DIRECTLY COMPRESSIBLE "MEDICATED CHEWING GUM (MCG)" FOR STAYING ALERT

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Introduction

Medicated chewing gums are defined by the European Pharmacopoeia 1 and the guidelines for pharmaceutical dosage forms as ''solid single dose preparations with a base consisting mainly of gum that are intended to be chewed but not swallowed, providing a slow steady release of the medicine contained''2. It can be either used for local treatment of mouth disease or systemic delivery by direct intraoral absorption through the buccal mucosa3.Medicated chewing gum offers numerous advantages over other drug delivery systems, among which some important advantages are highlighted here in triangle.

There is an increasing need to reformulate existing drugs into Novel Drug Delivery Systems (NDDS) to extend or protect product patents thereby delaying, reducing or avoiding generic erosion at patent expiry. By formulating the drugs in MCG composition re-vitalization of old products and re-formulation of new patented products is possible to distinguish from future generics competition in the market.

Medicated **C**hewing **G**um (**MCG)** is a solid single dose preparation comprising gum base and other ingredients and containing active ingredient(s) which are released by chewing & intended for quick onset of action [4] by direct intraoral absorption into systemic circulation.

Traditionally, medicated chewing gum has remained as a niche category due to its complex formulation and manufacturing that uses hot mixing and extrusion procedures involving specific technology and equipment that most pharmaceutical companies are not familiar with. Moreover the use of heat and liquids in these processes prevents many APIs from being considered due to their sensitivity to high temperature levels and moisture.

However, in the recent past a new door has opened with the launch of innovative directly compressible powder excipients for production of medicated or functional chewing gums.
These are designed specifically to bring gum technology closer to pharmaceutical companies by adapting to traditional oral solid formulation and production requirements in the Pharma industry.

They are made as a "all in one" combination of different ingredients that promote long chewing consistency, because they contain the essential gum base and at the same time they have great flowability and compressibility properties due to their polyol and glidant content in order to be easily compressed and adapt to pharmaceutical production standards.

The combination of these readymade gum excipients allows multiple possibilities of formulation with an active ingredient and different flavors of choice, all in a dry room temperature process.

In the present study MCG was formulated using Health in Gum® directly compressible powder (**Gum powder**) with 100 mg of Caffeine .
Pharmacopoeia quality control parameters were measured along with a human volunteer study to measure the API release rate from the chewing gum matrix.

Caffeine is a highly soluble & highly permeable CNS (central nervous system) stimulant used in management of fatigue & increasing alertness [2] and from studies it has been revealed that **Chewing action** itself enhances **25% blood flow** to the brain resulting in improvement in alertness [3]. So, Caffeine chewing gum, can solve the same purpose of staying alert from both sides one from drug (caffeine) & another from Drug delivery system (chewing gum) itself. Thus caffeine chewing gum can be a synergistic delivery option for staying alert especially for sportsman's, and other jobs who need to stay alert for long times.

FORMULATION DEVELOPMENT

The starting raw material of the formulation is the gum powder, which will account for at least 85% of the total weight of the tablet, in order to have chewing gum consistency over time.
Once the API and flavor combination was figured out in the correct proportions the mixing process started:

Mixing procedure

- Mixing of liquid flavor on the powder gum preparation for 5 minutes
- Screening of the mixed preparation through #22 sieve
- Mixing of API, antisticking agent, flavouring ingredients, lubricant and glidant
- Sieving and blending (10 minutes)

Finally, formulation was compressed. In process quality control (IP-QC) parameters for optimized batch were mentioned in Table 1, which indicates it had very good flow property & compressibility.

Table 1 – Results of properties of the powder gum

PARAMETERS	RESULT WITH INDICATION
Angle of repose of gum powder	**29.11°** -Very good as per EP
Carr's compressibility index of gum powder	**8.00** -Very good as per EP
Compatibility of caffeine with gum powder by DSC	In DSC spectrum separate peaks at 92°c(xylitol),95°c(sorbitol) & **236**°c(caffeine) - No Incompatibility

CFN-MCG QUALITY EVALUATION

A. OFFICIAL (BP/EP) PRODUCT QUALITY ASSESSMENT TESTS

Assay for content uniformity & Friability test was carried out as per European pharmacopoeia.
Final MCG formulation passed test for uniformity of mass with average mass of & no one was deviated from ±5% of average mass of MCG. All 10 MCGs, which were sampled randomly have passed the test for uniformity of content because contents of CFN in all 10 MCGs have fallen within compliance limit of 85-115% & average content of CFN was found to be 99.21 ± 0.53%.In friability testing, after 100 rotations total weight loss of 10 MCG was found to be 0.14% which was less than compliance limit of 1.0%; So final MCG formulation have passed in friability test also.

Table 2. Results Of Official Product Quality Assessment Tests				
No.	**Official Tests**	Observations	Compliance criteria	Result
01	**Uniformity of Mass**	No one deviated from ±5%	NMT 2 deviate from ±5%	Pass
02	**Uniformity of Content**	All 10 MCG contain CFN Within limits	85% < x < 115%	Pass
03	**Friability testing**	Total Weight loss=**0.14%** of 10 MCG	Weight loss< 1.00%	Pass

CFN-MCG Performance Evaluation for determination of % Drug Release by "CHEW OUT" Study by 6 volunteers in which each person chewed one sample of the caffeine chewing gum for different time periods (5, 10, 15, 20 min). Then residual drug had been cut into small pieces, frozen & then ground till obtaining fine powder & then analyzed to determine residual drug content by UV visible spectrophotometer at 273 nm.
So, Actual drug content – Residual drug content = Released drug content from MCG.

The drug contained within the MCG is released in the saliva for the duration of the chewing process, and then it would be either absorbed through oral mucosa or if swallowed then it would be absorbed through the gastrointestinal tract. Pharmacokinetics can be determined from withdrawn blood samples at specific time intervals.

SELECTION & OPTIMIZATION OF FACTORS AFFECTING %DRUG RELEASE FROM MCG BY 3^2 FULL FACTORIAL EXPERIMENTAL DESIGN

Independent significant Factors [Chewing time(A) & Amount of gum powder(B)] affecting dependent factor (%CFN release from MCG) were first extracted out by means of ANOVA and then extracted factors were optimized by 3^2 Full factorial experimental design. Here full factorial 3^2 designs was used for optimization procedure, because it is suitable for investigating the quadratic response surfaces and for constructing a second-order polynomial model, thus enabling optimization of the chewing time & amount of gum base to achieve sufficient drug release from MCG. Mathematical modeling, evaluation of the ability to fit to the model and Response Surface Methodology (RSM) were performed by employing Design-Expert® software (Version 7.1.2, Stat-Ease Inc., Minneapolis, MN). *Response Surface Methodology* (*RSM*) is a collection of mathematical and statistical techniques useful for the modeling and analysis of problems in which a response of interest is influenced by several variables and the objective is to optimize this response. The most extensive applications of RSM are in the industrial world, particularly in situations where several input variables potentially influence some performance measure or quality characteristic of the product or process. This performance measure or quality characteristic is called the response.

Table 3 summarizes the independent and dependent variables along with their coded & actual levels.

Table 3. Independent & Dependent variables along with their levels				
Factors (Independent variables)	Levels used			Response (Dependent variable)
	-1	0	+1	
A. Chewing time (mins.) **B.** Amount of gum powder (%)	5 70	10 75	15 80	**% Drug Release**

Total 4 experimental testing runs which were carried out are enlisted in Table.

Table 4. Experimental testing runs with values of variable factors		
Experimental Test Run	Variable factors in coded terms (actual terms)	
	Chewing time (mins.)	Amt of gum powder (%)
1	-1(05)	-1(70)
2	0(10)	-1(70)
3	+1(15)	-1(70)
4	- 1(05)	0(75)
5	0(10)	0(75)
6	+1(15)	0(75)
7	-1(05)	+1(80)
8	0(10)	+1(80)
9	+1(15)	+1(80)

It was illustrated from **Surface Response graph** that as chewing time (A) increases %drug release also increased but increasing amount of gum powder (B) have very little drop off effect on %caffeine release.
%DRUG RELEASE = +88.33 + 5.67A - 1.50B + 0.25 AB - 2.00A^2- 0.50B^2

The quadratic models generated by regression analysis were used to construct 2-Dimensional contour plot & 3-dimensional response surface plot in which response parameter DR was represented by a curvature surface as a function of A & B. **Figure 29** shows the effect of chewing time & amount of gum powder in contour plot as well as response surface plot.
A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. In this study optimization was performed with constraints for DR (90 % < DR < 95 %) set as goals to locate the optimum settings of the independent variables in the new formulation. The optimal parameters to achieve predicted CFN release of 92% (90.0%-95.0%) as calculated from predicted equation of Drug Release

A. Chewing Time=**15 minutes**
B. Amount of Gum powder = **75.00%**

CONCLUSION

Optimized formulation of directly compressed CFN-MCG

- Has passed all official MCG Quality tests including uniformity of mass, assay for uniformity of content & Friability testing as per compliance criteria mentioned in official monograph of MCG in BP.
- **Released average 92% of CFN (n=6) within 15 minutes of chewing** (which is half of the normal average chewing time) in *in vivo* chew out study.
- **Interindividual variability in % CFN-release** was remained only up to 1-3 minutes, afterwards very less interindividual variability was observed in %CFN release.

So, the present study demonstrated that CFN could be successfully delivered by MCG into systemic circulation via direct intraoral buccal absorption.
Concerning statistical analysis, it was shown that 3^2 Full Factorial Experimental Design (FFED) and optimization technique can be successfully used in the development of optimized formulation of MCG & for deciding appropriate chewing time for sufficient drug release. The optimized formulation exhibited drug release profiles which were close to the predicted responses which was confirmed by high significant r^2=0.988 (>0.9) value.

From overall results, it was concluded that developed formulation of directly compressible taste masked Medicated Chewing Gum of Caffeine present a better alternative to any other dosage form including tea or coffee because it will be a synergistic delivery option for staying alert. Moreover CFN-MCG can be taken anywhere anytime without preventing patient from living an active life which promotes very high patient acceptance & higher patient compliance.

Moreover today it is known that chewing gum has other benefits: promotes oral health, it is a mild stress relief and reduces the appetite sensation, which stand as added positive characteristics that increase the value of a caffeine drug delivery system in the form of chewing gum.
This eventually can lead to the development of a new attractive market directed to energy and sports products, which is already flourishing in occidental countries.

Other potential applications for MCG include areas like Allergy, Cough& Cold, Digestive and Oral Care , added to the consolidated available Nicotine and Motion sickness gums.

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