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Research Article

DEVELOPMENT AND EVALUATION OF TASTE MASKED FORMULATION OF OFLOXACIN & ORNIDAZOLE SUSPENSION.

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ABSTRACT

Taste is an important factor in the development of dosage form. The problem of bitter and obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmacist in the present scenario.The major problem of these bothdrugswas very low solubility & bitter taste.So to solve both criteria taste masked suspension was made. The present work focus on bitter taste masking of OfloxacinOrnidazole.Batch method wasused for formation of drug resin complex. Various ion exchange resins such as Doshion P542, Doshion P514 and Indion 204weretried to obtained taste masked drug resin complex (DRC). About 18 trails were taken and On the basis of their data further optimization of batches were carried out. In order to ensure patient compliance bitterness masking becomes essential.Among all formulation F4 was considered best.

Keywords: Ornidazole, Ofloxacin, Doshion P514, Doshion P 542, Indion 204.

INTRODUCTION

Any medication which imparts an unpleasant taste is likely to result in poor patient compliance to a drug regimen especially for the children and elderly. Taste is a sensory response resulting from a chemical stimulation of taste buds on the tongue.In the topical countries like India, the majorproblems of health arise due to improperlifestyle, unhealthy environmental conditions,unhygienic and substandard food. Infectionscaused by the microorganisms like, fungi,protozoa, are the most common. Drugs withantifungal and antiprotozoal activity have beenused in the treatment of the same. In manycases, drugs with two active ingredients areprescribed to the patients to have an addedadvantage. Many of these antibacterial drugsare found in combination with antifungal andantiprotozoal drugs which are highly

effectiveagainst fungal and protozoal infections.**[1]**

The fluoroquinolones are important antimicrobial agents that have demonstrated activity against a wide range of Gram-positive and Gram-negative organisms and have proved useful against micro-organisms that are resistant to other antibacterial agents. **[2]** Some examples include

Ofloxacin, ciprofloxacin, perfloxacin, levofloxacin and norfloxacin with newer ones entering the scene almost every five years. **[3]**Ofloxacin (OFL) is a second generation fluoroquinolone acting as antimicrobial agent with a 6- fluoro substituent and a 7-piperazinyl substituent on the quinolone ring structure.

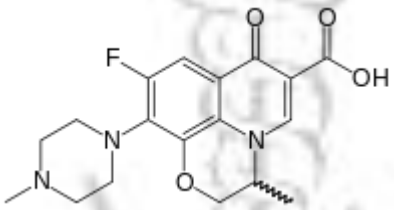

Fig 1.Chemical Structure of Ofloxacin.

The chemical name of Ofloxacin is (±)-9-Fluoro-2,3- dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-7oxo-7Hpyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid.**[4]**

Ornidazole is a 5-nitroimidazole derivative, chemically-chloromethyl-2-methyl-5nitro-1Himidazole- 1-ethanol with molecular formula C7H10N3O3Cl1 used as antimicrobial agent. Ornidazolehasantiprotozoal and antibacterial properties againstanaerobic bacteria. The antimicrobial activity of thiscompound is due to reduction of the nitro group to a more reactive amine group that attacks microbial DNA, inhibiting further synthesis, and leading to degradation of existing DNA. **[5]**

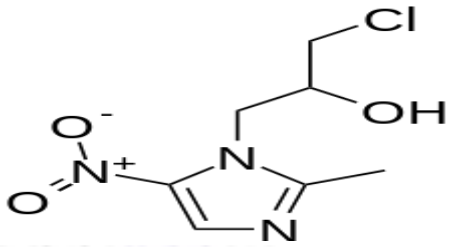

Fig 2: Chemical Structure of Ornidazole

2.0 MATERIALS AND METHOD

2.1 Materials

Ofloxacin and Ornidazole drugs were procured as gift sample from Anuja healthcare pvt. Ltd.Doshion P 542, Doshion P 514 &Indion 204 were purchased from S.D fine chemicals.

2.2 Method. [6]

2.2.1 Preparation of drug resin complex: -

1. **Doshion P514 &Doshion P542: -**

Drug and resin were accurately weighed in required ratio. Then slurry of resin was made in demineralised water and stirred for half an hour at 900 rpm in order to allow polymer structure to swell uniformly.Drug was added slowly under stirred condition. The drug resin mixture was continuously stirred for half an hour.

2. **Indion 204: -**

Drug and resin were accurately weighed in required ratio. Sodium citrate was added into demineralised water then slurry of resin was made and stirred for half an hour at 900 rpm in order to allow polymer structure to swell

uniformly. Drug was added slowly under stirred condition. The drug resin mixture was continuously stirred for half an hour.

Table 1: Quantities of drug and resin taken for different drug to resin ratios.

DRUG TO RESIN RATIO	AMOUNTOF OFLOXACIN AND ORNIDAZOLE IN (g)	AMOUNT OF DOSHION P514/INDION204 TAKEN IN (g)
3.57:1/0.5	3.57(1.02/2.55)	1/0.5
3.57:2/1.0	3.57(1.02/2.55)	2/1
3.57:3/1.5	3.57(1.02/2.55)	3/1.5
3.57:4/2.0	3.57(1.02/2.55)	4/2.0
3.57:5/2.5	3.57(1.02/2.55)	5/2.5
3.57:6/3.0	3.57(1.02/2.55)	6/3

- Quantity of Resin (Doshion P514 &Doshion P542) will be same in above Table no 1.

2.2.2 Selection of Optimum Resins and Drug to Resin Ratio: -

Several trials were carried out for preparation of resinate using different resins in different drug to resin ratio as shown in table 2. For the selection of the proper drug resin ratio, the concentration of resin was varied, keeping concentration of drug constant. The pH of the solution was maintained at 5 to 6.

Table 2: Selection of optimum resins and drug to resin ratio

RESIN	BATCH NO	RATIO OF DRUG TO RESIN
DOSHION P 542	T1	1.02:2.55:1
	T2	1.02:2.55:2
	T 3	1.02:2.55:3
	T 4	1.02:2.55:4
	T 5	1.02:2.55:5
	T 6	1.02:2.55:6
DOSHION P 514	T 7	1.02:2.55:1
	T 8	1.02:2.55:2
	T 9	1.02:2.55:3
	T 10	1.02:2.55:4
	T 11	1.02:2.55:5
	T 12	1.02:2.55:6

INDION 204	T 13	1.02:2.55:0.5
	T 14	1.02:2.55:1
	T 15	1.02:2.55:1.5
	T 16	1.02:2.55:2
	T 17	1.02:2.55:2.5
	T 18	1.02:2.55:3

2.2.3 Evaluation of Taste of Resinate

Taste of resinate was checked by time intensity method. For this purpose 6 human volunteers wereselected. In this method a sample equivalent to a normal dose 10 mg (Ofloxacin) and 25mg (Ornidazole) was held in mouth for 60 seconds and volunteers were asked to evaluate the resinate for taste. Bitterness levels were recorded at 2, 10. The bitterness level was recorded against pure drug using a numerical scale (3– StrongBitter, 2 – Moderate Bitter, 1 –Slight Bitter, X – Threshold Bitter, 0 – No Bitter).These volunteers were instructed not to swallow the Resinate, which were placed on the tongue. They were instructed to thoroughly gargletheir mouth with distilled water after the completion of test.

2.2.4 Formulation of Oral Taste Masked Suspension: -

A series of formulations were prepared as given in table 3 with various concentrations of resin and were evaluated for bitter taste masking, sedimentation volume and redispersibility. F1 was formulated using plain drug without resin, to provide clear distinction between actual taste of drugbefore masking and taste after masking by making complex with Resin.

Table 3: - Formulation of oral taste masked suspension.

S.NO	INGREDIENTS	F1 (g)	F2(g)	F3(g)	F4(g)
1.	OFLOXACIN	10.200	10.200	10.200	10.200
2.	ORNIDAZOLE	25.500	25.500	25.500	25.500
3.	DOSHION P 514	-	60	-	-
4.	DOSHION P542	-	-	60	-
5.	INDION 204	-	-	-	30
6.	SODIUM CITRATE	0.66	0.66	0.66	0.66
7.	TWEEN 80	4.0000	4.0000	4.0000	4.0000
8.	GLYCERIN	80.000	80.000	80.000	80.000
9.	SORBITOL SOLUTION	300.00	300.00	300.00	300.00

10.	SUCROSE	250.00	250.00	250.00	250.00
11.	SODIUM SACCHARIN	9.1000	9.1000	9.1000	9.1000
12.	SODIUM METHYL PARABEN	2.0000	2.0000	2.0000	2.0000
13.	SODIUM PROPYL PARABEN	0.2000	0.2000	0.2000	0.2000
14.	SODIUM BENZOATE	2.0000	2.0000	2.0000	2.0000
15.	SODIUM ALGINATE	2.0000	2.0000	2.0000	2.0000
16.	XANTHAN GUM (GERMANY)	3.5000	3.5000	3.5000	3.5000
17.	PROPYLENE GLYCOL				
18.	ASPARTAME	2.0000	2.0000	2.0000	2.0000
19.	SUCRALOSE	1.0000	1.0000	1.0000	1.0000
20.	MENTHOL	0.2000	0.2000	0.2000	0.2000
21.	LEMON FLAVOUR	1.5000	1.5000	1.5000	1.5000
22.	ORANGE FLAVOUR	6.000	6.000	6.000	6.000
23.	COLOUR SUNSET YELLOW	0.5000	0.5000	0.5000	0.5000

2.2.5 Procedure: -

Syrup was prepared by heating between 60-80 oC under constant stirring and the stability of preparedsyrup was improved by addition of preservatives. Xanthan gum mucilage and Sodium alginate were prepared by boiling it with water and stirred well to allow it swell completely and add Tween 80 with constant stirring. Drug resin complex was prepared. Further Swelled Xanthan Gum & Sodium alginate were added into DRC complex with stirring for half an hour. Dissolve Sucrose, Sodium saccharin and aspartame one by one with constant stirring in hot water and add into DRC complex with constant stirring for ten minutes. Syrupy solution was added into DRC with continuous stirring. Glycerin, Sorbitol solution & PG mixed with menthol were added into above bulk syrup solution one by one with constant stirring at least for twenty minutes. Colouring agent was dissolved in water and transferred to above mixture. At the end flavouring agent was added and stirred for 5 min. Finally volume was made up to 100ml with distilled water and pH was adjusted to (5-6) + 0.05 with sodium citrate solution (1%). Developed batch was homogenized (Polytron PT 6100 Homogenizer) for 20 mins at 10 × 1000 rpm.

3.0 EVALUATION OF DEVELOPED ORAL OFLOXACIN ORNIDAZOLE SUSPENSION: - [7]

3.0.1 Colour, odour and taste

All the developed batches of suspension were evaluated for organoleptic properties such as colour, odour and taste.

3.0.2 pH

pH of the suspension was determined by the use of Metler Toledo pH meter.

3.0.3 Viscosity

The viscosity of suspension was determined at ambient condition using DV III+, Brookfield Programmable Rheometer.In adapter 15ml of suspension was taken and the adapter is set over the viscometer by a stand such a way that spindle is completely immersed in the suspension. Spindle no.S0 was used to measure the viscosity of suspension.

3.0.4 Sedimentation Volume

Fifty ml each of suspension was taken in 50 ml stoppered graduated measuring cylinder. TheSuspension was dispersed thoroughly by moving upside down for three times. Later, the suspension was allowed to settle for three minutes and the volume of sediment was noted. This is the original volume of sediment (H0).The cylinder was kept undisturbed for 7 days. The volume of sediment read at 7 hr and every 24 hr for 7 days was considered as final volume of sediment (Hu).

Sedimentation Volume (F) = Hu / Ho

The ultimate height of the solid phase after settling depends on the concentration of solid and the

Particle size. To obtain an acceptable suspension, F should be at least 0.9 for 1 h but a longer period was preferred for our purpose.

3.0.5 Redispersibility

Fixed volume of each suspension (50 ml) was kept in stoppered cylinder which was stored at room temperature for 7 days. At regular interval, one stoppered cylinder was removed and moved upside down until there was no sediment at the bottom of the cylinder.

3.0.6 Assay of Oral Taste Masked Suspension

Suspension (5ml) was taken in 100 ml volumetric flask, 0.1 M HCl was added into it &sonicated it for 10 min. Volume was made up to 100 ml with 0.1 M HCl& filtered. Samples were prepared in duplicates. Area was measured using developed HPLC method &Compared with standard and then % drug content was calculated as per the following formula.

3.1 ACCELRATED STABILITY STUDY.

F4 suspension was packed in 100 ml Glass bottle. The packed bottles were placed in stability chamber maintained at 40 + 2 °C and 75 + 5% RH for 3 month. Samples were collected at days 0, 30, 60 and 90. The analyses comprised chemical testing of quantifiable parameters, which could possibly change during storage, such as viscosity, pH, drug contents, sedimentation volume, and Redispersibility, colour, taste, odour and drug release.

4.0 Result: -

Taste masking was tried using three different ionexchange resins and no taste masking was obtained using Doshion P514 and Doshion P542 so was rejected. Batch T17 i.e.; with Indion 204, tastelesscomplex was obtained with ratio 1:3 hence it wasfinalized for the study. When the pH is lower than 4,the resin exists in the Free State. Therefore,drug/resin complex formation was carried out at pH 5-6.

Table 4: - Selection of Optimum Resins and Drug toResin Ratio and Optimization of Process ofPreparing Drug Resin Complex.

RESIN	BATCH NO	RATIO OF DRUG TO RESIN	TASTE	pH
DOSHION P 542	T1	1.02:2.55:1	Bitter	4.70
	T2	1.02:2.55:2	Bitter	4.79
	T 3	1.02:2.55:3	Bitter	4.96
	T 4	1.02:2.55:4	Bitter	5.22
	T 5	1.02:2.55:5	Bitter	5.52
	T 6	1.02:2.55:6	Bitter	5.74
DOSHION P 514	T 7	1.02:2.55:1	Bitter	7.00
	T 8	1.02:2.55:2	Bitter	5.44
	T 9	1.02:2.55:3	Bitter	6.63
	T 10	1.02:2.55:4	Bitter	6.52
	T 11	1.02:2.55:5	Less bitter	6.62
	T 12	1.02:2.55:6	Threshold bitter	5.23
INDION 204	T 13	1.02:2.55:0.5	Bitter	6.12
	T 14	1.02:2.55:1	Bitter	5.44
	T 15	1.02:2.55:1.5	Bitter	5.26
	T 16	1.02:2.55:2	Slight bitter	6.63
	T 17	1.02:2.55:2.5	Threshold bitter	5.49
	T 18	1.02:2.55:3	Tasteless(Not bitter)	6.97

Taste Evaluation of Resinate

Table 5: - Results of Taste Evaluation Study of DRC

Volunteers	Bitter level after					
	Plain Drug (F1)			Resinate (F4)		
	02sec	10sec	60sec	02sec	10sec	60sec
01	3	3	3	0	0	0
02	3	3	3	0	0	0
03	3	3	3	0	0	0
04	3	3	3	0	0	0
05	3	3	3	0	0	0
06	3	3	3	0	0	0
Mean human response	10	10	10	90	90	90

4.1 Taste Evaluation

Table 6: - Results of Taste Evaluation Study of Formulations

Volunteers	F2			F4		
	10sec	1min	2min	10sec	1min	2min
01	X	1	1	0	0	0
02	X	1	1	0	0	0
03	X	1	1	0	0	0
04	X	1	1	0	0	0
05	X	1	1	0	0	0
06	X	1	1	0	0	0
Mean human response	60	40	40	90	90	90

4.2 Discussion:

Formulation of oral taste masked suspension wasfound to be optimum with different concentration respectively. F1 and F2 batches showedsatisfactory assay result that is it fulfills the officialrequirements (To be complying with IP stated limits arebetween 90 to 110%). But bitternessofsuspension was not satisfactory. F3 is slightly bitter but it will not fulfill the requirement of taste so these three batches were rejected. F4 formulation did not show any bitter tastewhen suspension is kept on the tongue by using time intensity method, which showed excellent taste masking effect of the resin and also on every evaluation parameters.

4.3 Accelerated stability studies: -

Table 7: - Accelerated stability studies.

Accelerated stability study of F4 is shown in Table 7. Study revealed that prepared formulation can remain intact for a long period of time without major changes in assay, viscosity, taste evaluation and sedimentation volume. It was found that formulation remained palatable without any appearance of degradation in assay result.

5.0 CONCLUSION: -

The efficient taste masking was obtained from drug–resin a complex that was formulated as oral

suspension for better patient compliance. Use ofweakcation exchange resin offers superior methodfor preparing taste-masked substrates ofOfloxacin&Ornidazole. Results obtainedin this work shows that drug-resin complexeseffectively masked bitter taste of Ofloxacin&Ornidazole while liquid formulation provideseasier way to administer and getting the child to

Swallow. Also to overcome problem with noncompliance with child especially around 8 years oldfor whom swallowing other dosage form can bechallenging. Thus, the "patient friendly dosage form"of bitter drugs, especially for pediatric, geriatric,bedridden, and non cooperative patients, wassuccessfully formulated using this technology.

6.0 ACKNOWLEDGEMENT: -

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