TASTE MASKING IN HERBAL SYRUP CONTAINING BITTER DRUGS: FORMULATION, EVALUATION AND STABILITY STUDIES

Diksha Khobragade* & Rajesh Mujariya

Institute of Pharmaceutical Science and Research (IPSR) Balaghat M.P. India

Abstract:

Taste masking of bitter drugs has been challenge to scientists as taste is an important parameter governing patient compliance. Several oral pharmaceuticals, numerous food and beverage products and bulking agents have unpleasant bitter taste. In order to ensure patient compliance bitterness masking becomes essential. The desire of improving the palatability has prompted the development of numerous formulations with improved performance and acceptability. Several approaches namely sensory, barrier, chemical and complexation have been tried to mask the unpleasant taste of formulation. The purpose of the present was to evaluate the bitterness of the prepared syrup formulation by using human taste sensor.

Keywords: Taste masking, Human taste sensor, Bitterness, Complexation,

Introduction

Taste masking, a perceived reduction of an undesirable taste that would otherwise exist. The ideal solution to reduce or inhibit bitterness is the discovery of a universal inhibitor of all bitter tasting substances that does not affect the other taste modalities such as sweetness or saltiness, as bitterness, a taste modality since the earliest days of recorded civilization [1, 2]. Evolution and

adaptation of a sensitivity and negative hedonic response to bitter taste of materials from plant sources evolved mainly through forgoing alkaloids found in many plants. Bitter taste is unpleasant to the human oral sensation and, therefore, formulation of foods, beverages and oral pharmaceuticals attempt to alleviate bitter taste perception [3, 4]. Hence bitterness control has become of commercial importance to a pharmaceutical chemist.

Hence, masking the bitter taste of drugs is a potential tool for improvement of patient compliance, which in turn decides the commercial success of the product [5]. To improve the palatability of a pharmaceutical product, many techniques have been developed, which have not only improved the taste of the product, but also the stability of the drug in the formulation and the overall performance of the product [6, 7]. The available technologies effectively mask the objectionable bitter taste of drugs but require skillful application without affecting delivery of the drug. With application of these techniques and proper evaluation of taste masking effect one can improve product preference to a large extent [8]. Moreover, the development of taste masking methodology requires great technical skill, and the need for massive experimentation. We have previously reported the quantitative evaluation of bitterness of various drug formulations, such as antibiotics and amino acid preparations, etc. using a taste sensor [9-11].

The goal of the present study, therefore was to minimize the bitter taste of a syrup prepared by using Bhuineem and Phyllanthus extracts as both the herbs are well known for imparting bitter taste by using the human taste sensor for their hepatoprotective activity.

Materials and Methods:

Materials: Bhuineem extract, Phyllanthus Extract and the other excipients like Glycerine, Sorbitol solution, Xanthum gum, Citric acid, Sucrose IP, Methyl paraben, Propyl paraben,

Sodium citrate, Propylene glycol, etc were purchased from SD Fines Chemical, Mumbai. All other chemicals were used as analytical grade.

Preformulation study: The overall objective of preformulation testing is to generate information useful to the formulator in developing stable & bioavailable dosage forms, which can be mass produced. Preformulation studies include studies of the physiochemical properties of herbal extracts and an assessment of their relevance to the final formulation, the chemical and physical stability of the herbal extracts and chemical/physical compatibility of the active constitute with potential excipients.

Methodology:

a) Preparation of syrup.

Preparation of extract solution:

Extracts of Bhuineem and Phyllanthus were weighed accurately and mixed separately with specified quantity of purified water and stirred thoroughly by using mechanical stirrer..

Preparation of syrup base:

Weighed accurate quantity of sucrose, purified water, citric acid & allowed to boil at a temperature about $110^0C \pm 2^0C$ over hot plate, until a clear light yellow syrupy liquid was formed and after the solution comes to room temperature, Sodium Citrate in purified water solution was added and stirred continuously.

Preparation of preservatives solution:

Combination of Methyl Paraben & Propyl Paraben dissolved in propylene glycol as a cosolvent before addition to the syrup and the weighted quantity of other excipients was added and make up the required volume with purified water shown in **Table -3.**

Stability studies

Stability study of the prepared syrup was carried out for three months data. The syrup was kept at different temperature and relative humidity as per ICH guidelines (25^0 C & 60 % RH, 30^0 C & 65 % RH, 40^0 C & 75 % RH). The Physical Parameters like pH, taste, odour and other chemical parameters were checked on the weekly basis.

Results and Discussion:

An acceptable syrup formulation containing Phyllanthus and Bhuineem extracts as active bitter principles was developed by modifying the taste of final preparation using citric acid, xanthum gum, sodium chloride, masking agent, and flavors like Honey, Orange, Melon. Finally, sensory evaluations of ten expert tasters have shown that Honey flavor was the best among these three flavors [12-17].

Conclusion:

In the present study attempt has been made to minimize the bitter taste of a syrup prepared using Bhuineem and Phyllanthus extracts. It is possible to prepare taste masked syrup formulation with improved palatability by using Citric acid, Sodium citrate, Xanthum gum, Sodium chloride, Sodium saccharine, Masking agent, and flavors like Honey, Orange and Melon. Finally, sensory evaluations of ten expert tasters have shown that Honey flavor was the best among these three flavors. The optimized syrup formulation during this experiment was quite acceptable in comparison to the syrup prepared without taste masking efforts.

Step 1: Optimization of sugar quantity & process

Five samples have been prepared and evaluated for the following parameters

Syrup base	Parameters					
	Bitterness	**Aftertaste**	**Mouthfeel**	**Sweetness**	**Overall acceptability**	**Scores**
A	Moderate	Strong	OK	Moderate	No	1
B	Moderate	Strong	OK	Moderate	No	2
C	Moderate	Moderate	OK	Moderate	No	3
D	Moderate	Moderate	OK	Moderate	No	4
E	Mild	Mild	OK	Strong	Yes	5

Inference: Taste evaluation of samples under evaluation containing 90 % w/v sugar was better tasting than the remaining samples.

Step 2: Selection and optimization of Acids/Buffering agents

Six samples have been prepared and evaluated for the following parameters**.**

Syrup Base	Parameters					
	Bitterness	**Aftertaste**	**Mouthfeel**	**Sweetness**	**Overall acceptability**	**Scores**
A	Moderate	Moderate	OK	Moderate	NO	7
B	Moderate	Moderate	OK	Moderate	NO	5
C	Moderate	Moderate	OK	Moderate	NO	4
D	Moderate	Moderate	OK	Moderate	NO	2
E	Mild	Mild	OK	Moderate	YES	1
F	Moderate	Moderate	OK	Moderate	NO	3
G	Moderate	Moderate	OK	Moderate	NO	6

Inference: Taste evaluation of samples under evaluation containing Citric acid 0.5 % & Sodium citrate 1.0 % was better tasting than the remaining samples.

Step 3: **Selection and optimization of salts concentration**

Five samples have been prepared and evaluated for the following parameters

Syrup Base	Parameters					
	Bitterness	**Aftertaste**	**Mouthfeel**	**Sweetness**	**Overall acceptability**	**Scores**
A	Moderate	Moderate	OK	Moderate	NO	1
B	Mild	Mild	OK	Moderate	YES	6
C	Moderate	Moderate	OK	Moderate	NO	4
D	Moderate	Moderate	OK	Moderate	NO	5
E	Moderate	Moderate	OK	Moderate	NO	2
F	Moderate	Moderate	OK	Moderate	NO	3

Inference: Taste evaluation of samples under evaluation containing Sodium chloride 1.0 % was better tasting than the remaining samples.

Step 4: Selection and optimization of viscosity modifiers

Five samples have been prepared and evaluated for the following parameters

Syrup Base	Parameters					
	Bitterness	**Aftertaste**	**Mouthfeel**	**Sweetness**	**Overall acceptability**	**Scores**
A	Moderate	Moderate	OK	Moderate	NO	1
B	Mild	Mild	OK	Moderate	YES	6
C	Moderate	Moderate	OK	Moderate	NO	4
D	Moderate	Moderate	OK	Moderate	NO	5
E	Moderate	Moderate	OK	Moderate	NO	2
F	Moderate	Moderate	OK	Moderate	NO	3

Inference: Taste evaluation of samples under evaluation containing Xanthum gum 0.1 % was better tasting than the remaining samples.

Step 5: Selection and optimization of Artificial sweetners

Six samples have been prepared and evaluated for the following parameters.

Syrup Base	Parameters					
	Bitterness	**Aftertaste**	**Mouthfeel**	**Sweetness**	**Overall acceptability**	**Scores**
A	Moderate	Moderate	OK	Moderate	NO	1
B	Mild	Mild	OK	Moderate	YES	7
C	Moderate	Moderate	OK	Moderate	NO	5
D	Moderate	Moderate	OK	Moderate	NO	6
E	Moderate	Moderate	OK	Moderate	NO	4
F	Moderate	Moderate	OK	Moderate	NO	2
G	Moderate	Moderate	OK	Moderate	NO	3

Inference: : Taste evaluation of samples under evaluation containing Sodium Saccharine 2 mg/ml was better tasting than the remaining samples.

Step 6: Selection and optimization of masking agent

Five samples have been prepared and evaluated for the following parameters

Syrup Base	Parameters					
	Bitterness	**Aftertaste**	**Mouthfeel**	**Sweetness**	**Overall acceptability**	**Scores**
A	Moderate	Moderate	OK	Moderate	NO	1
B	NO	Mild	OK	Moderate	YES	5
C	Moderate	Moderate	OK	Moderate	NO	2
D	Moderate	Moderate	OK	Moderate	NO	3
E	Moderate	Moderate	OK	Moderate	NO	4

Inference: Taste evaluation of samples under evaluation containing Masking flavour (0.3 %) from Symrise was better tasting than the remaining samples.

Step 7: Selection and optimization of Flavouring agent:

Eight samples have been prepared and evaluated for the following parameters.

Syrup Base	Parameters					
	Bitterness	**Aftertaste**	**Mouthfeel**	**Sweetness**	**Overall acceptability**	**Scores**
A	Moderate	Moderate	OK	Moderate	NO	1
B	Mild	Moderate	OK	Moderate	NO	3
C	NO	Mild	OK	Moderate	YES	6
D	NO	Mild	OK	Moderate	YES	6
E	Mild	Moderate	OK	Moderate	NO	2
F	NO	Mild	OK	Moderate	YES	6
G	Mild	Moderate	OK	Moderate	NO	4
H	Mild	Moderate	OK	Moderate	NO	5

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Inference: Taste evaluation of samples under evaluation containing Masking flavour (0.3 %v/v) and of flavouring agents (0.1 % v/v) Melon, Orange, Honey flavours was better tasting than the remaining samples.

Step 8: Comparative evaluation of Flavouring agents:

Syrup Base	Parameters					
	Bitterness	**Aftertaste**	**Mouthfeel**	**Sweetness**	**Overall acceptability**	**Scores**
A	Moderate	Moderate	OK	Moderate	NO	1
B	Mild	Mild	OK	Moderate	NO	2
C	Mild	Moderate	OK	Moderate	NO	3
D	NO	NO	OK	Moderate	YES	4

Inference: 40 % of the participants preferred Honey flavour over other three samples under evaluation.

Table 1: Phyllanthus Extract Compatibility studies data

S.No.	Sample	Drug: Excipient Ratio	Initial	Observations 40^0 C			
				1 wk	2 wk	3 wk	4 wk
1.	Phyllanthus Ext.+ Purified Water	0. 5: 100	Clear Solution	NC	NC	NC	NC
2.	Phyllanthus Ext.+ Methyl paraben+ Water	0. 5: 0.18: 100	Clear Solution	NC	NC	NC	NC
3.	Phyllanthus Ext.+ Propyl paraben+ Water	0. 5 :0.02:100	Clear Solution	NC	NC	NC	NC
4.	Phyllanthus Ext +Methyl paraben+ Propyl paraben+ Water	0. 5: 0.18: 0.02: 100	Clear Solution	NC	NC	NC	NC
5.	Phyllanthus Ext + Methyl paraben + Propyl paraben + Sorbitol + Water	0. 5: 0.18: 0.02: 5:100	Clear Solution	NC	NC	NC	NC
6.	Phyllanthus Ext + Methyl paraben+ Propyl paraben + Propylene glycol + Water	0. 5:0.18: 0.02 :1:100	Clear Solution	NC	NC	NC	NC
7.	Phyllanthus Ext + Methyl paraben+ Propyl paraben + Glycerin + Water	0. 5: 0.18:0.02 :5: 100	Clear Solution	NC	NC	NC	NC
8.	Phyllanthus Ext + Methyl paraben + Propyl paraben + Sodium chloride + Water	0. 5: 0.18: 0.02: 1: 100	Clear Solution	NC	NC	NC	NC
9.	Phyllanthus Ext + Methyl paraben + Propyl paraben + Honey flavour + Water	0. 5: 0.18: 0.02: 0.5:100	Clear Solution	NC	NC	NC	NC
10.	Phyllanthus Ext + Methyl paraben + Propyl paraben + Sod. saccharin+ Water	0.25: 0.18: 0.02: 2:100	Clear Solution	NC	NC	NC	NC
11.	Phyllanthus Ext + Methyl paraben + Propyl paraben + Citric acid + Water	0. 5: 0.18: 0.02: 0.5 : 100	Clear Solution	NC	NC	NC	NC

Table 2: Bhuineem Extract Compatibility studies data

S.N.	Sample	Drug Excipient Ratio	Initial	Observations			
				40^0 C			
				1wk	2wk	3 wk	4 wk
1.	Bhuineem Ext.+ Purified Water	1:100	Clear Solution	NC	NC	NC	NC
2.	Bhuineem Ext + Methyl paraben+ Water	1: 0.18: 100	Clear Solution	NC	NC	NC	NC
3.	Bhuineem Ext + Propyl paraben+ Water	1: 0.02: 100	Clear Solution	NC	NC	NC	NC
4.	Bhuineem Ext +Methyl paraben+ Propyl paraben + Water	1: 0.18: 0.02: 100	Clear Solution	NC	NC	NC	NC
5.	Bhuineem Ext + Methyl paraben + Propyl paraben + Sorbitol + Water	1: 0.18: 0.02: 5 :100	Clear Solution	NC	NC	NC	NC
6.	Bhuineem Ext + Methyl paraben+ Propyl paraben + Propylene glycol + Water	1: 0.18: 0.02: 1: 100	Clear Solution	NC	NC	NC	NC
7.	Bhuineem Ext + Methyl paraben+ Propyl paraben + Glycerin + Water	1: 0.18: 0.02: 5:100	Clear Solution	NC	NC	NC	NC
8.	Bhuineem Ext + Methyl paraben + Propyl paraben + Sodium chloride + Water	1: 0.18: 0.02: 1: 100	Clear Solution	NC	NC	NC	NC
9.	Bhuineem Ext + Methyl paraben + Propyl paraben + Honey flavour+ Water	1: 0.18: 0.02: 0.5:100	Clear Solution	NC	NC	NC	NC
10.	Bhuineem Ext + Methyl paraben + Propyl paraben + Sod. Saccharin+ Water	1: 0.18: 0.02: 2 : 100	Clear Solution	NC	NC	NC	NC
11.	Bhuineem Ext + Methyl paraben + Propyl paraben + Citric acid + Water	1: 0.18: 0.02: 0.5 : 100	Clear Solution	NC	NC	NC	NC
12.	Bhuineem Ext + Phyllanthus Ext + Water	1: 0.5 : 100	Clear Solution	NC	NC	NC	NC

NC – No change in description **PM – Particulate matter**

In Process Observation:

S.No.	Parmeters	Purified Water	Extract solution	Final syrup
1.	pH	6.40	5.24	4.02
2.	Description	Clear	Hazy	Brown syrupy liquid

Table 3: Stability data sheet [Accelerated]

Accelerated Stability Data (ICH ZONE: I, II, III & IV)					
Storage condition/ sampling interval	**Description**	**pH**	**Wt/ml (gm/cc)**	**Assay (By HPTLC)**	
Specification	Brown coloured syrup with characteristic taste of Honey flavour.	3.5-4.5	1.11- 1.16	Phyllanthin Content % w/w	Rutin Content % w/w
Initial	Brown coloured syrupy with characteristic taste of Honey flavour.	3.98	1.1432	0.0106	0.0603
1 Month @ 40°C & 75% RH	Brown coloured syrupy with characteristic taste of Honey flavour.	4.01	1.1544	0.0115	0.0601
2 Months @ 40°C & 75% RH	Brown coloured syrupy with characteristic taste of Honey flavour.	4.02	1.1231	0.0121	0.0689
3 Months @ 40°C & 75% RH	Brown coloured syrupy with characteristic taste of Honey flavour.	4.04	1.1318	0.0110	0.0585

Table 4: Stability data sheet [Real time]

Real Time Stability Data (ICH ZONE: I & II)					
Storage condition/ sampling interval	**Description**	**pH**	**Wt/ml (gm/cc)**	**Assay (By HPTLC)**	
Specification	Brown coloured syrupy liquid characteristic taste of Honey flavour.	3.5-4.5	1.11- 1.16	Phyllanthin Content % w/w	Rutin Content % w/w
a) Initial	Brown coloured syrupy liquid Characteristic taste of Honey flavour.	3.98	1.1432	0.0106	0.0603
b) 3 Months @ 25°C & 60 % RH	Brown coloured syrupy liquid Characteristic taste of Honey flavour.	4.00	1.1420	0.0123	0.0600

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