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PREPARATION AND *IN VITRO* EVALUATION OF DISULFIRAM LOZENGES

[1]Ms. Arifa Banu, [2]Mohd Aftab Uddin, [3]Saboor Arshi, [3]Sania Naaz, [3]Noorjaha Begum, [3]Aaine Ashfaq,

[1]Assistant Professor, Dept of Pharmaceutics, Deccan school of Pharmacy
[2]Dept of Pharmacology, Nizam Institute of Pharmacy
[3]B. Pharmacy Student, Dept of Pharmaceutics, Deccan school of Pharmacy.

Abstract:
Disulfiram, an alcohol deterrent agent, has been reformulated as a medicated lozenge to enhance patient compliance and enable sustained drug delivery through the oral mucosa. This research focuses on the evaluation and preparation of disulfiram lozenges using the heat and congealing method, incorporating natural polymers such as microcrystalline cellulose and acacia in varying concentrations across five formulations (F1–F5). The aim was to identify a formulation that offers optimal hardness, friability, weight uniformity, and sustained drug release. Organoleptic, physicochemical, and dissolution profile assessments were conducted, and drug release kinetics were analyzed using multiple models. Among the formulations, F3, containing 50 mg of acacia, demonstrated superior performance with 98.75% drug release at 40 minutes and obey constant-rate model and Higuchi release kinetics, showing a diffusion- and erosion-based release mechanism. The study highlights F3 as a promising candidate for the effective, sustained oral delivery of disulfiram, offering a convenient, water-free alternative that bypasses first-pass metabolism and enhances bioavailability for the management of alcohol dependence.

Key Words: *Lozenges, Disulfuram, Alcohol*

Corresponding author:
Arifa Banu,
Assistant Professor,
Dept of Pharmaceutics,
Deccan school of Pharmacy
Hyderabad, India

QR CODE

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INTRODUCTION:

Lozenges, also known as troches or cough drops, are solid dose form usually formulated to dissolve slowly in the mouth. They are commonly used for the localized treatment of various conditions affecting the mouth, throat, or respiratory system. Lozenges are often formulated to deliver medicinal or soothing agents to the affected area, providing relief from symptoms such as cough, sore throat, or irritation.

The primary purpose of lozenges is to provide a targeted and sustained release of active ingredients in the oral cavity. Lozenges are designed to be kept in the mouth, allowing the active ingredient to dissolve and absorbed through the mucous membranes. This localized delivery helps to alleviate symptoms by providing direct contact with the affected tissue.

Lozenges are available in a wide range of formulations, flavors, and shapes to cater to different needs and preferences. They can contain various active ingredients, including analgesics, antiseptics, antitussives, anesthetics, or natural remedies. Some common ingredients found in lozenges include menthol, eucalyptus oil, benzocaine, honey, herbal extracts, and vitamin C. The formulation of a lozenge typically involves combining the active ingredients with binders, fillers, and flavoring agents. These components are mixed and compressed into solid tablets or molded into lozenge shapes. Various excipients may also be added to enhance the stability, texture, and taste of the lozenge.

Figure No. 1.1.1 Lozenge

Disulfiram lozenges are a specific formulation of the medication disulfiram, which treats the alcohol dependence. Disulfiram is an alcohol-sensitizing agent that works by causing unpleasant symptoms when consume alcohol. It keeps individuals away from drinking alcohol by creating a dislike reaction in the body.

Disulfiram lozenges are formulated for gradual dissolution in the oral cavity, enabling the drug to be absorbed directly through the mucosal lining of the mouth. This localized delivery helps to achieve the desired effect of disulfiram when alcohol is consumed.

Alcohol Statistics:

Statistics on alcohol can cover various aspects, including consumption rates, health effects, economic impact, and social consequences. The following are some significant alcohol-related facts:

1. **Global Alcohol Consumption:** World Health Organization (WHO), reveals that per capita consumption of an alcohol worldwide in 2016 was 6.4 liters among people 15 years and older.

2. **Alcohol-related Deaths:** In 2016, (WHO) The use of alcohol was a significant factor in worldwide death tolls and was associated with nearly 3 million deaths which accounted for around 5.3% of total deaths globally. It includes deaths caused by alcohol-related diseases, injuries, accidents, and violence.

3. **Alcohol Harmful Use:** alcohol usage has been harmful is associated with various health and social problems. The World Health Organization reports that alcohol usage is associated with over 200 different health conditions and injuries, including diseases like liver cirrhosis, various types of cancer, heart-related illnesses, and mental health issues.

4. **Binge Drinking:** Consuming a significant amount of alcohol in a short period is referred to as binge drinking. It carries a high risk of serious health problems. As of 2021, around 25% of Americans 18 and older said they had engaged in excessive drinking in the past month, according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

5. **Alcohol and Youth:** Alcohol consumption among youth is worrisome because of cumulative effect over time. The Substance Abuse and Mental Health Services Administration (SAMHSA), this issue requires significant attention, in 2020 around 7.3 million individuals aged 12 to 20 in the United States has reported drinking alcohol in the past month.

6. E**conomic Impact:** Alcohol-related problems have economic implications. In the United States, the Centers for Disease Control and Prevention (CDC) estimated that excessive alcohol use cost the country approximately $249 billion in 2010, considering healthcare expenses, productivity losses, and other factors.

Merits of Lozenges:

1. It is suitable for those individual, who experience difficulty in swallowing traditional tablets or capsules.

2. It offers a convenient option for administration to both elderly and young patients.
3. It increases the amount of time the medication remains in the oral cavity, resulting in a specific effect.
4. The drug can be absorbed systemically via the buccal mucosa.
5. Sweeteners and flavoring agents in the formulation help conceal the drug's taste.
6. It may enhance the drug's bioavailability.
7. It can lessen the frequency of dosage.
8. There is no disintegration.
9. Easy to organize, with a minimum amount of kit and time.
10. The local and systemic effects through the mouth.
11. Avoid the first-pass metabolism of medicine.
12. Can be consumed without the need for water.
13. Suitable for patients who have trouble swallowing (dysphagia).
14. It is inexpensive to produce.

Limitations of Lozenges:

1. Some drugs may not be suitable for aldehyde candy bases, e.g., Benzocaine.
2. The non-ubiquitous distribution of the drug within in saliva for local therapy.
3. Possible draining of the drug from the oral cavity to the stomach along with saliva.
4. Children may mistakenly use the lozenges' dosage form as candy.
5. A hard candy lozenge requires a high temperature for its preparation.
6. There is a risk that children might confuse lozenges with candy and consume them unintentionally
7. Medications that degrade at high temperatures are unsuitable for this formulation method
8. Lozenges are not considered safe for children under the age of six
9. Medicinal compounds that have a minimal bitter taste are acceptable. The whole dosage form might be unintentionally swallowed
10. Application of Lozenges:

- The treatment of both local and systemic ailments makes use of lozenges.
- They may contain a wide range of potential medications for treating and alleviating symptoms of oral and throat illnesses, Used for ailments like fungal mouth infections, sore throat, cough, gum diseases, pharyngeal inflammation, and nasal blockage.
- These are also utilized for systemic administration of drugs to treat pain, support smoking cessation, and manage alcohol intake.
- It's used to treat the mouth and throat in order to gradually administer cough remedies or aid in digestion.
- A demulcent, an antiseptic, or an anaesthetic might be included in lozenges.
- For those patients who cannot swallow other forms of tablet or capsule formulation, lozenges offer a nice dosage form.

Materials and Methods:

Materials:

S.NO	INGREDIENTS	CATEGORY
1.	DISULFIRAM	DRUG
2.	SUCROSE	SWEETENING AGENT AND LOZENGES BASE
3.	CORN SYRUP	BINDING AGENT
4.	ACACIA	POLYMER
5.	MICROCRYSTALLINE CELLULOSE	POLYMER
6.	AMARANTH SOLUTION	COLORING AGENT
7.	VANILLIN	FLAVORING AGENT
8.	CARDAMOM OIL	LUBRICATING AGENT

Table 4.1.1 List of Materials

Method:

1. Lozenges were made using the heat and congealing technique
2. This approach involved combining water and sugar to make sugar syrup
3. Until the sugar completely dissolved in a small quantity of water and the mixture reached a temperature of 110°C, the

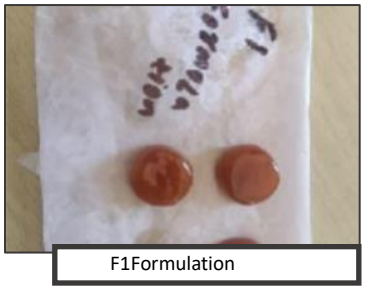
solution was heated. At this temperature, the sugar breaks down and creates a clear, thick syrup.

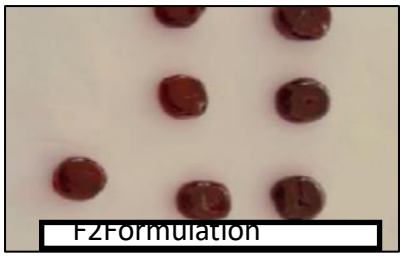
4. Corn syrup was prepared by adding the required amount of sucrose, sodium chloride, acetic acid & water and heating to dissolve completely.
5. Prepared corn syrup was added to the sugary syrup, which acts as a binding agent.
6. The sugar syrup and corn syrup were warmed to 160°C till the color changed to brilliant yellow.
7. Then add the required amount of disulfiram drug to the above solution.
8. Acacia & Micro crystalline cellulose as a polymer was added in different concentrations to the above sugar syrup to make five formulations (F1-F5).
9. Vanillin as a flavoring agent and amaranth solution as a Coloring agent were then included.
10. The temperature was lowered to 90°C.
11. The entire preparations were then filled into the cavities of molds.
12. The lozenges that were produced were maintained in desiccators to prevent moisture absorption and wrapped in aluminum foil.

Formulation table :
Total weight of each lozenge: 3 mg

INGREDIENTS (mg)	FORMULATION				
	F1	F2	F3	F4	F5
Drug (mg)	200	200	200	200	200
Sucrose (mg)	2100	2100	2100	2100	2100
Corn Syrup(mg)	830	830	830	830	830
Microcrystalline cellulose (mg)	50	100	_	_	_
Acacia (mg)	_	_	50	75	100
Vanillin (Odour)	Q. S	Q. S	Q. S	Q. S	Q. S
Colouring agent	Q. S	Q. S	Q. S	Q. S	Q. S

Table no. 4.1.1formulation


F1Formulation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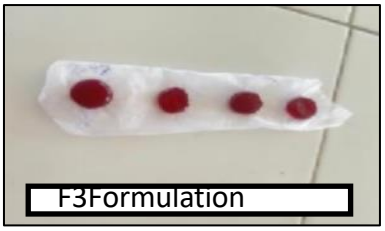
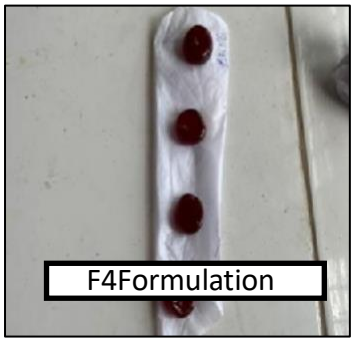
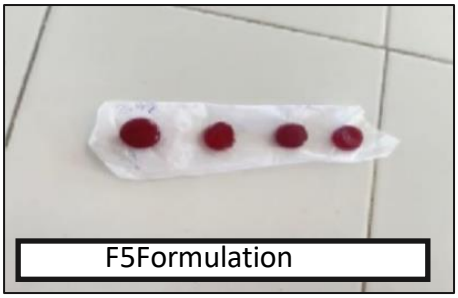

F3Formulation


F4Formulation


F5Formulation

Evaluation

Preparation of Standard graph using Methanol

Formulation of Concentrated Solution:100 mg of disulfiram was dissolved in methanol and diluted to 100 ml. in a volumetric flask, yielding a 1000 µg/ml stock solution.

Preparation of working standard solution:

10ml of stock solution is pipetted out and diluted up to 100ml with methanol.

The resulting solution had a concentration of 100mcg/ml and was labelled as "Working Standard"

Figure No. 6.5.1 Stock Solution

Preparation of serial dilutions for standard calibration curve:

Required dilutions were made by using working standard solution to give the different concentrations of disulfiram (2-10 mcg/ml) solutions. The absorbance of above solutions was recorded at λmax (216nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted by taking the concentration (on X-axis) and absorbance (on the Y-axis).

General Appearance:
Disulfiram is a white to off-white, odorless, crystalline powder with a bitter taste. It is soluble in alcohol and other organic solvents but not in water.

Solubility: Solubility was examined in a variety of solvents. It is insoluble in water but soluble in alcohol and other organic solvents like methanol, acetone, DMSO, etc

Colour: The lozenges of batches f1 to f5 exhibited a smooth appearance and no cracks were found while inspecting using magnifying glass [5x and 10x] with a very smooth flat surface and visual evaluation of the color from f1 to f5 yielded a reddish brown hue, which is aesthetically pleasing.

Odour: it was determined manually with aromatic fragrance and acceptable elegance.
Taste: sweet taste observed for all the formulations**.**
Organoleptic Properties:

Formulation	Colour	Odour	Taste
F1	Reddish brown colour	Pleasant and aromatic	Sweet
F2	Reddish brown colour	Pleasant and aromatic	Sweet
F3	Reddish brown colour	Pleasant and Aromatic	Sweet
F4	Reddish brown colour	Pleasant and Aromatic	Sweet
F5	Reddish brown colour	Pleasant and aromatic	Sweet

Table 7.3.1 Organoleptic Properties

.

Post Formulation Parameters of Disulfiram Lozenges:

Formulation	Weight Variation [gm]	Thickness [mm]	Hardness [kg/cm2]	Friability [%]	Content uniformity
F1	2.97	3.5	7.20	0.12	96.23
F2	3.01	3.12	8.12	0.13	97.43
F3	3.00	3.43	7.40	0.09	99.12
F4	2.98	3.16	7.80	0.08	99.65
F5	2.99	3.07	7.20	0.11	97.72

Table of 7.4.1 post formulation parameters

Hardness: The hardness of all formulations was measured using hardness tester. The hardness of all formulations was found to be in the range of 7.20-8.12 **[kg/cm2]** which complied with Indian Pharmacopeial specifications.

Friability: Friability of all formulations was evaluated using Friabilator. The percent friability of all formulations was found to be in the range of of0.08-0.13 % which complied with Indian Pharmacopoeial specifications.

Thickness: The thickness of all formulations was measured using a vernier caliper. The thickness of all formulations was found to be in the range 3.5-3.43mm, which complied with Indian Pharmacopoeial specifications

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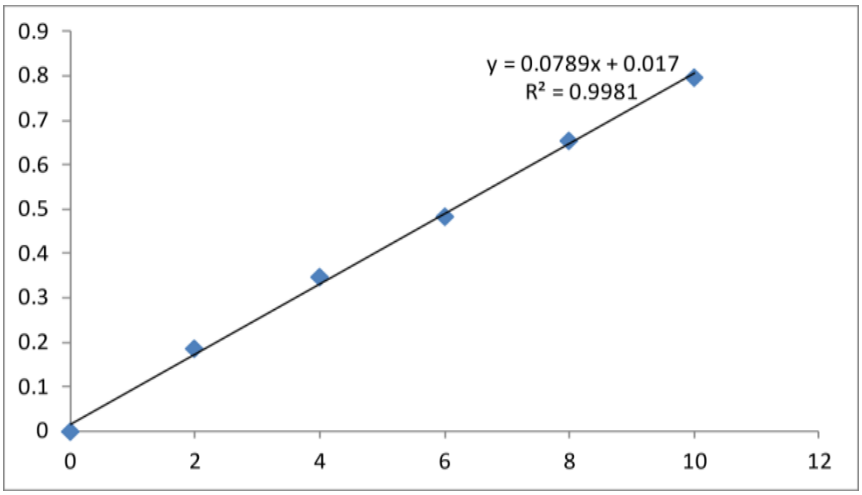
Weight Variation: The percent weight variations of all formulations were found to be in the range of lozenges dimensions were measured in the form of thickness. The values of tablet thickness were found to be in the range of 2.97-3.01gm respectively.

Content Uniformity: The drug content of all formulations was determined with the help of UV spectrophotometer. The values of all formulations were found to be in the range of 96.23-99.65%which complied with Indian Pharmacopeial monographs.

S.NO	CONCENTRATION	ABSORBANCE
1	2	0.187
2	4	0.347
3	6	0.485
4	8	0.654
5	10	0.797

Table of 7.5.1 standard graph of disulfiram

Calibration curve:



4.1 Standard Graph of Dilsufiram

- Linearity found in the range of 2-10µm/ml of concentration.
- Regression coefficient of disulfiram was found to be R^2=0.9981
- Slope of a graph was found to be m=0.2535

Dissolution Profile of Prepared Disulfiram Lozenges:

The prepared disulfiram lozenges were evaluated for dissolution. The result of all the test formulations was found within the limit and passed the test. The % drug release of all formulations (f1-f5) was found to be in the range of

22.1%-98.75%

4.1 Dissolution Profile of Disulfiram Lozenges

Time Interval(min)	Cumulative Percentage drug release (%)				
	F1	F2	F3	F4	F5
5	25.1	22.1	32.27	27.63	36.94
10	29.1	28.42	39.01	33.67	42.35
15	30.16	31.78	44.78	41.07	50.6
20	36.07	40.06	50.52	53.09	62.3
25	42.3	56.89	68.6	67.86	71.00
30	49.1	59.12	72.5	85.66	76.02
35	52.02	63.16	86.82	90.2	83.9
40	68.6	66.9	98.75	93.14	89.20

Table OF 7.8.1 cumulative percentage drug release

From the above dissolution studies, we conclude that F3 is the best formulation compared to all other formulations, it contains 50mg acacia as a natural polymer &releases 98.75% highest drug release at the end of 40 min that shows sustained action compare to other formulation unable to meet the requirements of drug release for sustained action.

f1 & f2 formulation contain MCC as a natural polymer in different amounts but did not form hard lozenges so it releases 66.9 – 68.6% drug release at the end of 40 min that does not comply for sustained action.

The optimized formulation is F3, shows steady and prolonged release of the drug at the end of 40 minutes.

Release Kinetics Study of F3 Optimized Formulation:

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT(T)	LOG (%) RELEASE	LOG(T)	LOG (%) REMAIN
0	0	0			2.000
32.27	5	2.236	1.509	0.699	1.831
39.01	10	3.162	1.591	1.000	1.785
44.78	15	3.873	1.651	1.176	1.742
50.52	20	4.472	1.703	1.301	1.694
68.6	25	5.000	1.836	1.398	1.497
72.5	30	5.477	1.860	1.477	1.439
86.82	35	5.916	1.939	1.544	1.120
98.75	40	6.325	1.995	1.602	0.097

RELEASE RATE (CUMULATIVE% RELEASE /t)	1/CUM % RELEASE	PEPPAS lo g Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
			100	4.642	4.642	0.000
6.454	0.0310	-0.491	67.73	4.642	4.076	0.565
3.901	0.0256	-0.409	60.99	4.642	3.936	0.705
2.985	0.0223	-0.349	55.22	4.642	3.808	0.834
2.526	0.0198	-0.297	49.48	4.642	3.671	0.970
2.744	0.0146	-0.164	31.4	4.642	3.155	1.487
2.417	0.0138	-0.140	27.5	4.642	3.018	1.623
2.481	0.0115	-0.061	13.18	4.642	2.362	2.279
2.469	0.0101	-0.005	1.25	4.642	1.077	3.564

	RELEASEKINEITCS				
	ZERO	**HIGUCHI**	**PEPPAS**	**FIRST**	**Hixson Crowell**
	1	**2**	**3**	**4**	**5**
	R(CvT)	**R(CvRoot(T))**	**LogT vs Log C**	**TIME vs LOG % REMAINING**	**TIME Vs (Q1/3-Qt1/3)**
Slope	2.165	14.709	0.504	-0.016	0.073
Correlation	0.9787	0.9756	0.9574	-0.8480	0.9355
R2	0.9578	0.9517	0.9166	0.7192	0.8752

From this data we can get the release kinetics of various kinetic models.

- Zero, Higuchi, first order kinetics indicates the order of release of the drug, i.e., the release.is dependent on time (first) / square root of time (Higuchi) / independent of time(zero)
- Peppa's model indicates the mechanism of drug release, i.e., release of the drug.
- The formulation is by diffusion, erosion, swelling, and by the combination of diffusion and swelling.
- Crowell model indicates that the release of drug is by dissolution.
- The values obtained in row no. 24 indicate the regression coefficient values of the respective kinetic models in order to cross-verify the formulae; the graphs are also plotted in the individual charts.
- The greater the regression coefficient greater the linearity towards the kinetic model.

From the above information it was concluded that the following F3 optimized formulation follows the zero-order kinetics and Higuchi model which reveals that the mechanism of drug release from the formulation is by dissolution, swelling and may be the combination of dissolution and swelling, Greater the regression coefficient greater the linearity towards the kinetic model.

CONCLUSION:

Medicinal lozenges contain active ingredients that are released by dissolving lozenges in the mouth and are intended to use for local and systemic treatment of oral diseases or other microbial diseases after absorption by the oral mucosa.

It is for patient comfort an easy administration without water that promotes greater patients' compliance since it can be taken anywhere and acts as best choice for alcohol dependence and other disease. It reduces the risk of SARS-COV-2 infection with disulfiram use. There were no COVID-19-related deaths among the 188SARS-COV-2 positive patients treated with disulfiram.

Disulfiram lozenges prepared by heat and concealing method using Acacia & microcrystalline cellulose as natural polymer for sustained action. In this study the disulfiram lozenges are prepared using sucrose as sweetening agent, corn sucrose as binding agent, and micro crystalline cellulose polymer were taken in 50mg & 100mg to make f1 & f2 and other three formulations (f3, f4, f5) were prepared using acacia another polymer was taken in 50mg,75mg, &100mg, total five formulations(f1-f5) were prepared to show the effect of drug release for sustained action. Vanillin as a flavoring agent was used.

So, from the above analysis it was concluded that F3 is an optimized formulation which contain 50mg acacia & releases 98.75% drug at the end of 40 minutes. It allows controlled release and increases the bioavailability of the drug in the oral cavity and bypasses first-pass metabolism. From the preformulation and post formulation parameters, it was revealed that f3 has good hardness, less friability & weight variation, which shows slow and steady drug release at the end of 40 mins.

From the release Kinetic studies, it was revealing that the f3 optimized formulation follows zero order kinetics i.e., independent of concentration, and the Higuchi model, the release of drug from this delivery system involves both dissolution and diffusion.

It provides a better dosage form that delivers the drug at a controlled rate and specific site. The lozenges provide a better option for increasing the bioavailability and decreasing the dose and dosing frequency of the drug by allowing better control of fluctuations, which cannot be observed with a conventional dosage form.

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