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Formulation and characterization of medicated chewing gum containing zingiberine for treatment of throat infections

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Abstract: The objective of this work was to formulate zingiberine as medicated chewing gum for improving its bioavailability. The objective was achieved by isolating zingiberine form ginger oil and formulating chewing gum using zein as the gum base by melting method. The formulation of ZCGs was achieved using melting method. Zein was used as the gum base, glycerine as the plasticizer, sucrose and mannitol as the sweeteners and peppermint oil as the flavoring agent. The amount of drug contained in the formulations was uniform in all the formulations and ranged from 94.4 to 96.2%. Release of drug from ZCGs in simulated saliva (pH 6.8 buffer solution) was studied by analyzing the samples at various time intervals up to 30 min. The drug release from the formulations was found to be in the range of 74.28 to 91.66 % in 30 min. Increasing the concentration of the gum base (zein) in the formulations led to a decrease in the release of the drug. The highest percentage of zingiberene was found to be released form ZCG1 after 30 min. Hence it could be considered the best formulation of all.

Keywords: Chewing gum, zein, zingiberene, isolation, HPLC

1. Introduction

The oral drug delivery system is most acceptable route of drug administration due to ease of administration than other dosage forms. In addition to confectionary role, nowadays, chewing gum is also showing best and convenient drug delivery system due to rapid absorption of agents which can be absorbed by oral cavity. Chewing gum is a drug delivery system which is going to advance more and more in nowadays researches and it seems to get more standardized in future industry because it can deliver either pharmaceuticals or nutrients which are known as medicated chewing gum (MCG) and non-MCG. MCG is supposed to act as an extended release dosage form that provides a continuous release of medicine contained [1]. Medicated chewing gums are used to deliver drug locally or systemically. Drug can be release locally for the oral treatment or may be absorbed rapidly by oral mucosa for systemic conditions, leading to fast onset of action and bioavailability. This avoids first-pass metabolism and also metabolism in gastrointestinal tract. Hence this delivery method is highly appreciable for delivery of drugs intended for quick onset of action. Several drugs worldwide are marketed as chewing gum [2] and several experimental work on chewing has drug delivery system has been reported [3-8].

Zingiberine is the active principle of ginger rhizomes and has found wide applicability in treatment of throat infections. It is poorly soluble and hence has a low bioavailability. Since throat infections need quick onset and good bioavailability for management of the infection, it must act locally as well as systematically [9]. Hence it was envisioned to prepare medicated chewing gum delivery system of zingiberine, thereby improving it patient compliance and have a quick onset of action by quick release and absorption of the drug.

2. Material and Methods

Isolation of Zingiberene from ginger oil [10]

In order to prepare the oil-sample for fractionation, ginger oil was dissolved in ethanol at a ratio of 2:1(v/w) of ethanol-to-ginger oil, and then folded in a capful of silica gel for mixed. This mixture was allowed to cool in refrigerator and kept in a desiccator until required. The column for chromatography was packed by pouring the activated silica gel into the glass column (60×2.0cm i.d.). The prepared sample was applied to the stationary phase. The contents of the column were eluted by employing hexane-diethyl ether (97:3,v/v) as the eluting solvent. The eluate was collected in fraction size of 4 mL, subjected to TLC identification. The fractions that exhibited same R_f value were pooled together, analyzed by UV-visible spectroscopy for absorption at 232 nm (λ_{max} for

zingiberene) and dried by rotary evaporation respectively. The second step fractionation process was performed as the above process taking the pooled samples with absorption at 232 nm.

Preformulation Studies of isolated zingiberene [11]

The isolated sample of zingiberene was examined for its physical appearance, color, odor and boiling point. The observed characters were compared to that reported in literature. A qualitative analysis of the miscibility of the sample of zingiberene was performed by adding a small volume of the sample to various solvents in the test tubes. The formation of separate layers indicated immiscibility (insolubility) of the sample.

Calibration curve of zingiberene by HPLC [12]

Exactly measured volume of zingiberene was dissolved in methanol to obtain a stock solution of 1 mg/mL. The stock solution was appropriately diluted with methanol to obtain working standard solutions of concentration 1-10 µg/mL. A hypersil ODS C18 column was used at column temperature of 25°C and the injection volume was 10 µL. A solvent mixture of methanol-water (7:3) was used as mobile phase and the flow rate of 1.0 mL/min was used for elution and the detection wavelength was set to 230 nm.

Formulation of Zingiberine chewing gum (ZCG) [13]

The ZCG were prepared using the conventional melting method. Briefly, the gum base (zein) was warmed on a heated water bath to obtain a molten mass and to the molten mass was added the plasticizer (glycerine) and mixed thoroughly while gently heating in a porcelain dish. The dish was kept on water bath and temperature was maintained at about 35-45°C. Accurately measured quantity of zingiberine (drug) was added to above mass. The required amount of sucrose and mannitol was added to above mixture with continuous stirring for up to 30 min. Finally the adequate amount of flavor (peppermint oil) was incorporated in the mixture. The mass was poured in to the mould and was allowed to cool at room temperature. The gum pieces were removed. The ZCG was coated with a solution of sweetener and glycerin. This mixture was heated at 60°C for 15 min and allowed to mix uniformly. Gum pieces were dipped in the solution for 1 minute to allow the liquid to spread evenly over the piece.

Table 1: Composition of ZCG

S. No.	Ingredient	ZCG1	ZCG2	ZCG3	ZCG4
1	Zein (%w/w)	25	35	45	55
2	Zingiberine (%w/w)	1	1	1	1
3	Mannitol (%w/w)	14.6	14.6	14.6	14.6
4	Sucrose (%w/w)	56	46	36	26
5	Peppermint Oil (%w/w)	0.6	0.6	0.6	0.6

Evaluation of ZCGs

Weight Variation Test

Weight of 10 chewing gums was taken in one batch and the average weight was calculated. The individual gums were then weighed and percent variation in weight from the average weight was calculated using the formula.

$$\%\ weight\ variation = \frac{(Individual\ weight - average\ weight) * 100}{Average\ weight}$$

Hardness

The hardness of the ZCG was determined using Monsanto hardness tester. The gum was placed between the plunger and the plunger was tightened to crush the ZCG. The force required was observed directly from the scale

Stickiness

On plain surface, medicated chewing gum was placed, it is subjected to collide with Teflon hammer with mass of 250 g for a period of 10 min. Hammering frequency was 30/min. After specified time, amount of mass stick to hammer was observed and reported.

Thickness

The thickness of the ZCGs was observed using vernier caliper along its lateral and longitudinal dimensions.

Uniformity of content

Chewing gum was manually divided in to pieces and transferred into a flask containing 10 ml of ethylacetate. The flask was vortexed for 15 min and the suspension was centrifuged at 10,000 rpm using a bench top centrifuge (Remi, Mumbai) for 15 min. The supernantant was collected and subjected for HPLC analysis for determining the zingiberene content as described in calibration curve method. The amount of zingiberine was calculated from the equation of the calibration curve.

In vitro release

A ZCG was immersed in pH solution maintained at pH 6.8 (buccal cavity) then placed on magnetic stirrer and subjected to stirring and after every 5 min interval 2 ml of solution taken out and replaced with fresh buffer solution. Sample was withdrawn at regular intervals of 5, 10, 15, 20, 25, and 30 min. On completion of process, all the collected samples were analyzed by HPLC for the amount of zingiberine and the release profile was determined.

3. Results and Discussion

Preformulation studies

The zingiberene isolated from the ginger oil was obtained as clear oil and its identity was confirmed by determining the absorption maximum wavelength by UV spectroscopy and later was subjected to mass spectroscopic analysis. The absorption maximum of 232 nm was obtained which was found in tandem to previously reported value for zingiberene. The mass spectra of the oil exhibited the molecular ion peak at m/z value 204 which was similar to the mass of zingiberene and also to previous study [13].

The organoleptic properties were examined and the isolated zingiberene was found to be clear, colorless oil with a characteristic strong spicy odor. The literature also reports similar organoletpic profile for zingiberene [14]. The boiling point of the isolated sample was found to be 132-134°C which has been reported in literature to be temperature at which pure zingiberene boils [9]. It was found that zingiberene was miscible with organic solvents whereas immiscible with water.

The HPLC chromatogram of zingiberene is represented in Figure 1 while the calibration curve is shown in Figure 2. The retention time of zingiberene using the selected eluting solvent system was found to be 7.4 min.

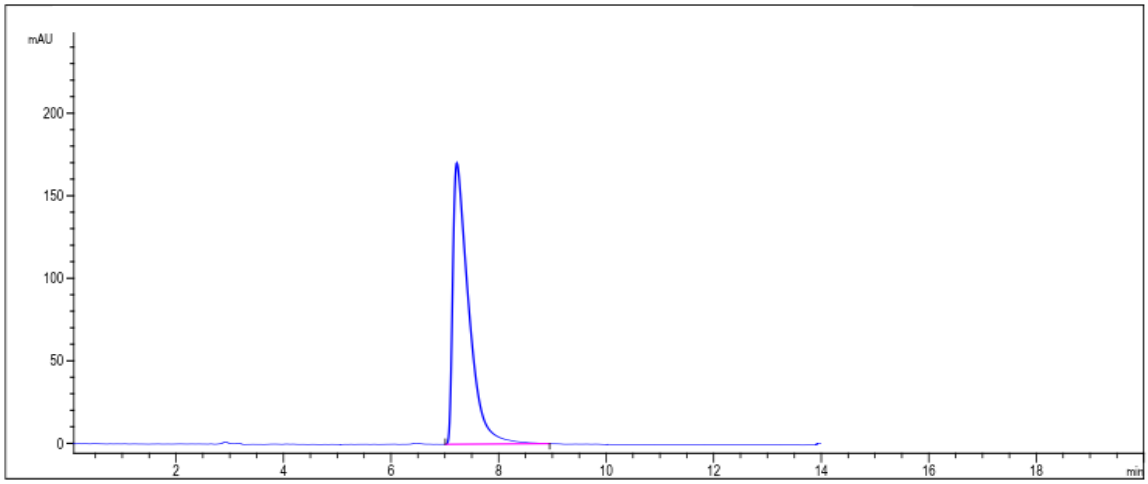

Fig 1: Chromatogram of zingiberene

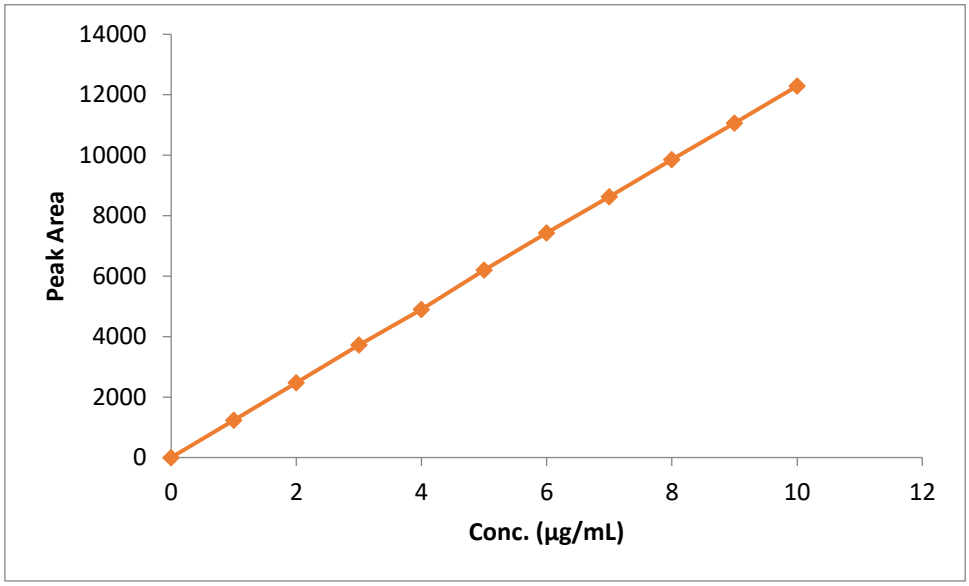

Fig 2: Calibration curve of zingiberene

Formulation of ZCGs

The formulation of ZCGs was achieved using melting method. Zein was used as the gum base, glycerine as the plasticizer, sucrose and mannitol as the sweetners and peppermint oil as the flavoring agent. The chewing gum comprises of a water insoluble portion, the gum base which has to remain in the oral cavity and a water soluble portion, the drug, which is dissolved in the gum base during the preparation process. The drug is released during the chewing process from the base and absorbs trough the vast capillary network present in the buccal cavity.

Evaluation of ZCGs

The ZCGs were evaluated for weight variation, hardness, thickness, uniformity of weight and drug release (Table 2).

Table 2: Quality parameters of ZCGs

Formulation code	Thickness (mm)		Hardness (Kg/cm^2)	Weight variation (%)	Stickiness	Drug content (%)
	Longitudnal	Lateral				
ZCG1	5.32	3.65	3.1	1.8	Non-sticky	94.9
ZCG2	5.43	3.71	3.3	2.1	Non-sticky	94.4
ZCG3	5.36	3.67	3.3	1.6	Non-sticky	96.2
ZCG4	5.39	3.72	3.5	2.4	Non-sticky	95.7

The lateral and longitudinal thickness of all formulation ranged in between 3.65 to 3.72 mm and 5.32 to 5.43 mm respectively. The uniform thickness of the formulation makes the packaging of the formulation easy and elegant. It also helps in ensuring personal compliance. Hardness of tablet of all formulation ranged from 3.1 kg/cm^2 and 3.5 kg/cm^2. The hardness of all formulation showed variation because of formulation combination. The low hardness of the formulations makes it simple to chew the formulation and depicts the proper distribution of the plasticizer throughout the formulation. The weight variation of all formulation was in the range of 1.6 to 2.4 %.

A lower variation in the weight of the gums ensures that each gum may be able to contain the same amount of drug. The amount of drug contained in the formulations was uniform in all the formulations and ranged from 94.4 to 96.2%. The uniformity in thickness, hardness, weight variation and drug content make all the formulations acceptable for ingestion.

The stickiness of the formulations was observed by hammering the gums to and observe the bells of the hammer and surface for any stuck material. All the formulations were found to be non-sticky in the test.

***In vitro* release**

Medicated chewing gums are having quite different drug release process compared to conventional oral drug delivery system. In Medicated chewing gums not only dosage form but also chewing activity of patient may also affects the drug delivery. Mechanical treatment is required to deliver the drug by the teeth but not involve in dissolution. Release of drug from ZCGs in simulated saliva (pH 6.8 buffer solution) was studied by analyzing the samples at various time intervals up to 30 min. The drug release from the formulations was found to be in the range of 74.28 to 91.66 % in 30 min (Table 3).

Table 3: In vitro release of zingiberene from ZCGs

Formulation	5 min	10 min	15 min	20 min	25 min	30 min
ZCG1	31.63	49.28	62.56	74.39	81.54	91.66
ZCG2	32.62	44.58	54.28	60.24	74.48	82.29
ZCG3	39.22	48.15	57.11	68.26	71.59	78.63
ZCG4	46.41	54.29	60.18	68.03	71.44	74.28

The drug was able to be released with ease from the formulations. As it can be seen from the observations in Table 3, increasing the concentration of the gum base (zein) in the formulations led to a decrease in the release of the drug. It could be due to the fact that the gum base is water insoluble and restricts the passage of the drug through it.

The highest percentage of zingiberene was found to be released form ZCG1 after 30 min. Hence it could be considered the best formulation of all (Figure 3).

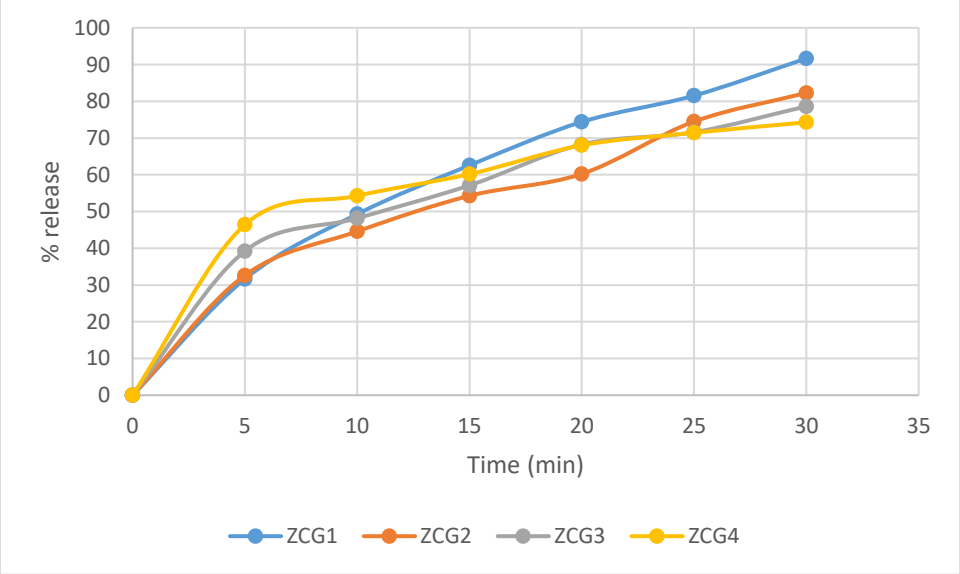

Fig 3: Percent release of zingiberene from ZCGs

4. Conclusion

Zein provides an excellent gum base for formulation of chewing gum by melting method. All formulation possessed the desired properties but the release was lower except for in ZCG1. Further studies will be needed in future to optimize the parameter for formulation of ZCGs with most desirabale properties.

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