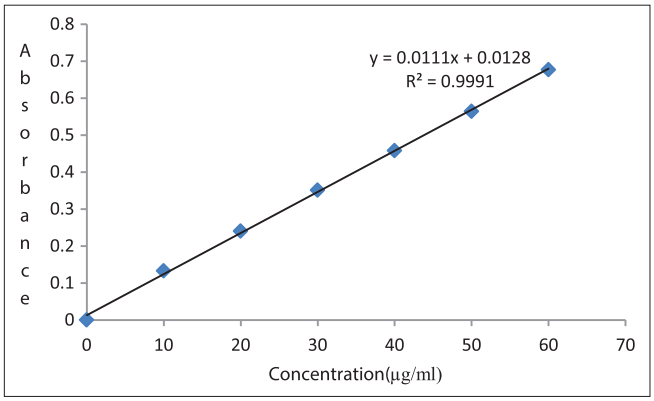

Figure 3: Graph of calibration curve

Therefore, from FT-IR spectra, it could be concluded that there is no incompatibility between drug and excipients.

The standard graph results were shown in Table 3. From the graph (Figure 3), From the graph, we can see that Beer and Lamberts law is obeyed between 0 and 60 µg/ml

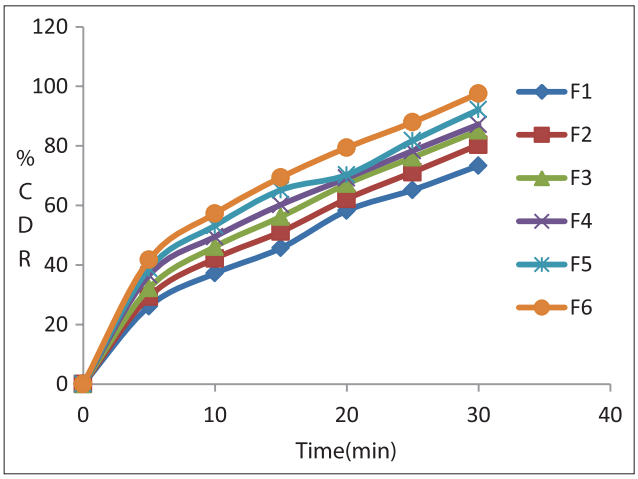

Figure 4: Cumulative percentage drug release profiles of formulations (F1-F6) prepared by direct compression method

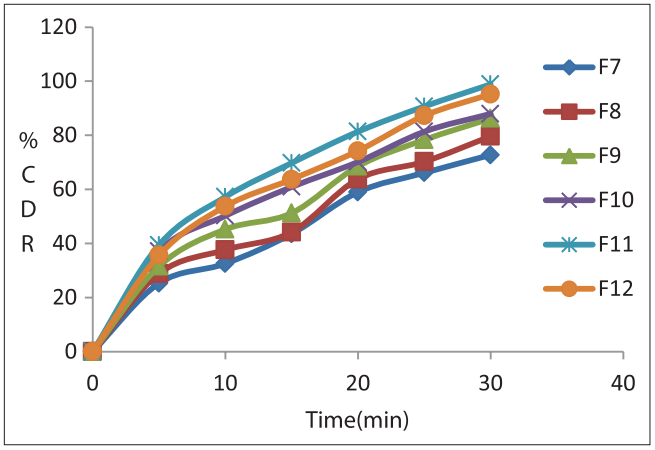

Figure 5: Cumulative percentage drug release profiles of formulations (F7-F12) prepared by direct compression method

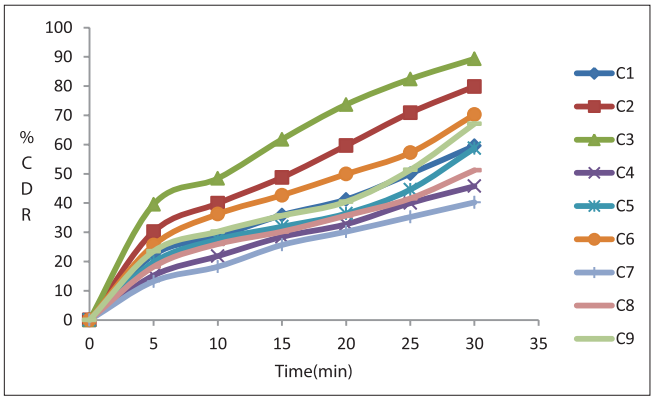

Figure 6: Cumulative percentage drug release profiles of formulations (C1-C9) prepared by melting method

Table 1: Formulae of chlorhexidine medicated chewing gums by direct compression method

Formulation code	Chlorhexidine (mg)	Bees wax (mg)	Glycerol (mg)	Castor oil (mg)	Dextrose (mg)	$CaCO_3$ (mg)	PVP (mg)	Flavor (mg)	Mg stearate (mg)	Aerosil (mg)	Total weight (mg)
F1	10	20	5	-	24	24	210	3	1	3	300
F2	10	20	10	-	24	24	210	3	1	3	300
F3	10	20	15	-	24	24	210	3	1	3	300
F4	10	20	20	-	24	24	210	3	1	3	300
F5	10	20	25	-	24	24	210	3	1	3	300
F6	10	20	30	-	24	24	210	3	1	3	300
F7	10	20	-	5	24	24	210	3	1	3	300
F8	10	20	-	10	24	24	210	3	1	3	300
F9	10	20	-	15	24	24	210	3	1	3	300
F10	10	20	-	20	24	24	210	3	1	3	300
F11	10	20	-	25	24	24	210	3	1	3	300
F12	10	20	-	30	24	24	210	3	1	3	300

PVP: Polyvinylpyrrolidone

Table 2: Formulation of chlorhexidine medicated chewing gums by melting method

Formulation code	Chlorhexidine (mg)	Gum base (mg)	Glycerol (mg)	Sucrose (mg)	$CaCO_3$ (mg)	Liquid glucose (mg)	Mannito (mg)	Aspartame (mg)	Flavor (mg)	Total weight (mg)
C1	10	300	10	200	30	50	195	3	2	800
C2	10	300	15	200	30	50	190	3	2	800
C3	10	300	20	200	30	50	185	3	2	800
C4	10	350	10	200	30	50	145	3	2	800
C5	10	350	15	200	30	50	140	3	2	800
C6	10	350	20	200	30	50	135	3	2	800
C7	10	400	10	200	30	50	95	3	2	800
C8	10	400	15	200	30	50	90	3	2	800
C9	10	400	20	200	30	50	85	3	2	800

Table 3: Calibration curve of chlorhexidine in 6.8 pH phosphate buffer

Concentration (µg/ml)	Absorbance (nm)
10	0.133±0.001
20	0.248±0.002
30	0.356±0.003
40	0.473±0.001
50	0.568±0.002
60	0.667±0.001

concentrations. The straight line is seen with r^2 value of 0.999 [Figure 3].

All the precompression parameter values were shown in Table 4. Bulk density and tapped density values of prepared blends were in between 0.57 and 0.63 g/ml, 0.61-0.66 g/ml,

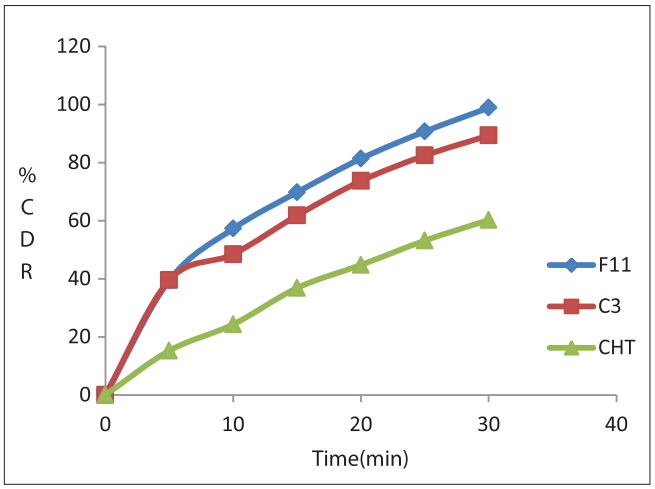

Figure 7: Comparison of cumulative percentage drug release profiles of optimized formulations of direct compression and conventional method

Table 4: Pre compression parameters

Formulation code	Bulk density (g/ml)	Tapped bulk density (g/ml)	% Compressibility	Hausner's ratio	Angle of repose (θ)
F1	0.582±0.12	0.623±0.061	6.58±0.032	1.07±0.06	28°85′±0.025
F2	0.591±0.24	0.631±0.043	6.33±0.014	1.06±0.13	29°93′±0.041
F3	0.604±0.09	0.636±0.025	5.03±0.021	1.05±0.16	27°86′±0.068
F4	0.621±0.08	0.653±0.024	4.9±0.061	1.05±0.098	28°68′±0.054
F5	0.623±0.32	0.659±0.012	5.46±0.059	1.05±0.004	27°99′±0.043
F6	0.630±0.21	0.662±0.014	4.83±0.043	1.05±0.075	28°78′±0.15
F7	0.570±0.15	0.610±0.022	6.55±0.045	1.07±0.032	27°78′±0.097
F8	0.572±0.16	0.615±0.013	6.99±0.054	1.07±0.046	28°72′±0.067
F9	0.579±0.23	0.618±0.026	6.31±0.018	1.06±0.051	26°84′±0.051
F10	0.585±0.18	0.624±0.021	6.25±0.042	1.06±0.046	27°88′±0.075
F11	0.588±0.15	0.627±0.018	6.22±0.056	1.06±0.081	27°69′±0.043
F12	0.592±0.21	0.629±0.024	5.88±0.048	1.06±0.043	28°82′±0.079

Table 5: Post compressional parameters of chewing gums prepared by direct compression method

Formulation code	Hardness (kg/cm²)	Thickness (mm)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.45±0.24	3.58±0.12	300.2±0.21	0.16±0.015	95.12±0.22
F2	3.5±0.21	3.60±0.25	299.5±0.44	0.29±0.023	92.51±0.24
F3	3.6±0.30	3.59±0.20	299.6±0.31	0.13±0.016	93.55±0.24
F4	3.8±0.15	3.5±0.10	300.4±0.64	0.11±0.15	94.25±0.14
F5	4.0±0.13	3.58±0.06	301.6±0.14	0.24±0.098	91.38±0.12
F6	4.02±0.20	3.59±0.15	300.2±0.52	0.38±0.065	92.14±0.05
F7	4.1±0.56	3.57±0.21	300.9±0.25	0.44±0.084	95.12±0.20
F8	3.5±0.80	3.58±0.39	299.4±0.53	0.39±0.074	92.25±0.04
F9	4.3±0.34	3.57±0.31	300.4±0.32	0.21±0.18	93.56±0.25
F10	3.5±0.24	3.59±0.27	299.9±0.34	0.18±0.068	92.19±0.01
F11	3.5±0.21	3.58±0.15	300.6±0.14	0.22±0.094	94.56±0.24
F12	3.6±0.20	3.58±0.50	299.6±0.12	0.12±0.086	97.56±0.13

Table 6: Evaluation parameters of formulations prepared by melting method

Serial number	Formulation	Color	Appearance	Stickiness	% Drug content
1	C1	Off white-light yellow	Soft	Nil	95.34±0.56
2	C2	Off white-light yellow	Soft	Nil	94.51±0.67
3	C3	Off white-light yellow	Soft	Nil	97.61±0.21
4	C4	Off white-light yellow	Hard	Nil	93.51±0.32
5	C5	Off white-light yellow	Soft	Nil	95.52±0.12
6	C6	Off white-light yellow	Soft	Nil	96.87±0.34
7	C7	Off white-light yellow	Hard	Nil	95.10±0.21
8	C8	Off white-light yellow	Soft	Nil	95.21±0.01
9	C9	Off white-light yellow	Soft	Nil	96.23±0.71

respectively. The angle of repose of powder blends values is 26°84′29°.93′. Compressability was found between 4.83% and 6.99%. From the above values, it was found that all powder blends had good flow properties.

Table 7: Cumulative percentage of drug release profiles of formulations (F1-F6) prepared by direct compression method

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	26.12±0.15	29.37±0.076	32.23±0.016	36.57±0.062	38.79±0.075	41.74±0.32
10	37.21±0.097	42.15±0.094	46.14±0.028	49.51±0.015	53.24±0.019	57.28±0.16
15	45.67±0.086	51.16±0.095	56.20±0.12	60.23±0.042	65.18±0.37	69.43±0.043
20	58.23±0.034	62.18±0.15	67.23±0.089	69.17±0.098	70.28±0.075	79.39±0.075
25	65.19±0.048	71.15±0.23	76.13±0.091	78.35±0.032	81.76±0.054	87.95±0.082
30	73.34±0.089	80.38±0.032	85.12±0.032	87.19±0.28	92.15±0.027	97.62±0.019

Table 8: Cumulative percentage drug release profiles of formulations (F7-F12) prepared by direct compression method

Time (min)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
5	25.31±0.023	28.89±0.016	31.56±0.046	37.12±0.052	39.45±0.019	35.67±0.098
10	32.56±0.068	37.65±0.053	45.23±0.015	50.23±0.039	57.23±0.042	53.74±0.065
15	43.56±0.018	44.23±0.072	51.23±0.080	60.89±0.048	69.75±0.087	63.71±0.082
20	58.98±0.045	63.82±0.081	68.56±0.024	70.15±0.097	81.34±0.078	74.26±0.093
25	66.12±0.023	70.25±0.052	78.31±0.022	81.34±0.071	90.67±0.056	87.23±0.052
30	72.74±0.052	79.63±0.027	86.23±0.029	87.95±0.049	98.85±0.065	95.23±0.080

Table 9: Cumulative percentage drug release profiles of formulations (C1-C9) prepared by melting method

Time (min)	C1	C2	C3	C4	C5	C6	C7	C8	C9
0	0	0	0	0	0	0	0	0	0
5	22.32	30.23	39.56	15.23	19.81	25.65	13.23	18.23	23.52
10	28.56	39.89	48.43	21.86	27.56	36.23	18.23	25.98	30.23
15	35.87	48.76	61.78	28.43	31.91	42.67	25.67	30.23	35.67
20	41.23	59.67	73.65	32.76	36.39	49.91	30.21	35.71	40.45
25	50.02	70.89	82.41	39.98	44.61	57.21	35.23	41.57	51.34
30	59.58	79.86	89.32	45.76	58.75	70.23	40.23	51.23	67.12

Table 10: Comparisons of cumulative percentage drug release profiles of optimized formulations of direct compression and melting method

Time (min)	F11	C3	CHT
0	0	0	0
5	39.45±0.019	39.56±0.058	15.23±0.013
10	57.23±0.042	48.43±0.023	24.29±0.026
15	69.75±0.087	61.78±0.054	36.82±0.064
20	81.34±0.078	73.65±0.026	44.75±0.017
25	90.67±0.056	82.41±0.058	53.12±0.073
30	98.85±0.065	89.32±0.082	60.23±0.054

The average hardness of tablets was found to be in between 3.45 and 4.3 kg/cm^2, average weight of prepared formulation was in between 299 and 301 mg, friability values are in the range of 0.11-0.44 and drug content was found to be in between 91.38% and 97.56%. All values are shown in Table 5 and found to be with in specifications.

All the formulations prepared by conventional method are off white-light yellow color, soft in nature and they show good consistency, no stickiness was found, drug content of all the formulations were found to be in between 93.51% and 97.61% which is satisfactory, results were shown in Table 6.

The percentage drug releases of formulations prepared by direct compression method and melting method are shown in Tables 7-10 respectively. Series of formulations from F1 to F6 prepared with glycerol as a Plastizer by direct compression method. In all these formulations amount of glycerol concentration increases % drug release also increased. Formulation F6 shows 97.62% of drug release in

30 min. Formulations from F7 to F12 prepared with castor oil as a plasticizer, in all these formulations F11 shows good drug release of 98.85%. All these results showed that as the concentration of plasticizer increases drug release also increased. The formulation prepared with melting method results showed that formulation C3 showed high drug release of 89.32%. Formulation series from C4 to C9 shows less drug release because these formulations are prepared with the high amount of gum base. Thus, as the amount of gum base increases the % drug release also increased. In melting method gum base is used, because of its gummy texture, drug release is lowered compared to melting method. The comparative results of optimized formulations (F11, C3), standard formulation (CHT) results were shown in Table 10 and Figure 7. Formulation CHT that is taken as a standard formulation of chlorhexidine and compared with optimized formulations of chlorhexidine prepared by direct compression and melting method shows less drug release.

CONCLUSION

The medicated chewing gums of chlorhexidine with good drug content and good drug release were achieved using different methods like direct compression method and melting method with optimized concentration of gum base and plasticizer. Formulations prepared with both methods shows good drug release but direct compression method shows maximum amount of drug release compared to formulations prepared with melting method. Based on the *in vitro* drug release profiles direct compression method showed maximum amount of drug release. The formulation F11 which is prepared with castor oil as a plasticizer prepared by direct compression method found to be best among all the formulations prepared by direct compression method and melting method. Hence, formulation F11 holds promise for further *in vivo* studies.

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Source of Support: Nil. **Conflict of Interest:** None declared.