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Formulation And Evaluation of Medicated Chewing Gum Containing Caffeine Salicylate

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ABSTRACT

Caffeine salicylate shows more CNS stimulant activity than caffeine along with mild analgesic and anti-inflammatory actions. Caffeine salicylate was synthesized in Pharmaceutical Chemistry Laboratory, Satara College of Pharmacy, Satara. Chewing gum formulation was prepared in tablet form by using direct compression method. Lecithin was used as an emulisifier and sorbitol as a softner and synthetic gum base along with other excipients. Nine different formulations were prepared by changing the concentration of emulsifier and softner. Evaluation of tablets i.e. diameter, thickness, friability, hardness, average weight, content uniformity, stickiness and dissolution study were performed. A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels. The amount of sorbitol (X_1) and lecithin (X_2) were selected as independent variables and the dependent variables were hardness and percent drug release at 30 min ($\%DR_{30min}$). The data obtained was treated using Stat-Ease Design Expert 8.0.7.1 software and analyzed statistically using analysis of variance (ANOVA).

Key-words: Caffeine salicylate, Medicated chewing gum, *In vitro* study

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INTRODUCTION:

CNS stimulants are medicines that speed up physical and mental processes, i.e. these are the agents that increase physical activity, mental alertness and attention span. They temporarily make patients feel more alert and improve mood. Caffeine salicylate is an ester derivative of methylxanthine and salicylate moiety in the basic structure. Caffeine salicylate shows more CNS stimulant activity than caffeine along with mild analgesic and anti-inflammatory actions. In caffeine salicylate equivalent concentration of caffeine enhances CNS stimulant activity. This enhancement may be due to more availability of caffeine in the active form to antagonize adenosine inhibitory action in presence of salicylate which has been shown to have anti-oxidant property. It has been known for centuries that buccal and sublingual administration drug solutes are rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa and transported through the facial veins, internal jugular vein, and braciocephalic vein and are then drained into the systemic circulation. Therefore the buccal and sublingual routes of administration can be utilized to bypass the hepatic first-pass elimination of drugs. (Kumar et al., 2010). Today chewing gum is a convenient drug delivery system which is appropriate for a wide range of active substances. Many therapeutic agents are absorbed in the oral cavity. Medicated chewing gums are solid, single dose preparations with a base consisting mainly of gum that is intended to be chewed and not to be swallowed. They contain one or more active substances which are released by chewing and are intended to be used for local treatment of mouth diseases or systemic delivery after absorption through the buccal mucosa. (European Pharmacopoeia, 6th ed.2008).

MATERIALS AND METHODS:

Materials:

Gum Base was procurred from Cafosa SPA, Spain. Caffeine salicylate was synthesized in Pharmaceutical Chemistry Laboratory of Satara College of Pharmacy, Satara. Mannozem EZ (Spay Dried Mannitol) was obtained from SPI Pharma, Bangalore. L-Menthol, Sorbitol was obtained from Gum Pharma, Nagpur. Soya Lecithine Powder was procured from Perfect laboratories, Nagpur.

Methods:

Formulation development of medicated chewing gum

1) Compatibility study between drug and excipients

Infrared Spectroscopy was determined by Fourier Transform Infrared Spectrophotometer (FTIR, Alpha-E, Bruker). FTIR spectra of formulation of medicated chewing gum containing caffeine salicylate was recorded in the wavelength region of 4000 to 400 ^{cm1}. Thermograms (DSC) of formulation of medicated chewing containing caffeine salicylate was obtained using DSC instrument Mettler-Toledo DSC 821e equipped with an intercooler.

2) Preparation of the chewing gum tablet

Direct compression method was used to prepare the chewing gum tablet. Weighed quantity of gum base powder and active ingredient were mixed well in morter. To it, accurately weighed soya lecithin and sorbitol and L-menthol were added. The sorbitol was added as sweetening agent. After thorough mixing, the lubricant and glidant were also mixed. The powder was compressed into tablets using flat faced punches of 15 mm diameter by keeping hardness between 3-4 kg/cm^2 using 12 station multitooling tablet compression machine.

Ingredients used for the preparation of chewing gum tablet formulation are summarized in Table No. 1

3) Evaluation of powder blends

The flow properties of powder (before compression) were characterized in terms of angle of repose, Bulk density, Tapped density , Carr's index and Hausner's ratio. Angle of repose for blend of each formulation was determined by fixed funnel method. The fixed funnel method employs a funnel that is secured with its tip at given height, h, which was kept 2 cm, above graph paper that was placed on a flat horizontal surface. With r, being the radius of base of conical pile, angle of repose can be determined using $\tan^{-1}$ (height of pile/radius of base). Bulk density, Tapped density , Carr's index and Hausner's ratio were calculated. An accurately weighed 20 gm powder was allowed to flow in a fine stream into a graduated cylinder and final volume was noted.(Banker et al., 2002)

Table No. 1: Chewing gum tablet compositions.

Sr. No.	Ingredients	Formulations								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Caffeine salicylate	150	150	150	150	150	150	150	150	150
2	Gum Base	300	300	300	300	300	300	300	300	300
3	Sorbitol	300	300	300	325	325	325	350	350	350
4	Lecithin	50	100	150	50	100	150	50	100	150
5	Flavour (L –menthol)	10	10	10	10	10	10	10	10	10
6	Mannitol	250	200	150	200	150	100	150	100	50
7	Magnesium Stearate	10	10	10	10	10	10	10	10	10
8	Aerosil	10	10	10	10	10	10	10	10	10
9	Sweetner (Sodium Saccharin)	10	10	10	10	10	10	10	10	10
Total		1000	1000	1000	1000	1000	1000	1000	1000	1000

**All quantities are in mg.*

***Formula for one chewing gum is shown in table.*

4) Evaluation of chewing gum tablet

The color of all the formulations was observed visually and reported. To evaluate stickiness of formulation **t**he chewing gum was placed on a plain surface. A mass of 250 gm was hammered on it for a period of ten minutes. The frequency of the hammering was about 30/min. After 10 min. sticking of the gum to the surface was manually observed and reported (Pandey et al.,2009).Thickness of tablets was measured using micrometer screw gauge (Rolex Scientific Engineers Limited), while diameter of the chewing gum tablets was measured using vernier calliper (Mitutoyo products, Japan). The study was carried out in triplicate (Banker et al., 2002). For friability test 20 tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. Percentage friability was calculated. Uniformity of weight was determined. 20 tablets were selected randomly and weighed. Average weight of the tablet was determined. For Uniformity of Content 20 chewing gum tablets were weighed and crushed. The powder equivalent to 10 mg was taken and dissolved in 10 ml of PBS pH 6.4. This solution was subjected for sonication for 20 min. From this stock solution 1 ml was taken and diluted to 10 ml with PBS pH 6.4 to achieve concentration up to 10 µg /ml and filtered through 45µm membrane. The absorbance was measured at 274.5 nm, using double beam UV spectrophotometer. Drug content was determined by using calibration curve (y = mx + c) method. In order to study the *in-vitro* drug release pattern from chewing gums, it was necessary to design an apparatus, which could give same impact on gums. This was necessary in order to simulate the human mastication. After an extensive literature survey and discussion it was decided to modify the I. P. disintegration test apparatus. This apparatus was

selected because it contained a rod, which was able to move upward and downward. The use of this motion was used to give the impact on the chewing gum preparations.(Kvist et al., 1999;Rider et al., 1992)

Figure No.1: Complete assembly of modified dissolution apparatus (Top View)

The vessel was filled with 500 ml. phosphate buffer (pH 6.4) and the gum was placed in the inner perforated vessel. The metal piston was attached to the rod, the height of the rod and bob was previously adjusted so that the bob completely touches the bottom of the perforated vessel.

The apparatus was switched on and the metal piston was allowed to impact on the chewing gum. This process was continued for the period of 30 min and 5 ml sample was withdrawn at a regular interval of 2 min and every time this was replaced with equal amount of phosphate buffer pH 6.4 to maintain the sink conditions which is having molarity 0.2M. Thus, the samples were collected after 0, 2, 4, 6....30 min.The cumulative amount of drug released vs. time was plotted graphically. The test was repeated for 3 chewing gum tablets of each types and statistical mean of 3 reading was taken. The effect of formulation variables on the response variables were statistically evaluated by applying ANOVA at 0.05 level using a commercially available software package Design-Expert® version 8.0.5.2 (Stat-Ease Inc.). To describe the response surface curvature, the design was evaluated by quadratic model, which bears the form of equation (Eq.1):

$$\mathbf{Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1^2 + b_4X_2^2 + b_5X_1X_2}$$ .....Equation 1

Where, Y is the response variable, b_0 the constant and b_1, b_2, b_3, b_4, b_5 the regression coefficient. X_1 and X_2 stand for the main effect; X_1X_2 are the interaction terms, show how response changes when two factors are simultaneously changed. X_1^2 and X_2^2 are quadratic terms of the independent variables to evaluate the nonlinearity.

The polynomial equation was established by applying ANOVA using the Design-Expert software version 8.0.5.2. Also, the data was subjected to 3-D response surface graph and contour plots to study the interaction of independent variables i.e. sorbitol (X_1) and lecithin (X_2) on dependent variable such as hardness in kg/cm^2 and drug release at 30 min. Amount of variables is given in Table no. 2.

Table No. 2: Amount of variables in 32 factorial design batches

Coded Values	Actual values (mg)	
	X_1	X_2
-1	300	50
0	325	100
+1	350	150

RESULT:

1) Compatibility study between drug and excipients

IR spectrum of formulation F9 of chewing gum tablet is shown in Figure No. 2

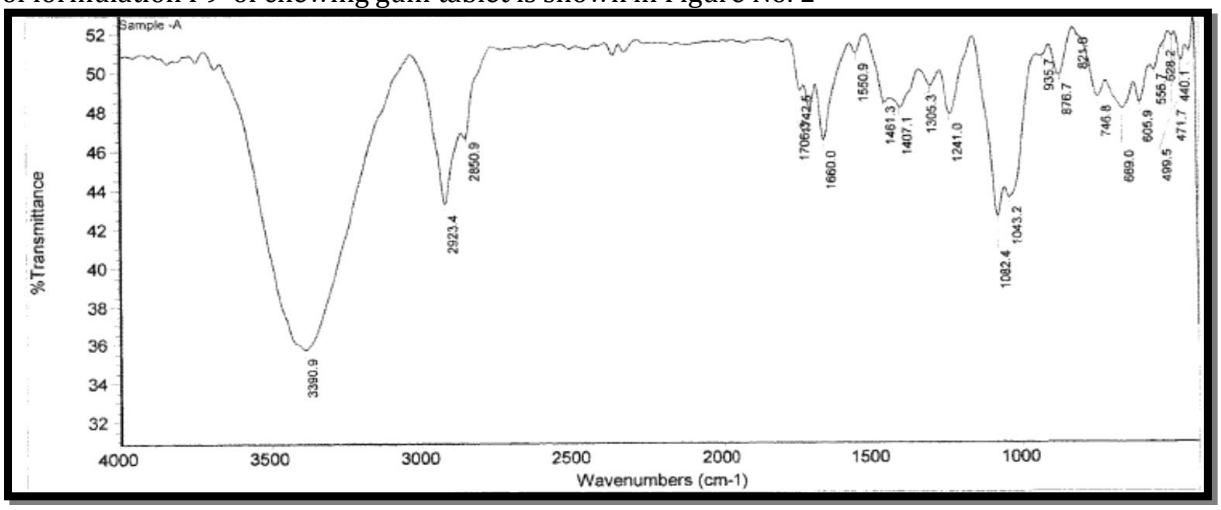

Figure No.2: IR spectrum of formulation F9

DSC thermogram of active compound and formulation F9 are shown in Figure No. 3 and Figure No. 4 respectively.

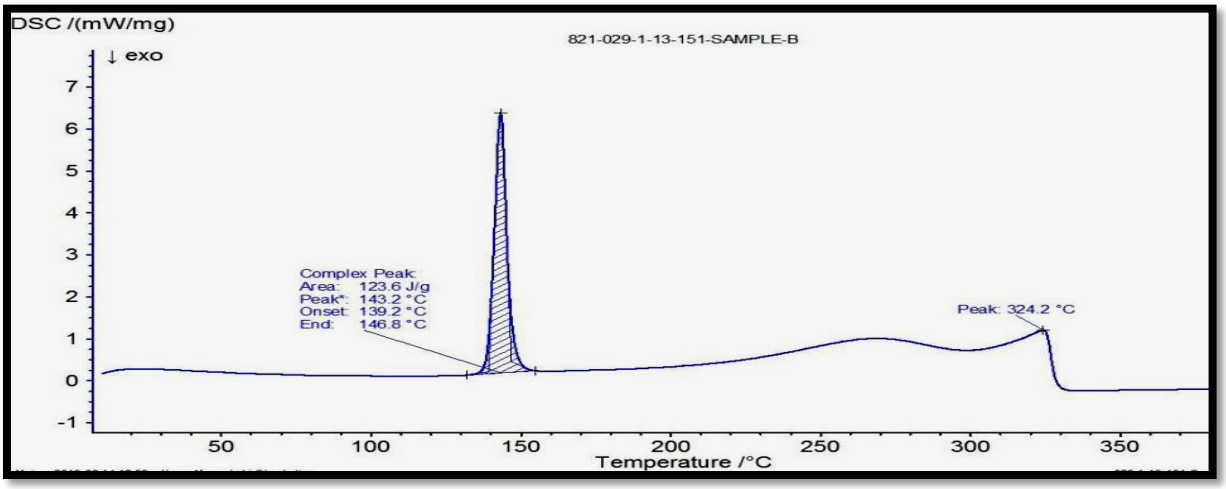

Figure No.3: DSC thermogram of active compound

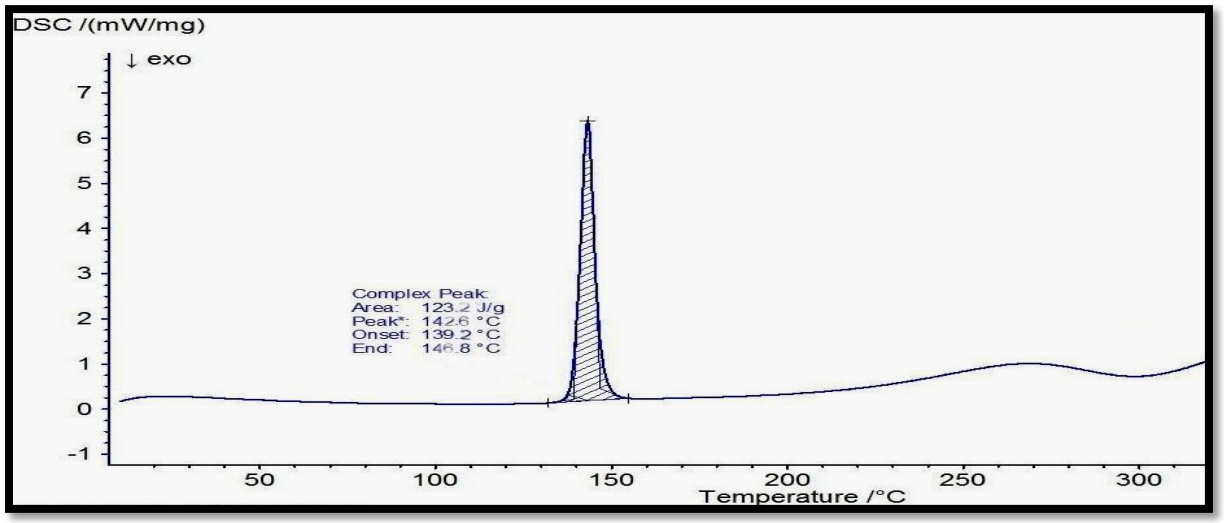

Figure No.4: DSC thermogram of formulation F9

2) Evaluation of powder blends

Data of all evaluation parameters of powder blends are given in Table3.

Table No.3: Evaluation parameters of caffeine salicylate chewing gum powder blends

Batch	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ°)
F1	0.587 ±0.002	0.712 ± 0.009	17.59 ± 0.763	1.21 ± 0.01	20.49 ± 0.30
F2	0.554 ±0.002	0.659 ± 0.007	15.96 ± 0.955	1.19 ± 0.01	21.54 ± 0.05
F3	0.547 ±0.010	0.621 ± 0.008	11.97 ±2.389	1.13 ± 0.03	22.23 ± 0.10
F4	0.523 ±0.004	0.641 ± 0.026	18.33 ± 3.884	1.22 ± 0.06	20.20 ± 0.14
F5	0.554 ±0.002	0.640 ± 0.023	13.36 ± 2.899	1.15 ± 0.03	20.53 ± 0.08
F6	0.530 ±0.008	0.681 ± 0.007	8.70 ± 1.778	1.09 ± 0.02	21.47 ± 0.07
F7	0.527 ±0.002	0.623 ± 0.007	15.34 ± 0.754	1.18 ± 0.01	19.33 ± 0.12
F8	0.533 ±0.011	0.586 ± 0.007	9.09 ± 1.312	1.12 ± 0.05	20.10 ± 0.08
F9	0.558 ±0.003	0.611 ± 0.020	10.64 ± 0.581	1.11 ±0 .03	21.09 ± 0.06

**All values are expressed as mean ± SD; n = 3*

The values for bulk density were found to be in the range of 0.523-0.587 g/cc where as the values for tapped density were found in the range of 0.586- 0.712 g/cc. The values for Carr's index were found to be in the range of 8.70 to 18.33 which were well within the range specified for Carr's index. The values for Hausner's ratio were found to be less than 1.25. Angle of repose of all the formulations was found to be less than 25 which indicated good flow property of all the powder blends.

4) Evaluation of chewing gum tablet

Data of evaluation of physical characteristics of chewing gum of caffeine salicylate is shown in Table No.4

The color of all the formulations was observed to be off brown. None of the chewing gum tablet was found to deviate from the mean weight of the tablets. Thickness of the tablets was found to be in the range of 4.01- 4.11mm. None of the formulations were found to be sticky. Friability was found to be less than 1% which indicates the strength of tablets and also exhibit that these tablets can withstand the shocks during shipping, transportation and handling. Uniform drug content was observed for all the formulations (98.65± 1.27% to 99.97± 0.47%). The values for these parameters are given in table4. Graphical representation of drug release is given in Figure no. 5

Table No. 4: Evaluation of caffeine salicylate chewing gum tablet

Formulation	Color	Uniformity of Weight * (mg) (± SD)	Thickness (mm)	Stickiness	Hardness (kg/cm²)	Friability* (%)	Uniformity content (%)
F1	O.B	987.83 ± 6.86	4.01 ± 0.00	N.S	4.1 ± 0.05	0.91 ± 0.02	99.09 ± 0.95
F2	O.B	989.17 ± 7.02	4.05 ± 0.05	N.S	4.2 ± 0.05	0.98 ± 0.01	99.97 ± 0.47
F3	O.B	989.10 ± 6.39	4.06 ± 0.05	N.S	4.1 ± 0.11	0.89 ± 0.02	99.91 ± 1.05
F4	O.B	990.73 ± 2.10	4.08 ± 0.05	N.S	3.8 ± 0.05	0.82 ± 0.03	98.65 ± 1.27
F5	O.B	991.07 ± 1.06	4.10 ± 0.04	N.S	4.0 ± 0.10	0.85 ± 0.02	99.17 ± 0.69
F6	O.B	988.03± 5.51	4.10 ± 0.01	N.S	4.0 ± 0.05	0.73 ± 0.02	98.95 ± 1.18
F7	O.B	992.77 ± 1.83	4.11 ± 0.02	N.S	3.8 ± 0.10	0.85 ± 0.01	99.50 ± 0.66
F8	O.B	988.80 ± 3.60	4.09 ± 0.05	N.S	3.8 ± 0.05	0.74 ± 0.01	99.33 ± 0.92
F9	O.B	990.37 ± 1.90	4.11 ± 0.04	N. S	3.5 ± 0.11	0.80 ± 0.01	99.58 ± 0.84

*Mean ± SD (n=3) O.B: Off brown * (n=20) N.S: Non sticky*

Cumulative percentage drug release of formulations F1 to F9 is given in Table No.5

Data analysis of formulations

The equations related with responses of hardness and $\%DR_{30min}$ to transformed factors is shown below.

Hardness (kg/cm²) = + 4.01 - $0.20X_1$ + $0.20X_2$ - $0.075X_1X_2$. $0.017X_1^2$ - $0.012X_2^2$ -

$0.017X_1^2X_2$ - $0.025X_1X_2^2$ .....Equation 02

(R^2= 0.9993)

$\%DR_{30min}$ (%) = + 71.30 +3.735X_1 + 16.625X_2 - 1.825X_1X_2 – 0.635X_1^2 + 2.625X_2^2 + 0.27$X_1^2X_2$ + 3.285$X_1X_2^2$ .....Equation 03

(R^2= 0.9997)

Table No. 5: Cumulative percentage drug release of formulations F1 to F9

Time	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
2	1.89 ± 0.51	8.28 ± 0.47	8.59 ± 0.39	2.39 ± 0.08	5.43 ± 0.12	6.12 ± 0.48	4.17 ± 0.61	7.42 ± 0.37	7.66 ± 0.05
4	2.36 ± 0.22	12.01 ± 0.41	12.07 ± 0.50	7.87 ± 0.24	6.79 ± 0.27	11.12 ± 0.35	7.54 ± 0.19	10.26 ± 0.25	12.37 ± 0.20
6	5.89 ± 0.37	15.77 ± 0.22	18.19 ± 0.72	10.18 ± 0.53	9.24 ± 0.39	15.37 ± 0.31	9.20 ± 0.55	11.88 ± 0.17	12.93 ± 0.03
8	9.08 ± 0.37	18.91 ± 0.42	20.32 ± 0.56	12.92 ± 0.30	10.92 ± 0.08	18.42 ± 0.47	14.04 ± 0.25	14.07 ± 0.32	16.58 ± 0.28
10	10.38 ± 0.69	24.24 ± 0.17	28.72 ± 0.47	17.37 ± 0.25	14.01 ± 0.20	20.27 ± 0.17	18.16 ± 0.27	16.58 ± 0.30	19.59 ± 0.27
12	16.89 ± 0.83	30.20 ± 1.14	32.70 ± 0.43	19.14 ± 0.08	18.02 ± 0.07	25.30 ± 0.07	20.21 ± 0.17	20.51 ± 0.08	22.46 ± 0.16
14	21.57 ± 0.58	34.67 ±0.17	40.20 ± 0.47	23.12 ± 0.28	22.49 ± 0.26	29.64 ± 0.16	25.31 ± 0.16	23.78 ± 0.29	26.26 ± 0.63
16	27.08 ± 0.51	35.62 ± 0.88	43.46 ± 0.25	25.68 ± 0.33	28.44 ± 0.10	30.79 ± 0.38	27.14 ± 0.37	28.74 ± 0.18	29.02 ± 0.58
18	32.46 ± 0.76	37.91 ± 0.51	55.52 ± 0.31	26.54 ± 0.17	33.57 ± 0.09	42.90 ± 0.09	34.42 ± 0.51	33.07 ± 0.47	36.68 ± 0.12
20	35.67 ± 0.36	42.92 ± 0.21	63.83 ± 0.30	28.79 ± 0.30	39.13 ± 0.27	57.62 ± 0.18	40.08 ± 0.28	40.11 ± 0.30	50.51 ± 0.33
22	39.23 ± 0.54	44.99 ± 0.37	71.91 ± 0.31	31.43 ± 0.07	43.98 ± 0.07	70.28 ± 0.51	44.00 ± 0.12	45.22 ± 0.21	60.92 ± 0.44
24	42.71 ±0. 47	49.96 ± 0.25	79.78 ± 0.91	37.23 ± 0.55	46.30 ± 0.26	74.58 ± 0.04	48.57 ± 0.17	48.67 ± 0.18	70.16 ± 0.33
26	45.22 ± 0.35	52.48 ± 0.32	81.40 ± 0.12	44.13 ± 0.30	53.40 ± 0.06	83.19 ± 1.22	52.42 ± 0.59	54.29 ± 0.11	83.78 ± 0.44
28	46.49 ± 0.52	58.09 ± 0.21	83.61 ± 0.34	49.34 ± 0.24	67.21 ± 0.57	89.27 ± 0.26	53.67 ± 0.17	65.97 ± 0.50	91.23 ± 0.24
30	47.39 ± 0.48	67.33 ± 0.58	84.83 ± 0.32	57.73 ± 0.23	70.52 ± 0.25	90.98 ± 0.30	65.08 ± 0.37	74.80 ± 0.23	95.22 ± 0.39

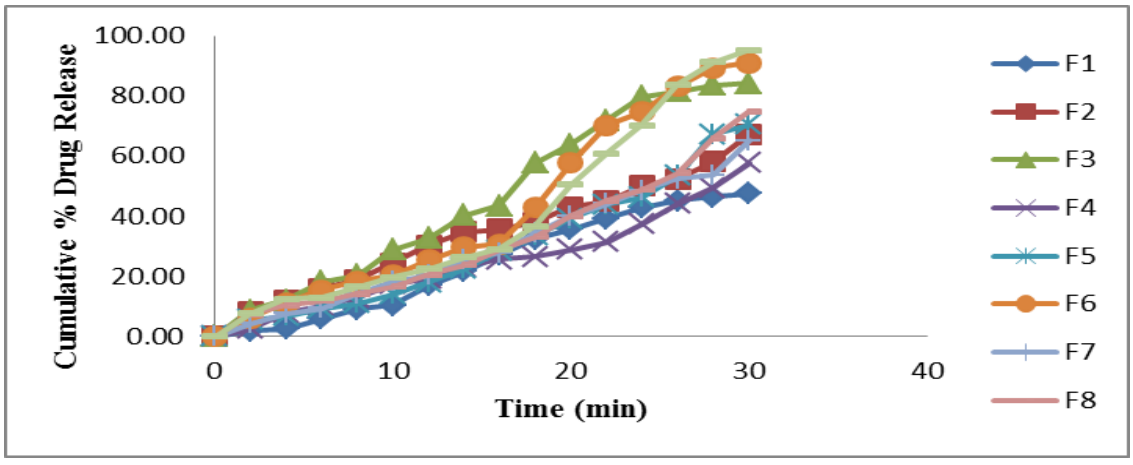

Figure No. 5: Comparative % cumulative drug release profile of formulations F1-F9

ANOVA Study

ANOVA and Multiple regression analysis were done using Stat-Ease Design Expert 8.0.7.1 software. Table No. 6 and 7 represents ANOVA for the dependent variables hardness and $\%DR_{30min}$ respectively.

Table No. 6 : Analysis of variance for hardness (kg/cm2)

Source	Sum of Squares	Degree of Freedom	Mean Square	F Value	P Value	Model Significant/ Non significant
Model	0.38	7	0.054	193.00	0.0554	Non significant
X_1	0.080	1	0.080	288.00	0.0375	Non significant
X_2	0.020	1	0.020	72.00	0.0747	Non significant
X_1X_2	0.022	1	0.022	81.00	0.0704	Non significant
$(X_1)^2$	5.556	1	5.556	2.00	0.3198	Non significant
$(X_2)^2$	0.027	1	0.027	98.00	0.0641	Non significant
$X_1^2X_2$	0.041	1	0.041	147.00	0.0524	Non significant
$X_1X_2^2$	8.333	1	8.333	3.00	0.3333	Non significant
Residual	2.778	1	2.778	-	-	-
Core Total	0.38	8	-	-	-	-

Table No.7: Analysis of variance for percent drug release at 30 min (%DR30min)

Source	Sum of Squares	Degree of Freedom	Mean Square	F Value	P Value	Model Significant/ Nonsignificant
Model	1947.79	7	278.26	199.84	0.0544	Non significant
X_1	27.98	1	27.90	20.04	0.1399	Non significant
X_2	552.78	1	552.78	397.00	0.0319	Non significant
X_1X_2	13.32	1	13.32	9.57	0.1997	Non significant
$(X_1)^2$	0.81	1	0.81	0.58	0.5859	Non significant
$(X_2)^2$	14.10	1	14.10	10.12	0.1938	Non significant
$X_1^2X_2$	0.097	1	0.097	0.070	0.8356	Non significant
$X_1X_2^2$	14.39	1	14.39	10.33	0.1920	Non significant
Residual	1.39	1	1.39	-	-	-
Core Total	1949.19	8	-	-	-	-

Response Surface Plot

The response surface plots were generated using Design Expert 8.0.7.1 software and are presented in Figure No.6-9. These were used to observe the effects of independent variables on the studied responses such as hardness and $\%DR_{30min}$ respectively.

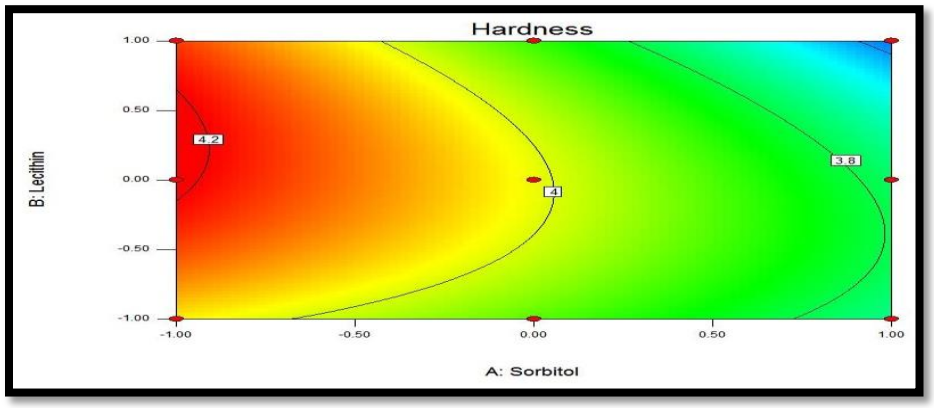

Figure No. 6: Contour plot for hardness

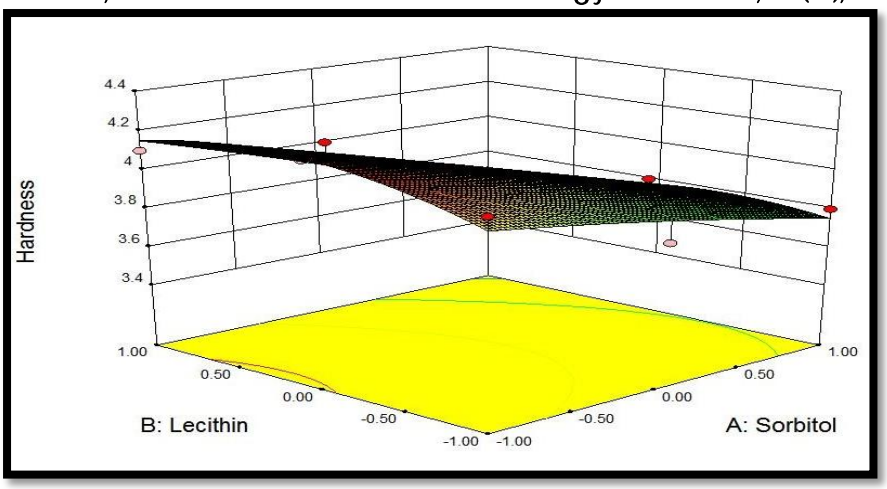

Figure No.7: Response 3-D surface plot for hardness

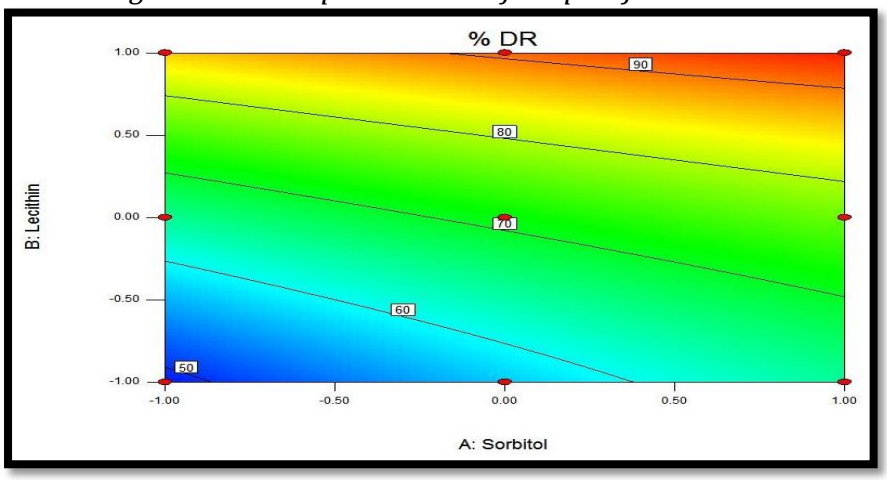

Figure No. 8: Contour plot for percent drug release at 30 min

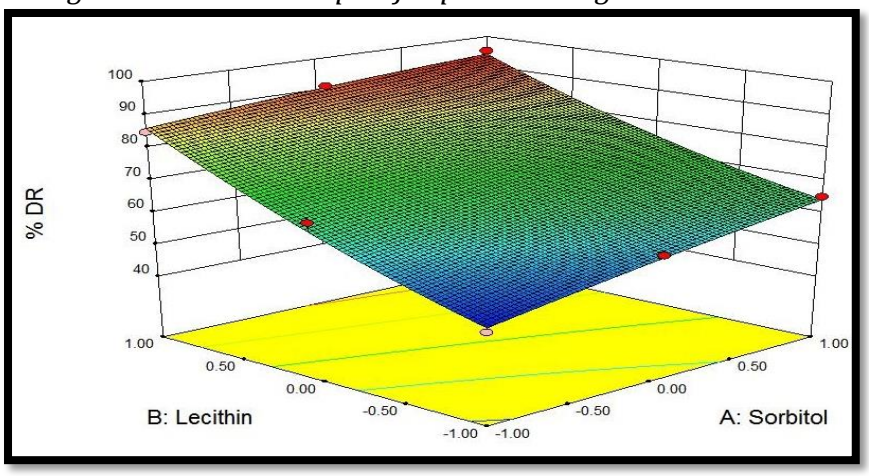

Figure No. 9: Response 3-D surface plot for percent drug release at 30 min

DISCUSSION:

The present work was aimed to develop the formulation of medicated chewing gum containing caffeine salicylate with fast onset of action and to avoid first pass metabolism.The flow properties of powder blends and evaluation tests of tablets were complied with standard and showed good results.

The drug release from various formulations was found to be in the range of 47.39% - 95.22 % for F1-F9. It was found to be least for F1 having the least concentration of both the sorbitol and the plasticizer soya lecithin whereas it was found to be maximum in F9 in which the concentration of both sorbitol and the plasticizer soya lecithin was found to be optimum. Hence formulation F9 was considered as optimized formulation. From the *in vitro* drug release data, it was observed that an increase in the concentration of softener may reduce the hardness of the chewing gum tablet also it was observed that the increase in the concentration of plasticizer and softner sorbitol may increase drug release from formulation.

For data analysis factorial design was used which serves as an essential tool to understand the complexity of the pharmaceutical formulations. A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels. The amount of sorbitol and lecithin were selected as independent variables and the dependent variables were hardness and percent drug release at 30 min ($\%DR_{30min}$). The data obtained was treated using Stat-Ease Design Expert 8.0.7.1 software and analyzed statistically using analysis of variance (ANOVA). Equation 02 showed that the hardness decreases as the amount of sorbitol and lecithin increases. Equation 03 indicates that percent drug release after 30 minutes increases as amount of sorbitol and lecithin increases. All the polynomial equations were found to be statistically not significant ($P > 0.05$), as determined using ANOVA, as per the provision of Design Expert software. The polynomial equation can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries; i.e. positive or negative.

The coefficient of X_1 and X_2 were found to be not significant at $P>0.05$ and thus confirmed not significant effect of both the variables on the selected responses. Increasing the amount of sorbitol resulted in the decrease in the hardness but drug release was found to be increased. Vice versa increasing the amount of lecithin resulted in the increases in the drug release but hardness was found to be decreased.

The quadratic surface model obtained from the regresion analysis was used to build up contour and 3-D graphs in which the responses were represented by curvature surface as a function of independent variables. The releationship between the response and independent variables can be directly visualized from the response surface plots. Graphical presentation of the data helped to show the relationship between the response and the independent variables. The information given by graph was similar to that of mathematical equation obtained from statistical analyses.

CONCLUSION:

In present work chewing gum formulation was prepared in tablet form by using method of direct compression by using soya lecithin as plasticizer, sorbitol as softner and synthetic gum base along with other excipients. The synthetic gum base is insoluble at salivary pH (pH 6.4). All the formulations were found to comply the weight variation test and uniformity of active content test. It was also found that the chewing gum tablets were not friable which confirmed the integrity of the formulation. All the formulations were found to be non-sticky.*In-vitro* release test was performed using modified disintegration apparatus for tablet. The apparatus was modified in such a way that the formulation was pressed continuously like mastication. From the *in vitro* drug release data it was concluded that drug release from the chewing gum tablet was satisfactory. In the formulation Soya lecithin was used as a plasticizer and it was found that it acted on the drug release to some extent. When concentration of Soya lecithin was increased, drug release was also found to be increased. From all the results formulation F9 was found to be optimized one as it gave good results as compared to other formulations. F9 showed drug release upto 95.22±0.39% within 30minutes with hardness 3.5±0.11 kg/cm^2.

Thus medicated chewing gum containing caffeine salicylate formulation prepared in this study can be promising and better alternative to caffeine for its enhanced CNS stimulant and mild analgesic effect for the patients suffering from depression, pain associated depression and sleep disorders.

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