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Formulation and Evaluation of Disulfiram Medicated Chewing Gum

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Abstract

Chewing gums are mobile drug delivery systems. Unlike chewable tablets, medicated gums must not be swallowed and can be removed from the application site without resorting to invasive means. Medicinal chewing gums are a solid single-dose preparation. They contain one or more active ingredients, which are released by chewing and are intended to be used for the local treatment of oral diseases or systemic intake after absorption by the oral mucosa. As for patient comfort, its discreet and easy administration without water promotes greater compliance. Since it can be taken anywhere, the chewing gum formulation is an excellent choice for acute medications. In the present study, chewing gum medicated with Disulfiram was formulated with beeswax as base, glycerol, castor oil, dextrose, calcium carbonate, polyvinylpyrrolidine, aerosol, magnesium stearate and peppermint oil.

This medicated chewing gum was prepared with a direct compression method and formulated using various compositions of plasticizer castor oil and dextrose.

The medicated chewing gums developed by Disulfiram were smooth, light yellow in color with a mint flavor. The presence of glycerine at an optimized concentration provided the softness for the medicated chewing gum developed. The average content of the drug in the developed medicated chewing gum was 94.14%, confirming the success of the formulation and the methodology used for its development. The drug release profile for medicated chewing gums can be significantly influenced by the frequency of chewing, therefore the drug release rate from the developed MCG was measured the maximum drug release of 94.37% was reported after 30 minutes of study on the dissolution of Batch F4.

Keywords: Chewing gum, Mouth diseases, Disulfiram, Mobile drug delivery system, Dental caries.

Introduction

The delivery system can have a significant impact on success by providing the distinction of the product on the market, as evidenced by nicotine gums. An innovative drug delivery system can offer additional patient benefits, including discreet and convenient administration, as well as the potential for buccal absorption, providing a quick action. It can also provide new commercial opportunities for drugs whose patents are about to expire. This sparked interest in the potential of chewing gum formulations containing a variety of active ingredients.

As a drug delivery system chewing gum has many advantages over other oral administration forms; its main attributes include its convenient manner; being able to chew discretely at any time and any place and the exclusion of the requirement of water.

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Disulfiram is a drug that is used to support the There may also be a particularly high acceptance in the paediatrics market, as some children may be more inclined to chew rather than swallow.[1] Disulfiram works by inhibiting the enzyme acetaldehyde dehydrogenase, which means that many of the effects of a "hangover" are felt immediately after alcohol consumption. It causes unpleasant effects when consuming even small quantities of alcohol. These effects include facial redness, headache, nausea, vomiting, chest pain, weakness, blurred vision, mental confusion, sweating, suffocation, shortness of breath and anxiety.[2]

Chewing gum provides new competitive advantages over conventional drug delivery system:

- Fast onset of action and high bioavailability
- Pleasant taste
- Higher compliance (easy and discreet administration without water)
- Ready for use
- High acceptance
- Fewer side effects

Low doses give high efficacy since first pass liver metabolism is avoided. The controlled release rate also reduces the risk of the side effects, as a high peak plasma concentration is avoided. [3]

Systemic effect

The active ingredients can be absorbed through the oral mucosa and / or through the gastrointestinal tract when saliva is ingested. Once the active substance is present in the blood, a systemic effect can be achieved.

Fast onset of action

Fast onset of systemic effect is seen for active substances absorbed through the buccal mucosa, as the active substances pass by the jugular veins directly to the systemic circulation.

Local effect

Chewing gum is an obvious drug delivery system for local treatment of diseases in the oral cavity and in the throat, as sustaining the release of active substances may deliberately prolong exposure.

Effect on dry mouth

Dry mouth is a side effect of many types of medicament (e.g. antidepressants) and it is also part of the symptomatology of several diseases (e.g. Sjogren's syndrome-an autoimmune disorder). Chewing gum stimulates salivary secretion thereby decreasing dryness in the mouth.[4]

There are plenty of commercially available MCG approved by USFDA. Some of the leading brands are listed in the table.

Table 1: Marketed brands of medicated chewing gums approved by USFDA

Brand Name	Drug/ API	Indication	Manufacturer
Nicorette®	Nicotin	Smoking cessation	Glaxo Smithklim
Nicotinell®	Nicotin	Smoking cessation	Novartis
Niquitin®	Nicotin	Smoking cessation	Glaxo Smithklim
Fluorette®	Fluride	Dental caries	Fertin Pharma
Vitaflo CHX®	Chlorhexidine	Gingivitis and Plaque	Fertin Pharma
Stay Alert®	Caffeine	Antibacterial	Stay Alert Safety Service Inc.
Travvell®	Dimenhydrinate	Motion sickness	Asta Medica

Merits of the Medicated Chewing Gum[5]

- Dose not requires water to swallow. Hence can be taken anywhere.
- Advantageous for patients having difficulty in swallowing.
- Excellent for acute medication.
- Counteracts dry mouth, prevents candidiasis and caries.
- Highly acceptable by children.
- Avoids First Pass Metabolism and thus increases the bioavailability of drugs.
- Fast onset due to rapid release of active ingredients in buccal cavity and subsequent absorption in systemic circulation.
- Relaxes and eases tension & freshens the breath.
- Decreases ear discomfort when flying.
- Satisfies snack craving & Cleans teeth after meals.

Material and Methods

Formulation of medicated chewing gum of Disulfiram

Chewing gum is a mixture of natural or synthetic gums and resins sweetened with sugar, corn syrup, artificial sweeteners and may also contain colouring agents and flavour. The basic raw material for all chewing gum is natural gum Chicle, obtained from the sapodilla tree. Chicle is very expensive and difficult to procure therefore other natural gum or synthetic materials like polyvinyl acetate and similar polymers can be used as gum base. Typically Chewing Gum comprises two parts viz.[6]

Optimization of Formula

Table 2: Formula for Chewing Gum

S.No.	Ingredients	F 1	F 2	F 3	F 4	F 5	F 6
1.	Disulfiram	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
2.	Bees Wax	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
3.	Glycerol	----	----	----	10 mg	15 mg	20 mg
4.	Castor Oil	10 mg	15 mg	20 mg	----	----	----
5.	Dextrose	24 mg	24 mg	24 mg	24 mg	24 mg	24 mg
6.	Calcium Carbonate	24 mg	24 mg	24 mg	24 mg	24 mg	24 mg
7.	Polyvinyl Pyrrolidine	210 mg	210 mg	210 mg	210 mg	210 mg	210 mg
8.	Magnesium Stearate	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
9.	Aerosil	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg
10	Peppermint Oil	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg

Each chewing gum containing 50 mg of Disulfiram*

Preformulation Study

Organoleptic Properties

The samples of Disulfiram for colour, odour and taste were identified by visual inspection.

Melting Point

The Melting point was determined by the capillary method using Melting point apparatus. Here, the capillary tube was filled by pressing the open end gently into Disulfiram. When the drug was packed into the bottom of the tube, the tube will be placed into the slot behind the eye-piece on the melt-temperature. Make sure the unit was plugged in and set to zero and then turn it on and near its reporting melting point then temperature knob adjust to downside.

Solubility Study

The solubility of the drug was studied in various solvents like water, acetone, methanol, chloroform, etc.[7]

UV Spectrophotometry

Instrument: Absorption spectral measurements were carried out with a UV- visible spectrophotometer (Shimadzu - 1601 Model) using UV Probe software version 2.20 was employed with automatic wavelength correction with a pair of 5 cm matched quartz cells.

Reagents and chemicals: The reference standard DSF pure was received as a gift sample from Unidrug Innovative Pharma Technologies Ltd, Indore. Methanol was used as solvent and obtained from Modern institute of pharmaceutical sciences Indore.

Selection of absorption maxima in methanol: Solution of strength 10µg/ml was prepared for drug from standard stock solution and scanned in the wavelength range of 200-400nm. The absorption maxima was found at 236.0 nm which was used for further analysis.

Preparation of stock solution in Methanol: 10 mg of DSF was accurately weighed and dissolved in 100 ml volumetric flask. The volume was made up to the mark with methanol to give 100 µg/ml stock solutions.

Preparation of working standard solutions in methanol: Prepared stock solution was further diluted with methanol to get working standard solution of 0.2, 0.4, 0.6, 0.8 and 1.0 µg/ml to construct Beer's law plot for DSF. The absorbance of each solution was measured at 236 nm against methanol as blank.

Calibration curve of Disulfiram in methanol: The Appropriate volumes of aliquots from standard DSF stock solution were transferred to different volumetric flasks of 10 ml capacity. The volume was adjusted to the mark with methanol to obtain concentrations of 0.2, 0.4, 0.6, 0.8 and 1.0 µg/ml. Absorbance of each solution against methanol as a blank was measured at 236 nm.

From that absorbance, regression equation, correlation coefficient was determined. The standard calibration curve for DSF was plotted by taking concentration of drug on X-axis and absorbance on Y-axis.

Drug Excipients Interaction Studies

Thin Layer Chromatography (TLC) studies:

Prepration of plate: Take a glass side and spread uniformly a mixture of silica gel G and water and form a thin layer on the plate. Allow the plate for air drying for few minutes and then kept into the oven to get activated.

Prepration of solvent: Take cyclohexane and ethyl acetate as a solvent in a ratio of 8:2 in a beaker. Put a filter paper in a beaker for saturation of solvent system.

Prepration of sample: Take all the excipients into the different beakers and dissolve them in acetone in a specific quantity.

Procedure: Take out the activated tlc plate and mark it, above the bottom. Now placed a sample on the one mark and the drug on the other mark. Placed the plate into the beaker and let the solvent to be run. After ¾ running of the solvent take out the plate and let it be dry in the air at normal temperature. After drying, put the plate into the iodine fumes for identifying the spot. After that note the distance of both the spot and solvent run from the mark of the plate and calculate the Rf value and check the drug interaction.[8]

Formulation of Medicated Chewing Gum

By Direct Compression Method

Weighed quantity of calcium carbonate and polyvinyl pyrrolidine were mixed in separate pestle mortar. Weighed quantity of Disulfiram drug was mixed in above mixture. Then the bees wax and caastor oil / glycerol was taken and melted. The melted bees wax and plasticizers are poured into the pistal and mortar. Then all the remaining ingredients dextrose, magnesium stearate, aerosil, peppermint oil were added and mixed well. The blends was taken for compression activity on compression machine. The chewing gum were compressed for formula F1, F2, F3, F4, F5, and F6.

Post Compression Studies

Weight variation

Weight variation of all formulation was done by method described in experimental work. Weight of 10 chewing gums was taken in one batch and then average weight is calculated from that standard deviation is calculated.[9]

Hardness

Due to absence of any reported method, it was decided to use the Monsanto type hardness tester for determination of hardness of all MCG formulations. The average values, standard deviation and relative standard deviation were calculated.[10]

Thickness

Chewing gum thickness is an important parameter to be controlled to facilitate packaging. Chewing gum thickness must be controlled within a ±5% variation of a standard value. Any variation within a particular lot should not be apparent to the unaided eye of the consumer. Thickness of all the formulations was measured using a Verniercalliper.[11]

Friability

Chewing gums were weighed and placed in the Roche's friabilator. The chewing gums were placed into the apparatus for four minutes, which was rotating at the speed of 25 revolutions/ min. Then the chewing gum was removed and de dusted and weighed. The Percentage loss in weight was calculated and taken as a measure of friability. Ideally there should not be more than 1% variation of weight loss.

$$\text{Percent Friability} = 1 - \frac{\text{Loss in weight}}{\textit{Initial weight}} \times 100$$

Uniformity of content

The individual contents of active substance of 10 dosage units which were taken randomly were determined. The 10 dosage forms were crushed in mortar and powder equivalent to 10 mg of Disulfiram was taken. The powder was dissolved in 100 ml of methanol. The absorbance measurements of these solutions were taken by UV–Visible spectrophotometer at 236 nm. The formulation complies with the test if the individual content is between 85% and 115% of the average content. [12]

In- vitro drug release profile:

The in-vitro dissolution study for MCG was performed using a specially designed in-house dissolution apparatus, which may mimic the normal mastication process of humans. The developed MCG was kept in cylindrical vessel containing PBS of pH 6.8 at 37.0±0.5 ºC

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temperature at 50 rpm. During the trials, 1 ml of sample was withdrawn every 5 minutes for duration 30 minutes. The sink condition was maintained throughout the study. The samples with drawn were measured for drug content by using UV Spectrophotometric method at 236 nm. Using the data, % drug release was calculated. [13-15]

Stability studies for developed MCG

An accelerated stability study for developed MCG was carried out as per ICH guidelines with necessary modifications. The MCG was exposed at different temperature conditions of 4±2° C, 30±2° C and 45±2° C for a period of 45 days. The MCG was tested for consistency, colour, odour and drug content. [13-14]

Result and Discussion

Preformulation Studies

Organoleptic Properties

The samples of Disulfiram was identified for colour, odour and taste which were found to be same as that of standard parameters.

Table 3: Organoleptic Properties of Disulfiram

Parameters	Result
Colour	White Powder
Odour	Odourless
Taste	Slightly bitter

Melting Range

The melting point of Disulfiram was found to be 69-72 ºC and compare with referencei.e 71ºC the drug was found to be in the pure form.

Solubility Studies

The solubility of the drug sample was determined by accurately weight 10 mg of Disulfiram was added in 6 test tubes and was added in aqueous and non aqueous solvents and solution was kept for 24 hrs and then samples were analyzed by U.V visible spectrophotometry and were found to be soluble in non polar and were found to be insoluble in polar solvents.

Table 4: Solubility Profile of Disulfiram

Solvent	Solubility
Water	Insoluble
Methanol	Very Soluble
Ethanol	Sparingly Soluble
Chloroform	Soluble
Ether	Soluble

UV-Visible Spectrophotometric Studies

Table 5: Absorbance of Disulfiram in Methanol

Concentration	Absorbance
0.2	0.2233
0.4	0.364
0.6	0.526
0.8	0.5994
1.0	0.7272

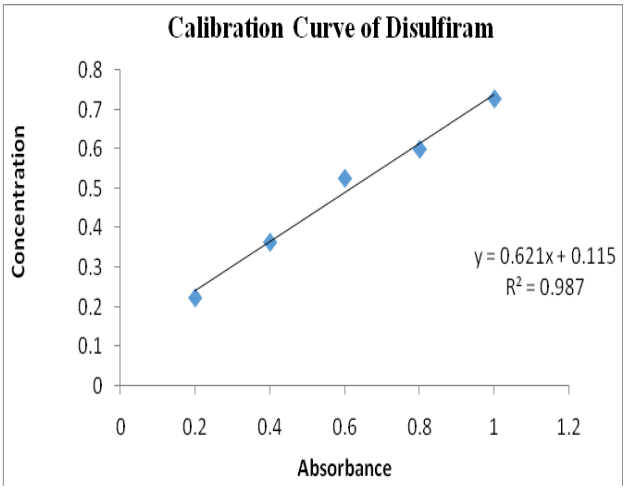

Fig. 1: Calibration Curve of Disulfiram

Drug Excipients Interaction Studies

Table 6: Disulfiram and Excipients Interaction Study by TLC

S. No.	Components	Rf values		Observation
		Initial	Final 28 Day	
1.	Disulfiram (Pure Drug)	0.82	0.83	No Change
2.	Disulfiram + Bees Wax	0.81	0.89	No Interaction
3.	Disulfiram + Glycerol	0.89	0.93	No Interaction
4.	Disulfiram + Castor Oil	0.89	0.93	No Interaction

5.	Disulfiram + Dextrose	0.92	0.95	No Interaction
6.	Disulfiram + Calcium Carbonate	0.82	0.91	No Interaction
7.	Disulfiram + Polyvinyl Pyrrolidine	0.92	0.95	No Interaction
8.	Disulfiram + Magnesium Stearate	0.83	0.89	No Interaction
9.	Disulfiram + Aerosil	0.91	0.93	No Interaction
10.	Disulfiram + Peppermint Oil	0.89	0.93	No Interaction

Pre-compression Studies of Disulfiram Drug

Bulk densities of powder blends were found between 0.49-0.53 g/ml. Tap densities of powder blends were found between 0.72-0.78 g/ml. The angle of repose values varied from 21.23-25.07 °. Carr's Index values varied from 12.17 % to 17.26 %. Hausner's Ratio was found to be between 1.42-1.57. From these values it was observed that all these blends had good flow properties.

Table 7: Precompression Studies

Batch	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (ɵ°)
F1	0.5267 ±0.0023	0.7883 ±0.0023	13.21 ± 0.64	1.43 ±0.008	22.3 ± 0.32
F2	0.5140 ±0.0017	0.7236 ±0.0023	12.17 ± 0.05	1.42 ±0.0006	24.39 ±1.38
F3	0.5013 ±0.0012	0.7932 ±0.0017	14.02 ± 0.05	1.57 ±0.0007	25.07 ±0.005
F4	0.5160 ±0.0035	0.7696 ± 0.0023	16.49 ± 0.71	1.44 ±0.009	22.75 ±0.56
F5	0.5340 ±0.0071	0.7243 ± 0.0011	17.26 ± 0.11	1.42 ±0.001	23.46 ±1.28
F6	0.4967 ±0.0012	0.7536 ±0.0015	16.90 ± 0.44	1.46 ±0.0059	21.23 ±0.44

Formulated Chewing Gum

Formulated chewing gum by direct compression method appears to be white to light yellow in color and circular and biconvex in shape.

Fig. 2: Directly Compressed Chewing Gum

Post Compression Parameters of Formulated Chewing Gums

All batches of prepared tablets were evaluated for the different parameters. Weight variation for prepared tablets was found within specifications. Average weight for tablet was in the range of 349 –350 mg. Hardness values for tablets of all formulations were in the range of 3.5-4.6 Kg/cm^2. Thickness values for of all tablets were in the range of 3.52-3.60 mm. Friability of all the formulations was in the range of 0.65-0.88 %. Drug contents for all the formulations were found in the range of 89.78-98.63 %.

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Table 8: Post Compression Parameters of Formulated Chewing Gums

Batch	Hardness (kg/cm^2±SD)	Thickness (mm)	Friability (%)	Weight Variation (Avg. Wt ± SD)	Uniformity of content (%)	Stickiness
F 1	3.5±0.21	3.60±0.25	0.69±0.023	349.5±0.44	94.24	N.S
F 2	4.6±0.30	3.59±0.20	0.73±0.016	349.6±0.31	93.54	N.S
F 3	3.8±0.15	3.52±0.10	0.71±0.15	350.4±0.64	89.78	N.S
F 4	3.5±0.80	3.58±0.39	0.69±0.074	349.4±0.53	98.63	N.S
F 5	4.3±0.34	3.57±0.31	0.81±0.18	350.4±0.32	92.9	N.S
F 6	3.5±0.24	3.59±0.27	0.88±0.068	349.9±0.34	95.76	N.S

N.S= Non Sticky,

In- vitro drug release profile

The medicated chewing gum tablet mainly consisted of gum base, active ingredient, plasticizer, sweetening agent and flavoring agent. The drug release from various formulations was found to be in the range of 75.30 % - 94.37 %. Where batch F4 shows the better release profile of all.

Table 9: In-Vitro % drug release profile

Time (mins)	% Drug release (in %)					
	F1	F2	F3	F4	F5	F6
0	0 ± 0	0 ± 0	0 ± 0	0.0	0 ± 0	0 ± 0
5	47.30 ± 0.53	39.72 ± 0.25	40.40 ± 0.26	31.61±0.34	35.80 ± 0.18	32.62 ± 0.24
10	55.72 ± 0.19	48.98 ± 0.21	47.95 ± 0.66	50.42± 0.49	45.15 ± 0.18	45.50 ± 0.30
15	62.22 ± 0.10	61.48 ± 0.21	62.78 ± 0.29	63.72± 0.39	60.33 ± 0.25	55.82 ± 0.13
20	68.03 ± 0.20	66.78 ± 0.25	70.28 ± 0.15	76.15± 0.45	71.00 ± 0.38	61.42 ± 0.13
25	73.72 ± 0.18	74.52 ± 0.16	74.32 ± 0.10	80.14± 0.33	83.25 ± 0.20	79.48 ± 0.43
30	75.30 ± 0.10	82.07 ± 0.38	81.00 ± 0.40	94.37± 0.25	88.98 ± 0.18	84.45 ± 0.35

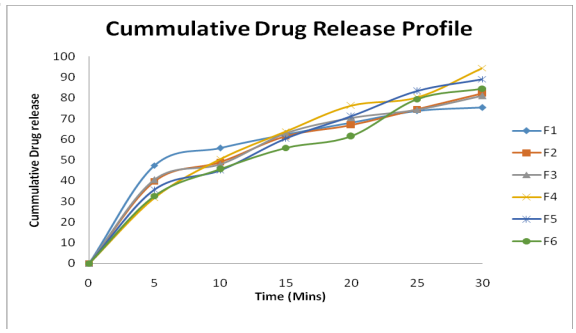

Fig. 3: Comparative % cumulative drug release profile of formulations F1-F6

Stability studies for developed MCG

Every formulation should maintain its physicochemical integrity to deliver its therapeutic goals. There was no significant change was reported with the developed MCG in terms of colour, odour and appearance Medicated chewing gum containing Disulfiram was able to maintain its drug content unchanged at 88.5% throughout the period of study. The study results substantiated the possibility of MCG as a stable formulation.

Conclusion

Chewing gum is an excellent drug delivery system for self-medication, as it is convenient and can be administered discretely without water. It offers several advantages compared to chewable tablets, lozenges and other related formulations. Hence in forth coming years it will become a much more common and popular drug delivery system. In present work chewing gum formulations were prepared in the tablet form by using glycerol, castor oil and gum base. This property is essential for the chewing gum base because it eliminates the possibility of dissolution of gum base in saliva.

From the results obtained in this work, it can be concluded that synthetic gum base can be used as an excellent agent for formulation of chewing gum. For tablet formulations all studies like stickiness, weight variation, friability and in-vitro release test were performed.

The developed medicated chewing gums of Disulfiram was soft, light yellow in colour with minty flavor. The presence of glycerine at optimized concentration provided the softness for

the developed medicated chewing gum. The average drug content in the developed medicated chewing gum was found to be 94.14 %, which confirmed the success of the formulation and the methodology employed for its development. The drug release profile for medicated chewing gums may significantly affected by the chewing frequency, hence the percentage drug release of the developed MCG was measured the maximum drug release of 94.37 % was reported after 30 min of dissolution study of batch F4.

The developed medicated chewing of Disulfiram was able to maintain its physical integrity during the entire duration of stability study. The results obtained from this investigation may strongly suggest the possibilities of formulating medicated chewing gums of Disulfiram for the successful and effective treatment of chronic alcoholism by producing an acute sensitivity to ethanol. Further In-vitro and In-vivo investigations may be recommended on the developed chewing gums of Disulfiram to substantiate its possibility as a better drug delivery tool.

Moreover, medicated chewing gum may be a choice for children as chewing gum is highly accepted in this age group. Medicated chewing gum should of course be considered as a drug delivery system and the same precautions should be taken as for other delivery systems. Children may prefer chewing gum as a route of drug administration than oral liquids or tablets. The use of medicated chewing gum is feasible as a local treatment of diseases or various conditions of the oral cavity. From a pharmaceutical and clinical point of view medicated chewing gum may also be an interesting drug delivery system compared with the traditional ways of administration. In the future, new medicated chewing gums are expected and may serve as a way of drug administration.

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