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DEVELOPMENT AND EVALUATION OF NOVEL ORAL MEDICATED JELLIES CONTAINING CINNARIZINE FOR EFFECTIVE TREATMENT OF VERTIGO

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ABSTRACT

Introduction: Today, one of the appropriate potential alternative oral dosage forms is jelly, similar to gelatinous food and confection. The jellies can address swallowing problems, ensure patient safety, and ease of handle and taken without water. **Objective:** The aim is to develop a novel dosage form oral medicated jelly of Cinnarizine which is capable of delivering the medicament contained. **Methods:** Melting point was determined by capillary fusion method. Cinnarizine gelly was prepared by using standard procedure. **Results:** The final optimized formulation found to have 99.6% drug release. Finally oral medicated jelly can be considered as faster and attractive novel drug delivery system for drug delivery, reduced risk of overdosing, easy administration, and faster action. **Conclusion:** Oral medicated jellies of batch F10 were found good in terms of physical appearance, initial taste, after taste and over all mouth feel. Finally oral medicated jellies can be considered as faster and attractive novel drug delivery system for drug delivery, reduced risk of overdosing, easy administration, and faster action.

KEYWORDS: Cinnarizine, Medicated Jelly, Gelatin Sodium methyl Paraben.

INTRODUCTION

Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. Among solid dosage forms, tablets and capsules are most popular dosage forms.[1] The main drawback for pediatrics and geriatrics is difficulty in swallowing of solid dosage forms, which is known as dysphagia.[2,3]

Today, one of the appropriate potential alternative oral dosage forms is jelly, similar to gelatinous food and confection. The jellies can address swallowing problems, ensure patient safety, and ease of handle and taken without water.[4] Thus, jellies can improve patient compliance in addition to their flavoring taste and esthetic pleasant appearance. Jellies have advantages of both solid and liquid preparations.[2,4] Jellies intended for oral administration mean "nonflowable gelatinous preparations of definite size and shape" and must meet the requirements of dissolution and content uniformity according to the Japanese pharmacopeia.[5]

The main excipients of jellies are a gelling agent, stabilizer, preservative, and flavoring and sweetening agents. Jellies act as a vehicle for a drug which presents either as dissolved or dispersed/suspended form that can release and mix with saliva to be absorbed through gastrointestinal tract mucosa.[6] By choosing the right gelling agent, which can be either natural or synthetic hydrophilic polymers at a suitable concentration, the drug can release immediately or sustained from the jelly vehicle.[7,8]

Cinnarizine is a specific calcium channel blocker that primarily works on the central vestibular system to interfere with the signal transmission between vestibular apparatus of the inner ear and the vomiting centre of the hypothalamus.[9] Cinnarizine is a drug used for the management of labyrinthine disorder symptoms, including vertigo, tinnitus, nystagmus, nausea, and vomiting. (58) In this work attempt have done to formulate oral medicated jelly of drug Cinnarizine for effective treatment of vertigo by using suitable optimization technique and to optimize the drug release profile.[10-12]

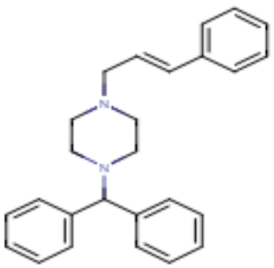


Figure 4.1: Structure of Cinnarizine.

MATERIAL AND METHODS

Cinnarigine pure drug obtained as gift sample from Ranbaxy Research laboratories, Gurgaon, India. Polymer such as Gelatin and excipients Methyl Paraben sodium,

Propyl Paraben sodium was procured from Salicylates and chemicals Ltd. Hyderabad, India.

METHODS

Organoleptic properties[13]

- **Color:** A small quantity of drug was taken in butter paper and viewed in well-illuminated place.
- **Taste and odour:** Very less quantity of drug was used to get taste with the help of tongue as well as smelled to get the odor.

Melting point: Melting point was determined by capillary fusion method.[14]

Drug Excipients compatibility study

The study was designed with different ratio for drug and excipients as per their functionality. The weighed amount of API was mixed well with a proposed proportion of individual excipients (Table 5). Blend was filled and sealed in 5 ml glass vials. Vials were subjected to 40°C ± 2°C/75% ± 5% RH and 25°C/60% RH for 4 weeks conditions. The initial samples were analyzed immediately and used as control.[25] The samples were observed for physical changes[26] like discoloration, liquefaction.

Formulation Development

Oral medicated jelly each weighing 20 g, containing 25 mg of drug was formulated as: 1st Gelatin was dissolved initially in known amount of water and was kept on sonicator for complete solubility. Now drug Cinnarizine was added to the above solution when solution becomes completely transparent and was mixed completely. Sweeteners and flavor was added. Preservatives Sodium methyl paraben and Sodium propyl paraben were added. Finally volume of gel was made up-to 20g with purified water.[4]

Table 1: Formulations of oral medicated jelly.

Ingredients (grams)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug Cinnarizine	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
Gelatin	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Sucrose	5	5	5	5	5	5	5	5	5	5
Sucralose	-	0.1	0.05	0.04	0.05	0.06	0.1	0.1	0.04	0.04
Strawberry flavor	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Butylated hydroxyl anisole	0.02	0.02	-	-	-	-	-	-	-	-
Propyl gallate	-	-	-	-	-	-	-	0.04	-	-
Sodium methyl Paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Sodium Propyl paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Tri-sodium citrate	-	-	-	-	-	-	-	-	0.02	0.02
Citric acid dehydrate	-	-	-	-	-	-	-	-	0.02	0.02
Demineralized water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight(g)	20	20	20	20	20	20	20	20	20	20

RESULTS AND DISCUSSION

A) API Characterization

- Description : Crystalline powder
- Color : White
- Odor : Bitter
- Melting point : 119-121.50 C

Drug-Excipients compatibility studies

The samples of Drug-excipients compatibility studies were periodically examined visually against control samples kept at 25^0C. And results are shown in below table.

RESULT: On visual observation it was found that no changes appeared at 2-8^{0}C, 40^{0}C, and 40^{0}C/75 % RH suggests that drug and excipients are stable at higher temperature and in the presence of moisture.

Evaluation and Optimization of formulation Batches: Appearance was found to be good in F1, Initial taste was found to be good but final taste was found to be slightly bitter in taste and less sweet. So in formulation F2, Sucralose has been added to mask bitter taste and get desired sweetness and good mouth feel.

In F2 formulation initial taste as found to be oversweet and after taste was found to be bitter along with poor mouth feel so to improve after taste BHA will be removed and sweetness will be optimized.

Table 2: Observation made for batches F1 and F2.

Ingredients(grams)	F1	Observation	Ingredients (grams)	F2	Observation
Drug Cinnarizine	0.12	Appearance- good	Drug Cinnarizine	0.12	Appearance- good
Gelatin	1.5	Initial taste- good	Gelatin	1.5	Initial taste- oversweet
Sucrose	5	Final taste- bitter	Sucrose	5	
Sucralose	-	Mouth feel- Poor	Sucralose	0.1	Final taste- bitter
Strawberry flavor	0.2		Strawberry flavor	0.2	Mouth feel- poor

Butylated hydroxy anisole	0.02		Butylated hydroxy anisole	0.02	
Sodium methyl Paraben	0.02		Sodium methyl Paraben	0.02	
Sodium Propyl paraben	0.02		Sodium Propyl paraben	0.02	
Demineralized water	q.s		Demineralized water	q.s	
Total weight	20		Total weight	20	

- In F3 formulation, appearance and initial taste was found to be good but still after taste was found to be bitter with poor mouth feel.
- In F4 formulation, appearance, initial taste and final taste was found to be good but overall mouth feel was poor.

Table 3: Observation made for batches F3 and F4.

Ingredients (grams)	F3	Observation	Ingredients (grams)	F4	Observation
Drug Cinnarizine	0.12	Appearance-good	Drug Cinnarizine	0.12	Appearance- good Initial taste- good Final taste-good Mouth feel- poor
Gelatin	1.5	Initial taste-good	Gelatin	1.5	
Sucrose	5	Final taste-slight bitter	Sucrose	5	
Sucralose	0.05	Mouth feel- poor	Sucralose	0.04	
Strawberry flavor	0.2		Strawberry flavor	0.2	
Sodium methyl Paraben	0.02		Sodium methyl Paraben	0.02	
Sodium Propyl paraben	0.02		Sodium Propyl paraben	0.02	
Demineralized water	q.s		Demineralized water	q.s	
Total weight	20		Total weight	20	

- Same F4 formulation was repeated and In F5 formulation also, appearance, initial taste and final taste was found to be good but overall mouth feel was poor. So sweetness will be optimized to improve the taste.
- In F6 formulation also, appearance, initial taste and final taste was found to be good but overall mouth feel was poor. So sweetness will be optimized to improve the taste.

Table 4: Observation made for batches F5 and F6.

Ingredients (grams)	F5	Observation	Ingredients (grams)	F6	Observation
Drug Cinnarizine	0.12	Appearance- good	Drug Cinnarizine	0.12	Appearance- good Initial taste- good Final taste-good Mouth feel- poor
Gelatin	1.5	Initial taste- good	Gelatin	1.5	
Sucrose	5	Final taste-good	Sucrose	5	
Sucralose	0.05	Mouth feel- poor	Sucralose	0.06	
Strawberry flavor	0.2		Strawberry flavor	0.2	
Sodium methyl Paraben	0.02		Sodium methyl Paraben	0.02	
Sodium Propyl paraben	0.02		Sodium Propyl paraben	0.02	
Demineralized water	q.s		Demineralized water	q.s	
Total weight	20		Total weight	20	

- In F7 formulation appearance, initial taste and final taste and overall mouth feel was found to be good.
- In F8 formulation also, appearance, initial taste and final taste was found to be poor and overall mouth feel was also poor. So in next formulation Propyl gallate will be removed.

Table 5: Observation made for batches F7 and F8.

Ingredients (grams)	F7	Observation	Ingredients (grams)	F8	Observation
Drug X	0.12	Appearance-good	Drug X	0.12	Appearance- good Initial taste- bitter Final taste-bitter Mouth feel-poor
Gelatin	1.5	Initial taste- good	Gelatin	1.5	
Sucrose	5	Final taste-good	Sucrose	5	
Sucralose	0.1	Mouth feel-good	Sucralose	0.1	
Strawberry flavor	0.2		Strawberry flavor	0.2	
Propyl gallate	-		Propyl gallate	0.04	
Sodium methyl Paraben	0.02		Sodium methyl Paraben	0.02	
Sodium Propyl paraben	0.02		Sodium Propyl paraben	0.02	
De-mineralized water	q.s		De-mineralized water	q.s	
Total weight	20		Total weight	20	

- In F9 formulation appearance, initial taste and final taste and overall mouth feel was found to be good.
- In F10 formulation also appearance, initial taste and final taste and overall mouth feel was found to be good.

Table 6: Observation made for batches F9 and F10.

Ingredients (grams)	F9	Observation	Ingredients (grams)	F10	Observation
Drug Cinnarizine	0.12	Appearance- good	Drug Cinnarizine	0.12	Appearance- good Initial taste- good Final taste-good Mouth feel-good
Gelatin	1.5	Initial taste- good	Gelatin	1.5	
Sucrose	5	Final taste-good	Sucrose	5	
Sucralose	0.04	Mouth feel-good	Sucralose	0.04	
Strawberry flavor	0.2		Strawberry flavor	0.2	
Tri sodium citrate	0.02		Tri sodium citrate	0.02	
Citric acid dehydrate	0.02		Citric acid dehydrate	0.02	
Sodium methyl Paraben	0.02		Sodium methyl Paraben	0.02	
Sodium Propyl paraben	0.02		Sodium Propyl paraben	0.02	
Demineralized water	q.s		Demineralized water	q.s	
Total weight	20		Total weight	20	

Evaluation of formulation

1. Physical Appearance: Texture and clarity of the oral medicated jelly will be evaluated in terms of stickiness and grittiness by mildly rubbing the gel between two fingers. Odour can also be evaluated by physical observation.

Result: The Texture and clarity of the oral medicated jelly was found to be good and odour was found to be pleasant.

2. pH of oral medicated jelly: The pH of oral medicated jelly can be measured by using digital Ph meter at room temperature. The pH has got the influence of the taste and stability of the oral medicated jelly.

Result: The pH of oral medicated jelly was found to be 5.8.

3. Syneresis: Syneresis means contraction of gel upon standing and separation of water from the gel. Syneresis is more pronounced where low concentration of gelling agent is used. Gel will be kept under scrutiny for sign of syneresis.

Result: When jellies were properly wrapped there was no water loss found and initial weight and final weight was found to be same for each jelly i.e. 20g each.

4. Taste masking: Five gram of optimized formulation will be evaluated by taking taste observation from different selected people or by giving to taste panel experts and they will be asked to comment on the bitterness, sweetness and flavor of the optimized formulation.

Result: Taste evaluation of F10: The final batch i.e. F10 was evaluated on the basis of organoleptic parameters. Oral medicated jellies were tested on human respondents for evaluation of following organoleptic parameters: Number of human respondents: 22

1. Initial Taste
2. After Taste
3. Mouth feel

Table 7: Taste Evaluation

Parameters	Parameters	No. of respondents
Initial Taste	Average	0
	Good	8
	Very good	14
After Taste	Average	2
	Good	13
	Very good	7
Mouth feel	Average	4
	Good	14
	Very good	4

Drug content: It can be determined by taking a weighed amount of oral medicated jelly and then transferring in 900 ml of buffer in a volumetric flask and final volume will be made up to 1000 ml. From that solution 1 ml will be pipette out and then will be diluted to 50 ml with buffer then the sample will be assayed by spectrophotometer after filtering the sample through 0.45µ filters.

Result: Assay for drug content: Assay was calculated for final optimized batch F 10.

Table 8: Absorbance calculated for assay.

Observation	Absorbance	Concentration (µg/ ml)	% Assay
Dilution 1	1.552	119.26	99.38
Dilution 2	1.552	119.26	99.38
Dilution3	1.554	119.41	99.50

Assay for final batch was calculated as 99.42%.
Calculation was done using the following equation of the calibration curve.

$$Y = 0.0645 X + 0.0135$$

Where, Y = Absorbance, X= Concentration.

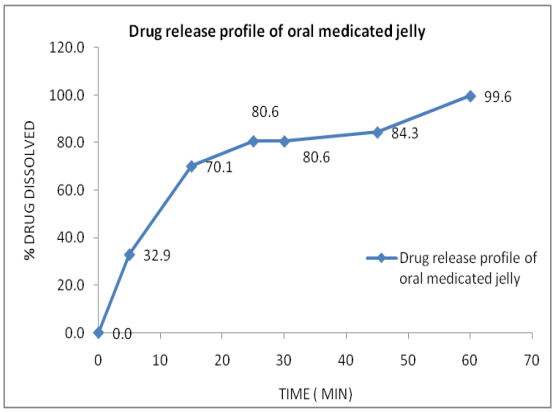
***6. In-vitro* Dissolution studies:** The *In vitro* dissolution rate will be studies by USP apparatus II employing a paddle stirrer.

RESULT

The in-vitro drug release studies of drug was performed in Phosphate buffer (pH 6.8, 900 ml) at agitation speed of 50 rpm in USP-dissolution apparatus type II. The percentage release (CPR) was calculated for final optimized batch and plotted against time.

Table 19: Percentage Cumulative release of batch F10.

Time (minutes)	Percent cumulative release
0	0
5	28.2
15	62.3
25	78.5
35	80.1
45	86.4
65	99.6



Calculation was done using the linear equation

The amount of drug released from Oral medicated jelly = 119.58 mg

The amount of drug released was calculated based on label claim i.e. 120 mg

The actual amount of drug released from Oral medicated jelly 99.6%

RESULT: The *in-vitro* drug release study of final batch was carried out. The final optimized formulation found to have 99.6% drug release. Finally oral medicated jelly can be considered as faster and attractive novel drug delivery system for drug delivery, reduced risk of overdosing, easy administration, and faster action.

CONCLUSION

The present study involved the preparation oral medicated jelly of drug in gelatin base and different concentration of sweeteners, preservative, antioxidants etc. Oral medicated jelly was evaluated for physical appearance, syneresis, pH, taste masking and in-vitro drug release studies. The various formulations of oral medicated jelly of drug were optimized on the basis of organoleptic parameters such as initial taste, mouth feel, and aftertaste.

Oral medicated jellies of batch F10 were found good in terms of physical appearance, initial taste, after taste and over all mouth feel. The in-vitro drug release study of final batch was carried out. The final optimized formulation found to have 99.6% drug release.

Finally oral medicated jellies can be considered as faster and attractive novel drug delivery system for drug delivery, reduced risk of overdosing, easy administration, and faster action.[15]

CONFLICT OF INTEREST

No conflicts of interest are mentioned by the researchers.

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