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FORMULATION DEVELOPMENT & EVALUATION OF RIBOFLAVIN CHEWABLE TABLET USING *MORINGA OLIFERA GUM POWER* FOR TASTE MASKING AND BETTER ABSORPTION

Muskan Kushwah[1], Shweta Shukla[2], Rupali Sharke[3]
Bhabha Pharmacy Research Institute, BHABHA University, Bhopal

Abstract:
The chewable tablets of taste masked Riboflavin were successfully prepared by direct compression method and wet granulation method. 12 batches using various additives were prepared and evaluated within aim of presenting Riboflavin taste masked by the chewable tablet. Drug Excipients compatibility study was performed by FTIR. The unpleasant taste of the Riboflavin was masked by intra-granular addition of dried calcium carbonate, calcium carbonate from oyster shell and the extra- granular addition of sweeteners and flavoring agents. Taste masking study was done by using alkalizing agent in different ratio. Riboflavin taste masking was increased when dried calcium carbonate quantity was increased because of reduction of the solubility of Riboflavin. Oyster shell calcium carbonate when added to the drug did not masked the taste due to the gritty nature of it.
F_5 batch showed less bitterness, low disintegration time and fast dissolution time and hence was taken further comparing with the innovator drug. In the present study disintegrating properties of Moringa olifera gum powder had been studied in comparison with other commercially available super disintegrates. The isolated natural disintegrant exhibits faster drug dissolution and disintegration. The isolated gum powder can be effectively used as disintegrate for Riboflavin with the added advantage of the folkloric immune booster activity of it.

Keyword: Riboflavin, Moringa olifera, Riboflavin, Taste masking, immune booster.

Corresponding author:
Muskan Kushwah,
Bhabha Pharmacy Research Institute, BHABHA University, Bhopal
.

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INTRODUCTION:

A solid dosage form is drug delivery system that includes tablets, capsules, sachets, and pills as well as a bulk or unit-dose powders and granules. Among the various dosage forms oral solid dosage forms have greater importance and occupy a prime role in the pharmaceutical market. Oral route of drug administration is widely acceptable and drugs administered orally as solid dosage form represents the preferred class of products. Over 90% of drugs formulated to produce systemic effects are produced as solid dosage forms. Because of these reason when ever New chemical entity (NCE) has discovered, which shows a sufficient pharmacological action, first the pharmaceutical company asks whether the drug is successfully administered by oral route or not. As a natural defense mechanism to prevent infection or dehydration many trees and shrubs are known to produce an aqueous thick exudation when the plants bark is injured. Eventually the solution dries up in contract with sunlight and air and a hard transparent brown-tint glass mass formed. This solid mass is known as Natural gum[1]. Excipients play an important role in dosage forms such as tablet, capsule, lotions, suspensions, syrups and ointments. Plant products serve as an alternative to synthetic products because of its local accessibility, environment friendly nature and low prices compared to imported synthetic products[2]. Plantago ovata mucilage has been evaluated in fast disintegrating tablet. Ocimum Americanum Linn, Mucilage has been evaluated in disintegrating tablet[3-4].

Chewable tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing[4]. These tablets are intended to disintegrate smoothly in mouth at a moderate rate either with or without actual chewing, characteristically chewable tablets have a smooth texture upon disintegration, are pleasant tasting and leave no bitter or unpleasant taste. Successful tablet formulation development involves the careful selection of ingredients in order to manufacture a robust solid dosage form. Choosing the appropriate excipients to perform a specific function in a tablet formulation such as disintegration or lubrication can be critical to achieving acceptable manufacturing performance. Sweeteners, both naturally occurring and synthetic are one type of functional excipient commonly used in chewable tablet formulations to mask the unpleasant tastes and facilitate pediatric dosing[5, 6].

2. Preformulation Study: In the Preformulation study there are some parameters which is important for the formulation of chewable tablets. The present work was carried out to formulate development and evaluate the chewable tablet by taste masking of Riboflavin.

2.1 Steps in the taste Masking of the Riboflavin Tablets:-

- ➢ Chewable tablet prepared by direct compression method.
- ➢ Mannitol is widely used as Excipients in chewable tablet for its non-hygroscopic nature for moisture sensitive drug.
- ➢ Using artificial sweeteners may provide a satisfactory alternative
- ➢ Taste masking method using dried calcium carbonate different concentration ratio. Taste masking method was performed by pH, Modification method.
- ➢ Adjustment of pH Values: Many drugs are less soluble at pH different from the pH value of the mouth [7-9].

2.2 Solubilization inhibitor, such as sodium carbonate, sodium bicarbonate, sodium hydroxide, or calcium carbonate, was added to increase the pH when granules' including a riboflavin dissolved in aqueous medium, the bitter taste of the drug was successfully masked by a sweetener alone.

➢ Performing in Drug-Excipients compatibility studies by IR studies.

2.3 Physic-chemical evaluation of the chewable tablet.

- ➢ Preformulation studies
- ➢ Evaluation of blend
- ➢ Angle of repose
- ➢ Bulk density
- ➢ Tapped density
- ➢ Compressibility index
- ➢ Hausner's ratio

3.2.2. Evaluation of chewable tablet

- ➢ Weight variation
- ➢ Hardness
- ➢ Friability
- ➢ Thickness
- ➢ Drug content
- ➢ disintegration time
- ➢ Wetting time

3. DRUG PROFILE

Riboflavin, Vitamin B2

3.1 Drug profile.27

3.2.1. Identification:
3.2.1.1. Drug name: Riboflavin
3.2.1.2. Structure:

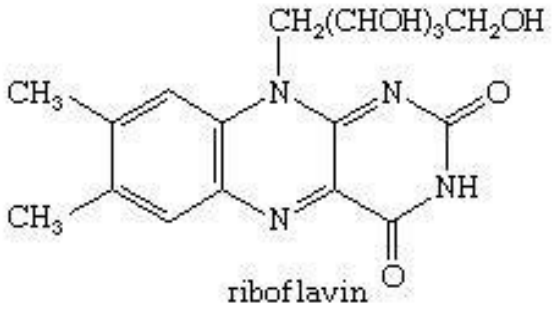


Figure No.01 Riboflavin structure

3.2.1.3. **Chemical formula: $C_{17}H_{20}N_4O_6$**
3.2.1.4**. Molecular weight**: 376.3639
3.2.1.5. **Melting point:** 290 ℃
3.2.1.6. **Dose:** 1mg-100 mg
3.2.1.7. **Type:** Small molecule
3.2.1.8. **Category:** Vitamin, Nutraceutical, Immunomodulatory,
3.2.1.9. **Description:** white to almost white, crystalline powder. Soluble in water.
3.2.2. **Route of administration:** oral route,
3.2.2.1**. BCS classification**: Class-III
3.2.3. **Storage:** Store below 150 to 300 c
3.2.4. **Mechanism of action:** Binds to riboflavin hydrogenase, riboflavin kinase, and riboflavin synthase. Riboflavin is the precursor of flavin mononucleotide (FMN, riboflavin monophosphate) and flavin adenine dinucleotide (FAD). The antioxidant activity of riboflavin is principally derived from its role as a precursor of FAD and the role of this cofactor in the production of the antioxidant reduced glutathione. Reduced glutathione is the cofactor of the selenium-containing glutathione peroxides among other things. The glutathione peroxides are major antioxidant enzymes. Reduced glutathione is generated by the FAD-containing enzyme glutathione reeducates.
3.2.5. **Taxonomy:**
3.2.5.1. **Kingdom:** Organic
3.2.5.2. **Classes :** Phosphodiesterase type-5
3.2.6. **Pharmacokinetic profile:-**
3.2.6.1. **Absorption:-**Absorbed from duodenum, by both active and passive processes
3.2.6.2. **Protein binding:** 60 % plasma protein binding.
3.2.6.3. **Half-life:** 60 to 90 minutes
3.2.6.4. **Metabolism:** - Hepatic.
3.2.6.5. **Excretion: -** Not available
3.2.6.6. **Adverse effect:** - A headache, urinary tract infection, diarrhea, Cardiac death, myocardial infection.
3.2.6.7. **Therapeutic use: -** For the treatment of Vitamin B2 deficiency.

4. MATERIAL & METHODOLOGY:

Table No. 01 Chemical used in the research work

S.NO	Materials	Name of the supplier
1.	Riboflavin	Chandra labs hydrabad
2.	Dried calcium carbonate	MYLCHEM MUMBAI
3.	Oyster Calcium Carbonate	Chandra labs ,hyd
4.	PvPk30	MYLCHEM Mumbai
5.	Cros povidone	MYLCHEM Mumbai
6.	Cros carmellose sodium	MYLCHEM Mumbai
7.	Mannitol	S.D Fine Chem.LTD Mumbai
8.	Aspartame	S.D Fine Chem. LTD Mumbai
9.	Lemon flavor	MYLCHEM Mumbai
10.	Peppermint flavor	MYLCHEM Mumbai
11.	Sunsetyellowlake	MYLCHEM Mumbai
12.	Aerosil	S.D Fine Chem.LTD Mumbai
13.	Talc	MYLCHEMMUMBAI
14.	Magnesium stearate	Chandra labs hydrabad
15.	Citric acid monohydrate	S.DFINECHEM.LTD.

Equipment: - The equipment used in the present work areas follows:

Table No. 02 Equipment used in the Research Work

S.no	Instruments	Source
1	Electronic balance	Shimadzu japan
2	UV/Visible Spectrophotometer	Corporation-BL-220H
3	FTIR spectrophotometer	Corporation Japan
4	Dissolution apparatus	Shimadzu japan
5	Hot Air Oven	Biotech India.
6	Compression machine	Cadmach machinery

METHOD:

Wet granulation method was used to prepare the granules for the tablets. Mass mixer was used to mix tri-calcium phosphate, mannitol-25, and sucrose. These materials were passed through 40 mess size and mixed for 20 minutes. A solution of PVPK-30 was prepared by dissolving it in hot DM water with continuous stirring. The solution was added in the mass mixer and a damp mass was formed. The damp mass was dried at 70-75 C for 2 hours in tray dryer and then transferred into multi-mill to reduce the size. Finally the semi-dry granules were again dried in tray dryer at 70- 75 C for 2 hours. Vitamin D3, aspartame, aerosol, strawberry powder flavor, talc and magnesium stearate were sieved through 40-mesh size and mixed thoroughly with dried granules in a blender.

Powder blend sample was taken for evaluation studies. Tablets were compressed on a rotary compression machine. Sample of compressed tablets was taken for evaluation studies. Evaluation of Chewable Compressed tablets Tablets properties were evaluated by pharmacopoeial and non-pharmacopoeial tests.

Drug–Excipients compatibility study

The IR absorption spectra of the pure drug and with different Excipients were taken in the range of 4000-500cm^{-1}using KBr disc method, 1-2mgofthesubstance to be examined was triturated with 300-400 mg, specified quantity, of finely powdered and dried potassium bromide. These quantities are usually sufficient to give a disc of 10-15 MM diameter and pellet of suitable intensity by hydraulic press. The infrared spectrum of riboflavin was recorded by using FT-IR spectroscopy and observed for characteristic peak of drug, and undisturbed drug structure of the drug, which indicates there was no drug [10].

Formulation of chewable tablet (direct compression method)

The chewable tablets containing 100mg riboflavin were prepared with a total tablet weight of 700mg. All the formulations were prepared by direct compression[10].

Procedure

Riboflavin and all other in gradients were individually passed through a sieve no.40. All the ingredients were mixed thoroughly by triturating up to 15 minutes. The powder mixture was lubricated with Magnesium stearate. The tablets were prepared by using direct compression method according to the formulation table.

Then the blend was compressed using 13 MM Flat beveledged scored on one side. **Organoleptic properties of tablets:** Colour, taste and flavour of tablets was checked manually by seeing, chewing and smelling the tablets. ‘

Weight variation test: 20 tablets were used to carry out the weight variation test. All tablets were weighed individually on a digital balance and average weight was calculated. Individual weights were compared with average weight.

Diameter and thickness test: Micrometre screw guage was used to determine the diameter and thickness of each tablet. Random sample of 10 tablets was selected and their diameter and thickness were calculated in mm.

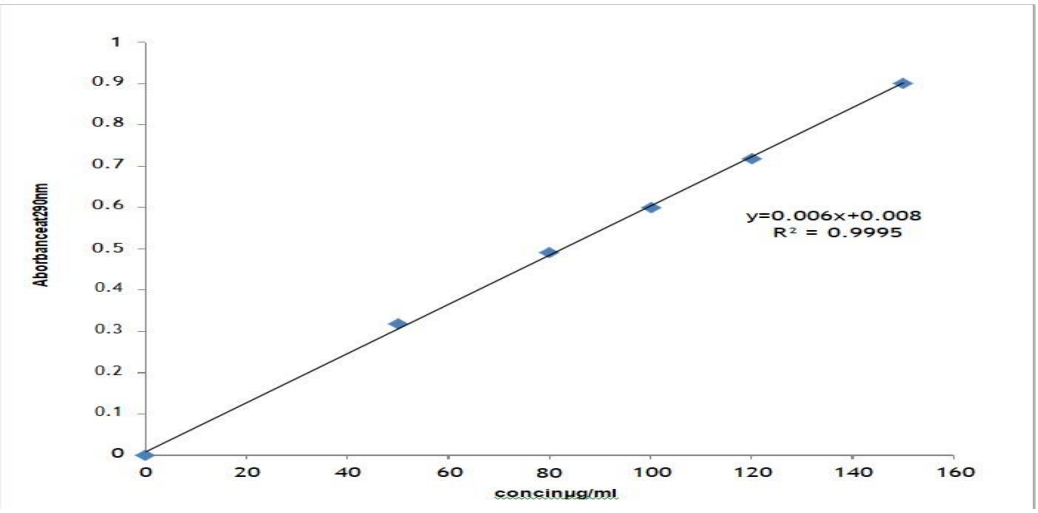
Hardness: Hardness test was done to measure the crushing strength of tablets. Hardness of randomly selected 10 tablets was measured using hardness tester. Friability: Friability test apparatus was used to determine the friability of tablets. Friability was calculated after 100 rpm.

5. RESULTS:

Table No. 03 Standard calibration curve of Riboflavin

S.No	Concentration[µg/ml]	Absorbanceat290nm
1.	0	0
2.	50	0.317
3.	80	0.419
4.	100	0.599
5.	120	0.718
6.	150	0.901

Graph No. 01 Concentration and absorbance of Riboflavin in 0.01N Hcl



Graph No. 2 IR Spectra of Riboflavin pure drug

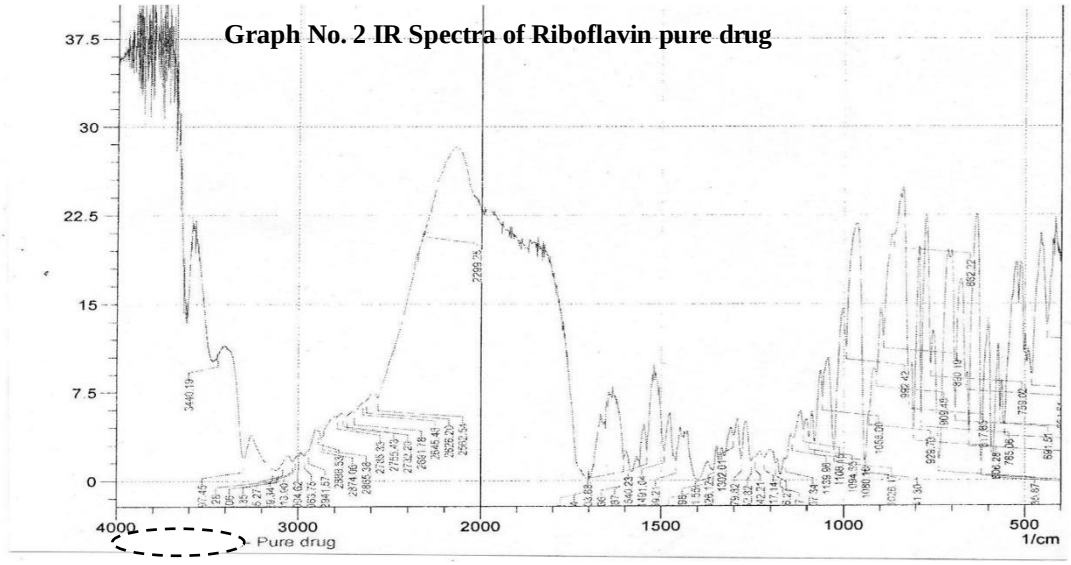


Table No. 4 Riboflavin pure drug peak

(wave number cm^{-1})	400-500	600-800	800-1000	1000-1200	1200-1400	1400-1600	1600-1800	2700-3000	3000-3700
Functional group	NH OH	(CH2) 4 C=C C≡CA ROMA TIC	=CHC=C AROMA TIC	AROMAT IC PHENOL ALCOHO L AMINE	CH3ARO MATIC PHENOL ALCOHO LAMINE NO2	CH3AR OMATI C PHENO L ALCOH OL AMINE NO2	=CHC=C AROMA TIC AMINE C=O	CH3 CH2 CH	=CH C=C ≡CHC≡C AROMATI C PHENOL ALCOHO L AMINE

Graph No. 3 IR Spectra of Moringagum

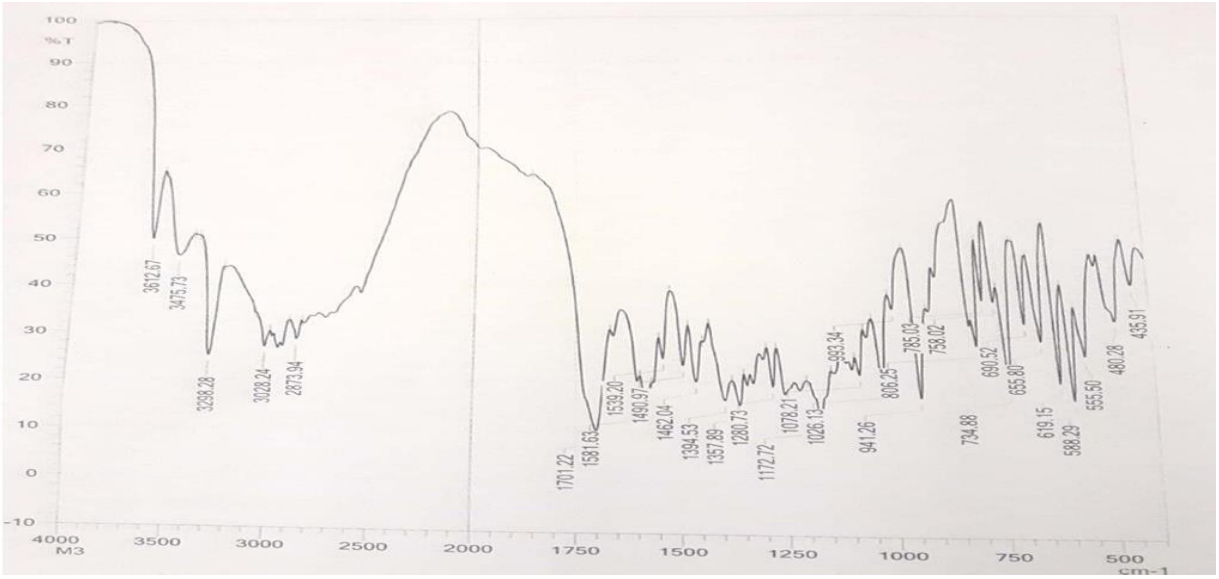


Table No. 5 *Moringagum* IR interpretation

(wavenumber cm^{-1})	400-500	1200-1600	2300-2400	2800-3000	3700-4000
Functional Groups	NH OHC =C	CH3C H2 Aromatic PhenolAl cholAmi neNO2	≡CH C≡C CN	CH3 CH2 CH	Phenol Alcohol

Graph No. 4 IR Spectra of Riboflavin & Moringagum

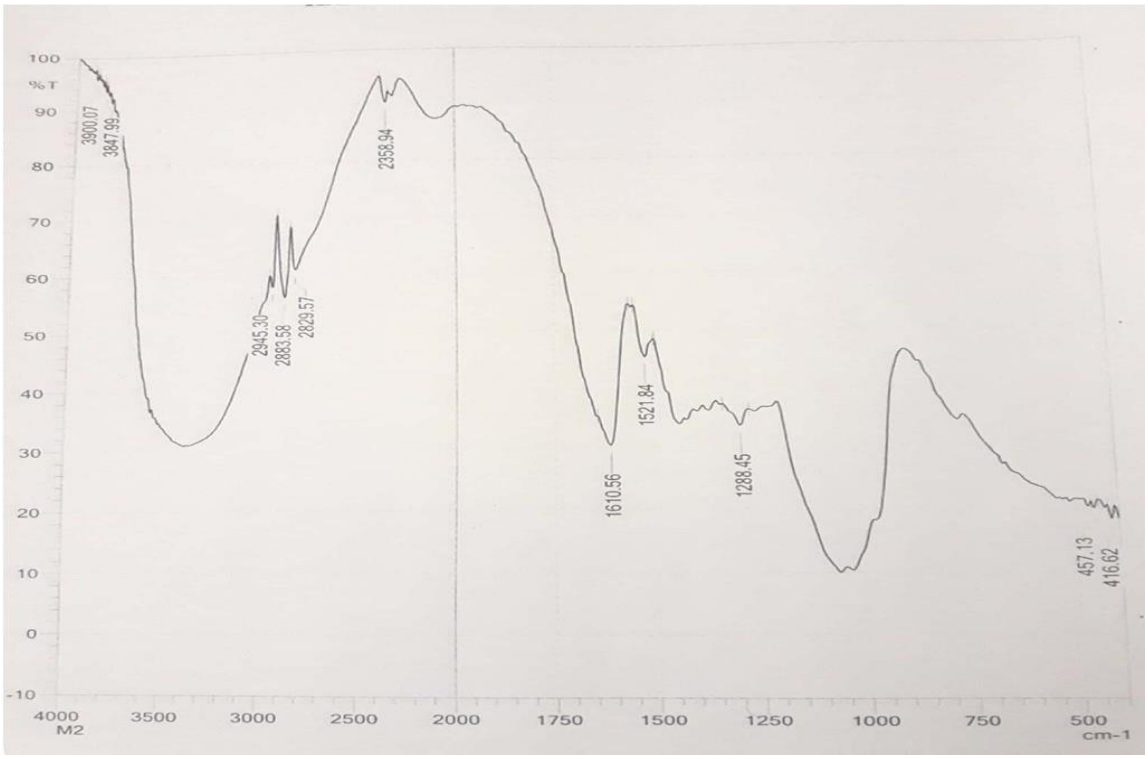


Table No. 6 Riboflavin with moringagum

(wave number cm^{-1})	400-600	600-800	800-1000	1000-1200	1200-1400	1400-1800	2600-3000	3000-3400	3400-3800
Functional Group	NH OH C=C	$(CH_2)_4$ C=C C≡C Aromatic	=CH C=C Aromatic	Aromatic Phenol Alcohol Amine	CH_3 Aromatic Phenol Alcohol Amine NO_2	CH_3 Aromatic Phenol Alcohol Amine NO_2 =C HC =C Aromatic Amine C=O	CH_3 C H_2 C H	CH C=C Aromatic ≡CC ≡CP heno lAmine	Phenol

FT-IR of the formulation and different that the peak points of the formulation were similar with that of pure Vitamin B-complex, it clearly indicate that there is no interaction of API with the Excipients.

Evaluation of pre compression parameters for chewable tablet

Table no.07 pre-compression parameters for chewable tablet (direct compression)

Formulation code	Bulkdensity (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angleof repose
F1	0.568	0.693	18.90	1.22	25°.12′
F2	0.574	0.726	20.99	1.26	27°.31′
F3	0.558	0.680	17.94	1.21	29°.46′
F4	0.574	0.765	24.96	1.33	25°.71′
F5	0.558	0.680	17.94	1.21	23°.86′
F6	0.562	0.685	17.95	1.21	24°.71′
F7	0.554	0.710	21.97	1.28	25°.10′
F8	0.574	0.735	21.90	1.28	28°.14′
F9	0.562	0.702	20.00	1.26	28°.14′

Angle of repose.

All the formulation prepared by direct compression method showed the angle of repose between 25° and 29° excellent flow property it show in the above table.

Bulk density, tapped density, compressibility index and hausner'sratio.

The results of, Bulk density, tapped density, compressibility index and hausner's ratio are shown in the table no. 11. The bulk density and tapped bulk density for all formulation varied from 0.554 gm/cm^{3}to 0.574 gm/cm^{3}respectively. Tapped density for all formulation varied from 0.680 to 0.735 gm/cm^3. The result of Carr's consolidation index or (%) compressibility index for the entire formulation blend ranged from 17 to 22 shows excellent compressibility index and Hausner's ratio for all formulation variedfrom1.21to1.33whichis an indicative of good flow property.

Post compression parameters

Table No. 08 Post compression evaluation parameters of chewable tablets

Formulation code	Average weight	Hardness (kg/cm^3)	Thickness (mm)	Friability	disintegration time (sec)	Wetting time (sec)	% Drug content
F1	701	5.68	5.18	0.134	90	60	99.2
F2	699	6.04	5.07	0.123	80	55	97.4
F3	700	5.54	5.22	0.093	65	50	99.6
F4	698	4.32	5.26	0.084	60	52	98.4
F5	700	4.10	5.17	0.124	40	45	99.3
F6	699	3.79	5.29	0.171	45	65	99.2
F7	698	3.05	5.20	0.138	70	59	100.1
F8	700	3.23	5.27	0.237	60	56	99.6
F9	698	3.38	5.31	0.264	78	50	99.6

Post-compression evaluation of Riboflavin

Average weight, Hardness test, Thickness test, Friability, Disintegration time, wetting time, Drug content.

The results of, Average weight, Hardness, Thickness, Friability, Disintegration time, wetting time ,Drug content are shown in the table no. 07. The bulk density and tapped density for all formulation varied from 698mg to 701 mg. All the formulations passed the weight variation test as results were found to be IP limits of ±5% weight. The maximum thickness of the formulation was found to be 5.29 ± 0.005 mm in batch F6 and minimum thickness of the was found to be 5.07 ± 0.001 mm in batch F2.The hardness of all the formulation tablets were determined by Pfizer.

Stability studies

Evaluation of tablet parameters after stability studies at storage condition- 40^0C/75%RH Period-3Month

Table No. 9 Stability studies

S.no.	Parameter	Time duration			
		0Month	1Month	2Month	3Month
1	Physical character	--	--	--	--
2	Friability%	0.42	0.45	0.45	0.42
3	Hardness[kg/^{cm3}]	6.85	6.81	6.82	6.84
4	% drug release of at 30min	100.5	100.25	99.04	98.12

Evaluation of pre compression parameters for batches with *Moringa* gum by wet granulation method.

Table No. 10 Pre-compression parameters for chewable tablet (wet granulation method)

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose
F10	0.558	0.685	17.94	1.21	26º.12
F11	0.554	0.680	18.90	1.33	27º.71
F12	0.560	0.726	21.90	1.28	29º.46

Angle of repose

All the formulation prepared by wet granulation method showed the angle of repose between 26º and 29º revealing excellent flow property as shown in the table no 09.

Bulk density, tapped density, compressibility index and hausner'sratio.

The results of, Bulk density, tapped density, compressibility index and hausner'sratio of batches prepared by wet granulation method are Shown in the table no. 16. The bulk density and tapped bulk density of the formulation varied from 0.554 gm/cm^3 to 0.560 gm/cm^3 respectively. Tapped density for all formulation varied from 0.680 gm/cm^3 to 0.726 gm/cm^3. The result of Carr's consolidation index or (%) compressibility index for the entire formulation blend ranged from 17 to 21 shows excellent compressibility index and hausner's ratio for all formulation varied from 1.21 to 1.33 result in good flow properties.

Post compression parameters

Tableno.11. Post compression evaluation parameters

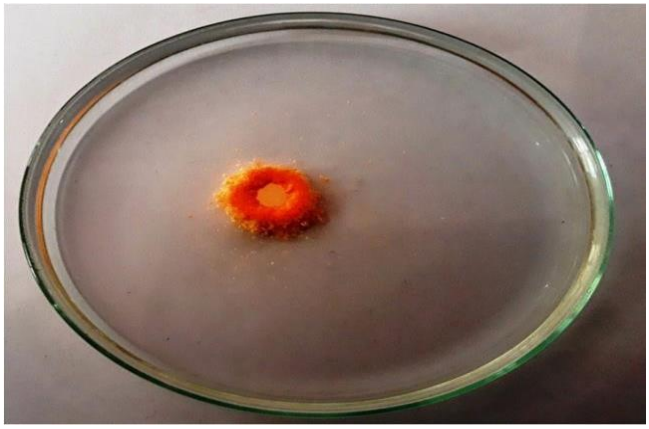
Formulation Code	Avg. Weight	Hardness (kg/cm^2)	Thickness (mm)	Friability	Disintegration time(sec)	Wetting time(sec)	%Drug content
F10	701	4.85	4.28	0.026	35	55	99.48
F11	699	4.81	4.41	0.021	25	58	97.56
F12	700	6.80	4.32	0.022	20	45	95.46

Post-compression evaluation of Vitamin B-complex Average weight, Hardness test, Thickness test, Friability, Disintegration time, Wetting time, Drug content.

The results of, Average weight, Hardness, Thickness, Friability, Disintegration time, wetting time, Drug content are shown in the table no.09. The average weight of the tablet varies from 699 mg to 701mg. All the formulation passed the weight variation test as results were found to be IP limits of ±5% weight. The maximum thickness of the formulation was found to F10 batch 4.28 ± 0.005 mm minimum thickness of the batch F11 was found to be 4.41±0.001mm F11.The hardness of all the formulation tablets were determined by Pfizer hardness tester and it was found to be in the range to be in the range of 4.80±0.01 to 6.04kg/cm^3. The Friability of the all-formulation tablet were determined by Roche friabiliators found to be in between 0.021±0.14% to 0.026%. Wetting time for all formulated tablet were found to be in the range of 0.50±0.056 to 0.38±0.56 minutes. The wetting time for tablets, closely releated to the pore size of the internal structure. Which is affected the penetration of water into the tablets. The maximum percentage of the drug content of the formulation was found to be 99.48±0.33 and maximum percentage of the drug content From all formulation was found 95.46±0.46, ensuring the uniformity of the drug content in the all formulation.

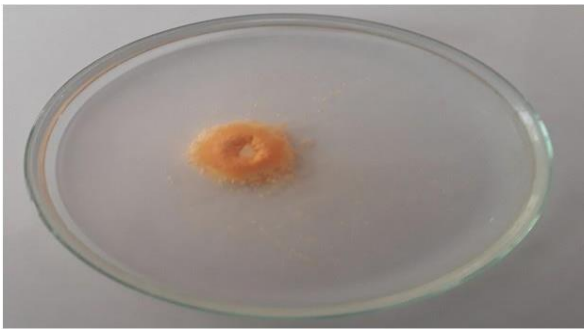
Hardness tester and it was found to be in the range of 3.05±0.01to6.04kg/cm^3. Friability of the various batches was found to be in between 0.264±0.14% to 0.084%. Wetting time for all formulated tablet were found to be in the range of 40.01±0.056 to 90.0±0.56 seconds. The wetting time for tablets closely relate to the pore size of the internal structure, which affects the penetration of water in to the tablets. The maximum percentage of the drug content of the formulation was found to be 100.1 ± 0.33 and maximum percentage of the drug content from all formulation was found 98.4 ± 0.46, ensuring the uniformity of the drug content in the all formulations.

Figure No. 4 wetting time for Vitamin B-complex F5



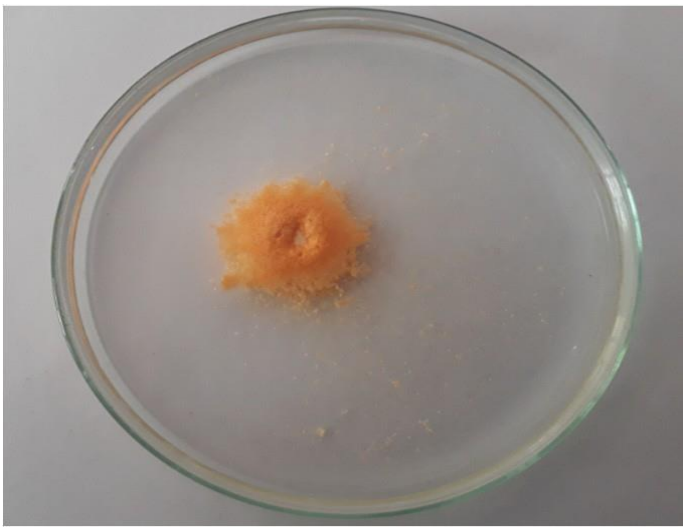
Riboflavin tablets after 5 seconds

Figure No. 5 Wetting time for Riboflavin tablet



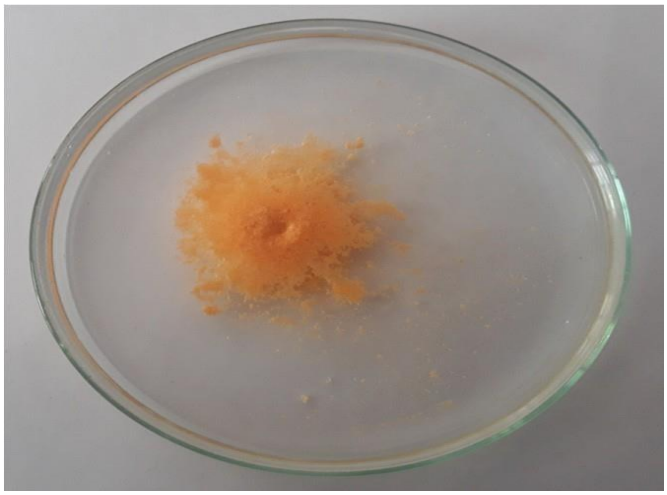
Riboflavintabletsafter15seconds

Figure No. 6 wetting time for Riboflavin tablet



Riboflavin tablets after25 seconds

Figure No 7 wetting time for Riboflavin



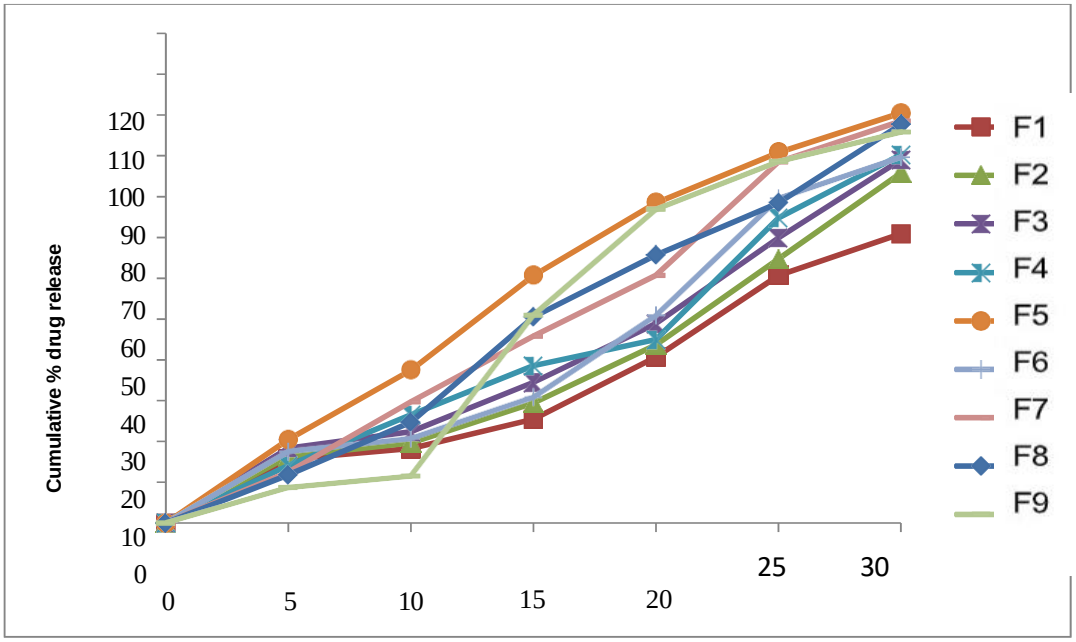
Riboflavintabletsafter40seconds

Dissolution data for chewable tablet

Tableno.12 Dissolution data of chewable tablets

Time in min	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	15.65	16.32	18.35	14.06	20.48	17.48	12.48	11.79	8.69
10	18.28	19.62	22.35	26.50	37.49	20.68	29.68	24.69	11.49
15	25.45	29.40	34.45	38.56	60.67	30.78	45.78	50.48	50.87
20	40.67	43.67	48.87	44.96	78.48	50.78	60.68	65.67	76.79
25	60.70	64.68	69.89	74.74	90.79	79.40	88.48	78.45	88.48
30	70.89	85.78	88.98	90.25	100.5	89.45	98.48	97.65	95.67

Graph No. 05 Dissolution Profile of *Moringa* Olifera gum



Time in Minutes

Dissolution graph for chewable tablet

All the formulations except batch F5 were not able to release 100 % of drug within 30 minutes. F5 formulation released the total drug within 30 minutes which will aid in the fast onset of action. This may be attributed to the presence of super disintegrates croscarmellose sodium and crospovidone in batch F5. This also might have increased by the increased wetting of the tablet resulting in fast dissolution.

6. SUMMARY & CONCLUSION:

The chewable tablets of taste masked Riboflavin were successfully prepared by direct compression method and wet granulation method. 12 batches using various additives were prepared and evaluated within aim of presenting Riboflavin taste masked by the chewable tablet. Drug Excipients compatibility study was performed by FTIR. The unpleasant taste of the Riboflavin was masked by intra-granular addition of dried calcium carbonate, calcium carbonate from oyster shell and the extra-granular addition of sweeteners and flavoring agents. Taste masking study was done by using alkalizing agent in different ratio. Riboflavin taste masking was increased when dried calcium carbonate quantity was increased because of reduction of the solubility of Riboflavin. Oyster shell calcium carbonate when added to the drug did not masked the taste due to the gritty nature of it.

F5 batch showed less bitterness, low disintegration time and fast dissolution time and hence was taken further comparing with the innovator drug. In the present study disintegrating properties of *Moringa olifera* gum powder had been studied in comparison with other commercially available super disintegrates. The isolated natural disintegrant exhibits faster drug dissolution and disintegration. The isolated gum powder can be effectively used as disintegrate for Riboflavin with the added advantage of the folkloric immuno booster activity of it.

The physic-chemical evaluation results for the powdered blend of all trials pass the official limits in the angle of repose, compressibility index, Bulk density, Tapped density, Hausner's ratio.

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