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FORMULATION AND EVALUATION OF TASTE MASKED AZITHROMYCIN SUSPENSION AND ITS COMPARATIVE EVALUATION WITH MARKETED SAMPLE

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ABSTRACT

Azithromycin, the macrolide antibiotic, is an azalide derived from erythromycin having bactericidal and bacteriostatic activity by inhibiting the mRNA of the bacteria. It is characterized by its bitter taste which is intensified by the amide group which limits its use for children as the oral liquid form is the most favorable form. The taste can be masked by different techniques and materials of which is the ion-exchange resin, flavors and adsorbing agents. Several formulations were carried out by Drug-resin complexation method. It was concluded that the formulation S-7 was satisfactory than other formulations of S-1, S-2, S-3, S-4, S-5 & S-6. The formulations S-7 was compared with a leading brand of marketed sample and it was found to match with formulations S-7 in all aspects. The bitter taste was masked in formulations S-7 better than the marketed sample.

KEYWORDS: Taste Making Suspension, Resins Macrolide Antibiotic.

INTRODUCTION

It may be defined as a coarse dispersion of finely subdivided insoluble solid drug suspended in a suitable liquid (usually aqueous) medium. It is a heterogeneous system consisting of a solid disperses in a solid, liquid or gas. It is a biphasic preparations particle of one or more solids basically it may be flocculated or deflocculated.[1]

ORAL SUSPENSION

It contains one or more active ingredients suspended in a suitable vehicle. Suspended solids may slowly separate on keeping but are easily redisposed. It should be packed in wide mouth bottles.

ADVANTAGES OF ORAL SUSPENSIONS

It is a better means of administration than of solid dosage forms such as tablet,capsules especially when swallowing is difficult.

1. It is an ideal dosage form for infants and old patients because of easyadministration.
2. It contains sub-divided solid particles; surface area is large and this istaken advantage of drugs which are adsorptive.
3. Suspensions are chemically more stable than solutions.

DESIRABLE PROPERTIES OF SUSPENSIONS[2]

It should not be rapid settling of suspended particles.

1. The particles do settle they must not form a hard cake at the bottom of the container.
2. It should be redispersible into uniform mixture when shaken.
3. A suspension should be easily pourable.
4. The colour and odour should be acceptable and pleasing for oral and externaluses.
5. Appropriate preservatives should be incorporated in order to minimize the microbialcontamination.

PROBLEMS OF SUSPENSIONS

1. Wetting of disperse phase.
2. Settling of disperse phase and resuspendibility of settled matter.
3. Particle – particle interactions leads to particle size growth or caking.
4. To formulate a suspension the above problems have to be overcome.

FORMULATION OF SUSPENSIONS[3]

In designing a suspension formula, a number of factors must be kept in sight. First of all a decision has to be taken whether a flocculated or non-flocculated system has to be evolved. Secondly, it's important to ensure that the disperse phase particles are well dispersing in the continuous phase. Then finally the decision have to be taken about suspending agents, dispersants, organoleptic additives and preservatives is required to produce satisfactory suspension.

The choice of an appropriate suspending agent depends upon the use of products,facilities for preparation and the duration of product storage.

Azithromycin is a broad-spectrum macrolide antibiotic with a long half-life and a high degree of tissue penetration. It was initially approved by the FDA in 1991. It is primarily used for the treatment of respiratory, enteric and genitourinary infections and may be used instead of other macrolides for some sexually transmitted and enteric infections. It is structurally related to erythromycin. Azithromycin [9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin] is a part of the azalide subclass of macrolides, and contains a 15-membered ring, with a methyl-substituted nitrogen instead of a carbonyl group at the 9a position on the aglycone ring, which allows for the prevention of its metabolism.[4]

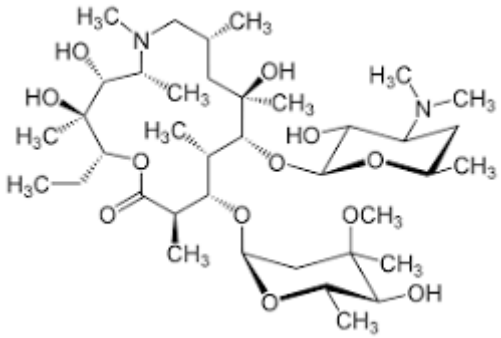

Figure 1: chemical structure of azithromycin.

EXPERIMENTAL WORK

MATERIALS AND METHODS

Azithromycin collected from Apex Laboratories P Ltd, Indion-204, Sucrose, Sorbitol Solutions (70%), Xanthan gum, Propylene glycol IP, Sodium Benzoate IP, Methyl paraben IP

Propyl Paraben IP, Citric Acid monohydrate, Sodium Citrate IP, Sodium chloride, Glycerin, Sunset Yellow FCF, Tween-80, Masking Flavour 2521, Orange oil Flavour purchased from the Analytical standard from the chemical distributors Hyderabad.

Preformulation studies[5]

Preformulation investigations are designed to deliver all necessary data (especially physicochemical and Biopharmaceutical properties of drug substance, excipients and packaging materials) which may influence

- Formulation design
- Method of manufacture of drug substance and drug product
- Pharmacokinetic/Biopharmaceutic properties of the resulting product
- Packaging of the product

Preformulation steps

Calculation of many of the important physico-chemical characteristics of drug Solubility.

PROCEDURE

Solubility of API and the excipients in different selected media was determined by dissolving the known quantity in cumulative manner with the aid of sonication till the API or the excipients remains insoluble in the media.

Preparation of 0.1N Hydrochloric Acid (1.2pH)

8.5ml of the hydrochloric acid was taken and dissolved in water andmade upto 1000ml to get 0.1N hydrochloric acid.

DETERMINATION OF λmax[8]

30g of Ammonium acetate was dissolved in 50 ml of water. 1 ml of Acetyl acetone was added and the final volume was adjusted to 100ml with water and stored in refrigerator. Freshly prepared reagent was used in the analysis. 250mg of Potassium permanganate was dissolved and diluted to 100ml with water. 10gm of Oxalic acid was dissolved and diluted to 100ml with water. 250mg of Azithromycin was accurately weighed and transferred to a 100ml volumetric flask. It was dissolved in 20ml of glacial acetic acid and diluted to 100ml with distilled water. 5ml 0f an aliquot was further diluted in 50ml of water to obtain the final concentration of 250 µg/ml.

In a 10ml volumetric flask, 2ml of standard Azithromycin solution and 1ml glacial acetic acid solution were pipetted successively. 0.2ml of potassium permanganate solution was added. The reaction mixture was heated on water bath at 37°C for 10min. Excess of potassium permanganate was neutralized with oxalic acid. 2ml of reagent solution was added to it and mixed thoroughly. The reaction mixture was heated on water bath at 37°c for 1min and cooled. The volume was adjusted upto the mark with water. Absorbance of the coloured solution was scanned on UV-Visible spectrophotometer from 600nm to 200nm against reagent blank. Maximum absorbance was obtained at 412nm

PREPARATION OF CALIBRATION CURVE

25mg of Azithromycin was weighed accurately and transferred to a 100ml standard flask. To that 1ml of Hydrochloric acid was added and the volume was made upto the mark using deionized water. From the stock solution 2, 4, 6, 8 and 10ml was pipetted out in a 10ml standard flask. To each of the standard flask, 0.2ml of potassium permanganate solution was added. The mixture was heated on water bath for 10 min at 37 ^{0}C. Excess of potassium permanganate was neutralized with oxalic acid. 2ml of reagent solution was added to it and mixed thoroughly. The mixture was heated on water bath for 1 min at 37^0 C and cooled. The volume was adjusted upto the mark with deionized water. Absorbance of the solution was measured against a reagent blank at 412nm

FORMULATION DEVELOPMENT[9-10]

Following ingredients were selected to develop the desired formulation.

Table 2: Formulation of suspension.

S.No	Ingredients	S-1	S-2	S-3	S-4	S-5	S-6	S-7
1	Azithromycin (g)	10	10	10	10	10	10	10
2	Indion-204 (g)	2.5	5	7.5	10	20	25	30
3	Sucrose (g)	300	300	300	300	300	300	300
4	Xanthan gum (g)	1.5	1.5	1.5	1.5	1.5	1.5	1.5
5	Tween 80 (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
6	Sorbitol (g)	100	100	100	100	100	100	100
7	Propylene glycol (g)	50	50	50	50	50	50	50
8	Methyl paraben (g)	1	1	1	1	1	1	1
9	Propyl paraben (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
10	Sodium citrate (g)	1.5	1.5	1.5	1.5	1.5	1.5	1.5
11	Citric acid (g)	1	1	1	1	1	1	1
12	Sodium chloride(mg)	1.25	1.25	1.25	1.25	1.25	1.25	1.25
13	Glycerin (g)	50	50	50	50	50	50	50
14	Mint flavour (ml)	10	10	10	10	10	10	10
15	Orange oil flavour(ml)	5	5	5	5	5	5	5
16	Sunset yellow FCF (mg)	25	50	50	50	50	50	50
17	DM Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s

PROCEDURE[11]

Drug and ion exchange resins were weighed accurately. Then the resin was poured into DM water. The drug was added in to the resinate with continuous stirring to get drug resinate. Sucrose was added to 150 ml of DM water and boiled for complete dissolving of sucrose. Then the sorbitol was mixed with the sugar solution. Xanthan gum was poured in to glycerin and mixed to dissolve the gum completely. Tween 80 was added in to the drug resinate. The sugar, sorbitol solution and xanthan gum solution were added in to the drug resinate formulation. Methyl paraben and propyl paraben were added separately into propylene glycol and dissolved completely. This was added to the drug resinate formulation. Sodium citrate, citric acid and sodium chloride were dissolved in DM water and poured in to the drug resinate formulation. The flavors and colour were added into the drug resinate formulation. Finally suspension was made up to 1000 ml with DM water and mixed for 30 minutes.

EVALUATION OF SUSPENSIONS[12-13]

Taste evaluation of optimized formulation

The taste evaluation was performed with 10 volunteers in the age group of 19-25 yrs. The Formulation (S-7) was held in the mouth for 15 seconds by each volunteer and the bitterness level was recorded against pure drug using a numerical scale.

pH

pH is be defined as the negative logarithm of hydrogen ion concentration.

Mathematically it is written as

$$pH = \log 1/ [H3O^+]$$

Since the logarithm of 1 is zero.

The equation may also be written

$$pH = - \log(H3O^+)$$

➢ **Determination of pH**[80]

pH of suspension was determined by using pH meter. pH of the phases of suspension also contributes to stability and characteristic of formulations. pH of the suspension was recorded from time to time.

Viscosity

Viscosity of suspension is a great importance for stability and palatability of suspensions. Suspensions have least physical stability amongst all dosage forms due to sedimentation and cake formation.[78]

Sedimentation is governed by stoke's law,

$$V = d^2 (\rho s - \rho l) g / 18 n$$

V - Terminal settling velocity

d – Diameter of the settling particle

ρs – density of the settling solid (dispersed phase) ρl - density of the liquid (dispersion medium)g

– Acceleration due to gravity

– Viscosity of dispersion medium

When the viscosity of dispersion medium increases the settling velocitydecreases.

➢ **Determination of viscosity**

The viscosity of suspension was determined at ambient condition using Brookfield digital viscometer taking adequate amount of the sample.

Sedimentation Volume

Sedimentation volume F is the ratio of equilibrium volume of sediment (Vu) to the total volume of suspension (Vo).[77]

$$F = Vu / Vo$$

Vu - Volume of sediment

Vo - total volume of suspension

The sedimentation volume F normally ranges from less than 1 to 1. When F=1, the sediment volume and the

total volume are equal and such a suspension is pharmaceutically acceptable.

Determination of sedimentation volume

Sedimentation volume was determined as a function of time. 50ml suspension was transferred to a 100 ml measuring cylinder of 2.5cm diameter. Thesedimentation volume F was determined.

Assay

Accurately measured volume (5ml) of suspension was transferred to a 50ml volumetric flask, the volume was made up with 0.1N HCl to break the complex and sonicated for 30min. To the above solution 0.2ml of potassium permanganate was added and heated for 10 mins at 37^0C. The excess of potassium permanganate was neutralized with oxalic acid. To the resulting mixture, 2ml of reagent solution was added and heated at 37^0C for 1 min. The absorbance of the resulting solution was measured at 412nm taking a reagent blank.

***In vitro* Dissolution study**

Dissolution profile of Azithromycin suspension was determined using the USP (type II) paddle apparatus with a speed of 50 rpm. Dissolution was tested in acidic buffer 0.1N HCl of 900ml at 37 ±0.5˚C. Aliquot volume was withdrawn at 10, 20, 30 and 60 min and filtered through 0.45µ membrane filter. To that 0.2ml of potassium permanganate was added and heated for 10 min at 37^0C. The excess of potassium permanganate was neutralized with oxalic acid. To the resulting mixture, 2ml of reagent solution was added and heated at 37^0C for 1 min. The absorbance of the resulting solution was measured at 412nm taking a reagent blank.

RESULTS AND DISCUSSION

PREFORMULATION STUDIES

Solubility Studies

Solubility studies were done for candidate drug and excipients as per requirement of development.

Table 3: Solubility of ingredients in different solvent.

Solute	Ethanol	Ether	Water	Acetone	Chloroform
API	Freely Soluble	ND	In soluble	Freely soluble	ND
Sucrose	ND	ND	Very Soluble	ND	In soluble
Xanthan gum	In soluble	In soluble	Soluble	ND	ND
Tween80	Soluble	In soluble	Soluble	ND	ND
Sorbitol	Slightly soluble	In soluble	Very Soluble	ND	In soluble
Sodium citrate	In soluble	ND	Freely Soluble	ND	ND
Citricacid monohydrate	Freely Soluble	Sparingly soluble	Very Soluble	ND	ND
Sodium chloride	Slightly soluble	ND	Freely Soluble	ND	ND
Sodium benzoate	Sparingly soluble	ND	Freely Soluble	ND	ND
Glycerin	Miscible	ND	Miscible	Slightly soluble	In soluble
Propylene glycol	Miscible	Soluble	Miscible	Miscible	Miscible
Methyl paraben	Freely Soluble	ND	Slightly Soluble	ND	ND
Propyl paraben	Freely Soluble	Freely Soluble	Slightly Soluble	ND	ND

*** ND – Not Dissolved**

Azithromycin was soluble in ethanol and insoluble in water. All theingredients were soluble in water.

CALIBRATION CURVE FOR AZITHROMYCIN

Table 4: Data for Calibration Curve of Azithromycin in 0.1N HCl.

Concentration(mcg/mL)	Absorbance
0	0.0000
2	0.1600
4	0.3300
6	0.4970
8	0.6570
10	0.8310

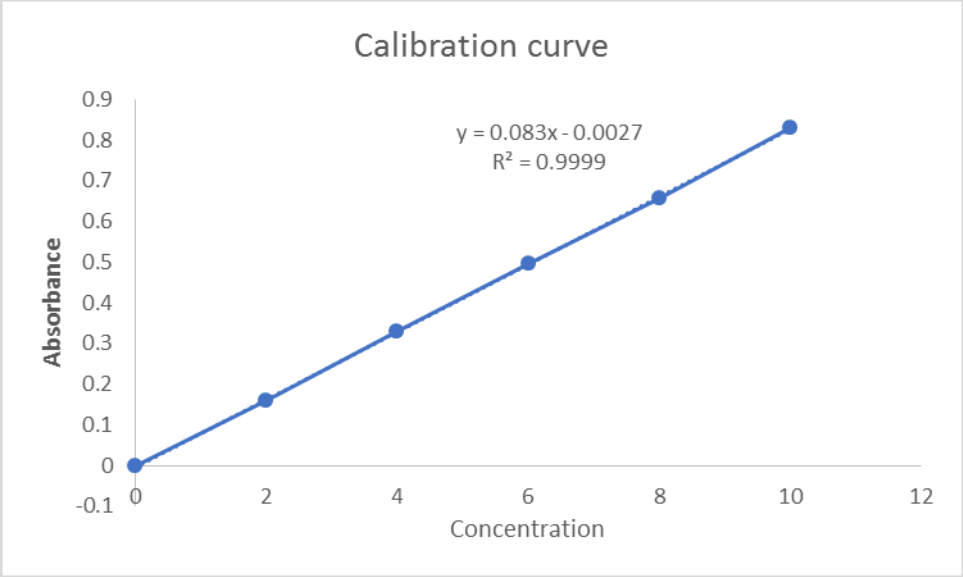

Fig. 2: Calibration Curve of Azithromycin.

It was found that the solutions of Azithromycin in 0.1N HCl show linearity (r^2= 0.999) in absorbance at concentrations of 2-10mcg/ml and obeys Beer Lambert Law.

FORMULATION DEVELOPMENT

(a) Evaluation of Formulated Azithromycin Suspension

Table 4: Evaluation of Azithromycin suspension.

S.No	Test for evaluation	Observation						
		S -1	S - 2	S- 3	S- 4	S -5	S – 6	S - 7
1	Taste	Bitter	Bitter	Bitter	Bitter	Bitter	Slightly Bitter	Not Bitter
2	Ph	3.54	3.58	3.61	3.67	3.70	3.64	3.66
3	Viscosity (Cps)	576	589	632	648	644	652	665
4	Sedimentation volume (F)	0.94	0.95	0.96	0.97	0.97	0.99	0.99

Oral suspensions were formulated in different combinations S-1, S-2, S-3, S-4, S-5,S-6,S-7 From the above formulations, it was found that the bitter taste was not masked for formulations S-1, S-2, S-3, S-4 & S-5.Slightly bitter taste was observed in the formulation, S-6. The taste was completely masked in formulation S-7.The pH of formulations S-1 to S-7 ranged from 3.54 to 3.70 and the viscosity ranged from 576 to 665 Cps. The sedimentation volume (F) ranged from 0.94 to 0.99.

Drug Content

Table 5: Drug content of formulated Azithromycin suspension.

S.No	Formulation	Drug content (%)*
1	S -1	98.9 ± 0.0031
2	S -2	97.85 ± 0.1021
3	S -3	99.70 ± 0.187
4	S -4	98.34 ± 0.1542
5	S -5	99.16 ± 0.0021
6	S -6	99.89 ± 0.078
7	S -7	99.78 ± 0.0245

***Mean ±SD (n=3)**

The drug content of the suspension ranged from 97.85% to 99.85%. The drug content of the formulation were within the limits.

Table 6: *In vitro* drug release of formulated Azithromycin suspension.

Time (min)	CUMULATIVE % DRUG RELEASE*						
	S- 1	S-2	S-3	S-4	S-5	S- 6	S- 7
10	79.44± 0.02	74.62±0.05	72.05±0.0360	69.05±0.0	67.02±0.0	65.44±0.03	59.82±0.056
20	95.81±0.005	91.86±0.02	83.43±0.0264	80.89±0.00	80.12±0.0	78-47± 0.03	75.02±0.05
30	99.79±0.010	99.88±0.01	97.92±0.0125	93.25±0.06	92.22±0.0	86.19±0.08	84.02±0.061
60	-	-	99.82±0.0264	99.72±0.04	99.72±0.0	99.86±0.03	99.62±0.085

***Mean ±SD (n=3)**

As the concentration of the resin was increased, the release of the drug from the formulation was sustained. Formulation S-1 & S-2 showed maximum release within 30 min.

Table 7: Comparative Evaluation Of Marketed Sample And Formulation S-7.

S.No	Test for evaluation	Observation	
		Marketed sample	Formulation S –7
1	Taste	Slight Bitternessobserved	Bitterness completelymasked
2	pH	3.68	3.66
3	Viscosity (Cps)	660	665
4	Sedimentation volume (F)	0.99	0.99
5	Colour	Orange	Pale yellow
6	Drug Content * (%)	99.03 ±0.0267%	99.78 ±0.0245%

***Mean ±SD (n=3)**

From the comparative study between marketed sample and S7 formulation it was found that the bitter taste of Azithromycin was completely masked in formulations S7. The other parameters were found to be the same as with marketed formulation.

Table 8: Comparative Dissolution Profile of OptimizedFormulation S-7 With Marketed Sample.

Time (min)	% DRUG RELEASED*	
	Marketedsample	Formulation S-7
10	61.98±0.0929	59.82±0.0568
20	75.35±0.0513	75.02±0.0512
30	83.98±0.0953	84.02±0.0611
60	99.79±0.0624	99.62±0.0850

***Mean ±SD (n=3)**

The *in vitro* drug release from the marketed sample and formulation S-7 aresimilar.

SUMMARY AND CONCLUSION

Several formulations were carried out by Drug-resin complexation method.

It was concluded that the formulation S-7 was satisfactory than otherformulations of S-1, S-2, S-3, S-4, S-5 & S-6. The formulations S-7 was compared with a leading brand of marketed sample and it was found to match with formulations S-7 in all aspects. The bitter taste was masked in formulations S-7 better than the marketedsample.

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