Research Article

Comparative Study of Resins in the Formulation of Taste Masked Suspension of Erythromycin

Saini Pradeep, Chakraborty Tulshi, Jain Akash, Chaudhary Jasmine, Saini Vipin
M.M. College of Pharmacy, Maharishi Markandeshwar University, Mullana (Ambala), India.
***Corresponding author's E-mail:** pradeepsainipharmacist@gmail.com

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ABSTRACT

Many patients have difficulty in swallowing tablets or hard gelatine capsules and consequently do not take medication as prescribed especially in case of paediatric and geriatric patients. The objective of present study is to provide a taste masked suspension of macrolide antibiotic i.e. erythromycin using the ion exchange resins which can deliver a Pharmaco- kinetically and Pharmaco-dynamically acceptable dosage form. In the present investigation the bitter taste of erythromycin is masked by using three different resins i.e. Indion-204, Doshion-p-542 and Kyron -T-114. A number of formulations have been prepared by using different ratio of resin with drug i.e.1:1, 1:2 and 1:3 for suitable combination along with a control formulation. The prepared formulation has been evaluated by using the different parameters such as particle size, pH, sedimentation volume, taste, color, *In-vitro* drug release and stability studies. These studies concluded that our prepared taste masked oral suspension of erythromycin Estolate S7 is easily redispersibility and at pH 1.5 has cumulative % of drug release is 98.1±0.06 within 60 minute. Moreover, the taste evaluation of prepared formulation has been evaluated through spectroscopic methods and palatable evaluation and thereby the macrolide antibiotic could be masked taste for the patient's compliance.

Keywords: Erythromycin, Optimization, Paediatric, Resin, Taste masking.

INTRODUCTION

Suspensions are heterogeneous systems, or more precisely biphasic systems may be defined as coarse dispersions in which insoluble solids are suspended in a liquid medium. A suspension is often chosen as pharmaceutical dosage form for drugs insoluble in water and aqueous fluids at the dosage required for administration and when attempts to solubilise the drug would compromise stability and safety. For oral administration, the taste of a bitter or unpleasant drug can often be masked by choosing an insoluble form of the active drug. Taste masking of liquid formulation present a major challenge because the majority of paediatric preparations are syrups and suspensions.[1] Some pharmaceutical compositions have utilized this concept and suspended the drug at a pH in which it remains insoluble.

Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide antibiotics. It is basic and readily forms salts with acids but it is the base which is microbiologically active. It was insoluble in water and soluble in 0.1N HCl and organic Solvents. [3]

When an ionisable drug reacts with ion exchange resin the drug resin complex formed known as drug resinate. The drug resinate can be made sufficiently stable that does not break down in the mouth so that the patient does not feel taste of drug when it is swallowed. However, when the drugs resinate comes in contact with gastrointestinal fluids, the complex is broken down quickly.

Indion-204[4]

Appearance: White to pale white or pale cream colour powder free from foreign matter.

Matrix: Copolymer of acrylic acid and methacrylic acid.

Solubility: Insoluble in water and in common solvents.

Ionic form: Sodium

It is a weak acid cation exchange resin. It is used as taste masking agent and tablet disintegrants. It forms a complex with drug, which does not release the drug in saliva, but weak enough to be broken by the hydrochloric acid present in stomach. It is a high molecular weight polymer therefore not absorbed by body tissues and is safe for human.[5]

Kyron T-114[4]

Resin type**:** Weak acid cation exchange resin

Synonym**:** Polacrilex resin

Matrix type**:** Cross linked polymethacrylic acid with divinyl benzene

Functional group**:** Carboxylic acid

Standard ionic form**:** H+

A drug polymer complex can be synthesized due to the Bonding between the bitter drug and the polymer thus masking the objectionable bitter taste of the drug. Since the polymer drug complex so formed is tasteless in the mouth but it dissociate in the acidic pH of the stomach, the bioavailability of drug is not affected. Example: Azithromycin, Roxithromycin, Erythromycin.

Storage

Stored in tightly closed container. Keep away from moisture. (If moisture is absorbed, dry at 90 0 C to 100 0 to remove moisture content below 10 %).

Doshion-P-542[5]

Resin type: Weak acid cation exchange resin

Appearance: White Powder

Matrix type: Methaacrylic acid divinyl benzene

Functional group: Carboxylic acid

pH Range :- 5.0 to 7.0

Standard ionic form: H+

Taste masking of bitter drugs in suspension like Azithromycin, Roxithromycin, and Erythromycin and tablets like Norfloxacine & combinations and used in water treatment.

MATERIALS AND METHODS

Erythromycin Estolate, indion-204 was obtained from K-pharma, Ambala Cantt. Doshion –p-542, Colouring and flavouring agent is procured from Orrison pharmaceuticals, Ambala Kyron-t-114 was obtained from Crystal Pharmaceuticals, Ambala City and all other material was provided by the college store which was supplied by Qualikem, Vadodara and Nice chemicals pvt. Ltd., Cochin and many others.

Method

Dose conversion of Erythromycin salt

Erythromycin is available as salt or ester forms. Estolate salt of erythromycin is used for the preparation of the taste masked suspension of Erythromycin in which 1 g of Erythromycin is equivalent to 1.44g of Erythromycin Estolate. The equivalent dose of Erythromycin Estolate is calculated as 125mg/5ml of the syrup based suspension. The each batch (100ml) of suspension was prepared with the different ratio of different resin using 2.5 g of Erythromycin Estolate.

Preparation of drug resin complex

Weighed quantity of resin was added in clean beaker containing specified quantities of water with stirring for 15 min. Weighed quantity of Erythromycin Estolate was added in resin solution and stirred for 4-5 hrs continuously. Liquid obtained after stirring was collected and used for further preparation of suspension.

Preparation of syrup base

A weighed quantity of Sucrose was dissolved in specified quantity of boiled water and filtered. Weighed quantities of Sorbitol, Glycerine, Tween-80, CMC, Citric acid, Methyl paraben and Propyl paraben, were added in sugar solution with stirring.

Mixing of Drug-Resin complex with Syrup

The drug resin complex (mother liquor) obtained was added in to sugar solution with stirring. Weighed quantities of colouring & flavouring agents were added in above solution & stirred for 10 min. The volume of suspension was made up to required quantity (100 ml) by using purified water. (Table 2)

Evaluation of Suspension

Colour, odour and taste

All the prepared batches of suspension were evaluated for organoleptic properties such as colour, odour and taste.[6,7]

Determination of sedimentation volume (F)

The formulated suspensions were evaluated for physical stability by determining the sedimentation Volume. Fifty ml each of suspension was taken in 50 ml stopped graduated measuring cylinder. The suspension 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 (H_0). The cylinder was kept undisturbed for 14 days. The volume of sediment read at 1 hr and on the 14th day was considered as final volume of sediment (Hu). The redispesibility of the suspensions was checked by moving the stoppered cylinder upside down until there was no sediment at the bottom of the cylinder. Results of Sedimentation Volume are shown in result and discussion.

$$\text{Sedimentation Volume (F)} = \frac{Hu}{H_0}$$

The sedimentation volume can have values ranging from less than 1. 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. [8]

Determination of Viscosity

The rheological parameters of the prepared suspensions, in terms of viscosity, are determined by use of the steady shear method, measuring the “non-Newtonian viscosity”. Viscosity studies were carried out using a Brookfield viscometer. The limits on viscosity were selected as such that the suspension reaches a physically stable state. Viscosity is a critical parameter of suspension. The help of a Brookfield synchrolectic viscometer determines. In a 25 ml glass beaker 15ml of suspension has taken and the viscometer is set over the beaker by a stand such a way that its bob is completely immersed in the suspension. Switch on the viscometer and run it till its indicator is shifted from red zone to green zone. Spindle no.1 was used to measure the viscosity of suspension. [9]

pH

pH of the suspension was determined by the use of pH meter

Assay of suspension

10 ml of suspension was taken in 100 ml volumetric flask & volume was made up to 100 ml with 0.1 N HCL. sonicate it for 15 min. Take 2 ml solution in to 200 ml volumetric flask, volume was made up to 200 ml with 0.1 N HCL & filtered. Absorbance was measured at wavelength 278 nm in U.V. Spectrophotometer & compared with standard and then % drug content was calculated. [10-12]

Taste evaluations

Bitter taste was evaluated based on human bitter taste recognized by volunteers.

Volunteers in the age group of 20 to 25 years performed taste evaluation of suspension. The study protocol was explained and written consent was obtained from volunteers. 5 ml suspension was tested in the mouth for 15 seconds by each volunteer, and the bitterness level was recorded against pure drug.[13-15]

In-Vitro drug release

In vitro drug release of the suspension was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 500ml 0.1N HCL, was placed into the dissolution flask maintaining the temperature of 37 + 0.5 ^{o}C and rpm of 50. 5 ml suspension was placed in each bucket of dissolution apparatus. The apparatus was allowed to run for 45 minutes. Samples measuring 10 ml were withdrawn after every 5, 10, 15, 20, 30, & 45, min. using auto sampler. During sampling samples were filtered through 10 µm filter which was in inline with auto sampler. The fresh dissolution medium was replaced every time with the same quantity of the sample. Collected samples were suitably diluted with 0.1N HCL and analyzed at 278 nm using 0.1 N HCL as blank. The cumulative percentage drug release was calculated.[16]

Particle size Analysis

The size was measured using an optical microscope and the mean particle size was calculated by measuring size of 200 particles with the help of a calibrated ocular micrometer. The slide containing suspension particles was mounted on the stage of the microscope and diameter of at least 100 particles was measured using a calibrated optical micrometer. Photomicrographs (10 x magnifications) of resin and suspension were taken.[17, 18]

Accelerated Stability Study

Erythromycin Estolate suspension was packed in 60 ml glass bottle. The packed bottles were placed in stability chamber maintained at 40 + 2 ^{o}C and 75 + 5% RH for 1 month. The samples were withdrawn after one month and were observed for changes on the physical parameter (i.e. change in colour, Assay, viscosity, any bad odour & pH). [19-23]

Table 1: Formulation of taste masked suspension of Erythromycin Estolate

Ingredients	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
Erythromycin Estolate(g)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Tween-80 (g)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Sucrose (g)	30	30	30	30	30	30	30	30	30	30
Sorbitol (g)	10	10	10	10	10	10	10	10	10	10
CMC (g)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Citric acid (g)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Methyl paraben (mg)	10	10	10	10	10	10	10	10	10	10
Propyl paraben (mg)	4	4	4	4	4	4	4	4	4	4
Glycerin(ml)	8	8	8	8	8	8	8	8	8	8
Butter scotch Flavour (ml)	1	1	1	1	1	1	1	1	1	1
Carmine Red (mg)	25	25	25	25	25	25	25	25	25	25
Indion-204	-	2.5	5	7.5	-	-	-	-	-	-
Kyron-T-114	-	-	-	-	2.5	5	7.5	-	-	-
Doshion-P-542	-	-	-	-	-	-	-	2.5	5	7.5
Distilled Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Where S1 is the control formulation

RESULTS AND DISCUSSION

Taste, odour and Colour are considered to be important factor for the suspension especially in case of children and elderly patients. All the developed batches of suspension were evaluated for organoleptic properties and the Formulation S7 was found to be most palatable formulation (Table 2).

Viscosity of Suspension is very important factor for the stability of suspension because viscosity contributes to rate of sedimentation, higher the viscosity, lower is the

rate of sedimentation. Viscosity studies were carried out using a Brookfield viscometer. The viscosity of the suspension is increased with increase in the ratio of resin. The optimize Viscosity of formulation S7was found to be 726 cps , pH is a considerable factor in case of taste masked suspension. pH is important for the complexation of drug and resin. The pH is very is important for release of drug from complex. pH of the suspension was determined by the use of pH meter. The pH of taste masked suspension is acidic range. The pH of suspension is increased in ratio of the resin and formulation S7 has a optimize pH of 4.17. Assay of Erythromycin Estolate Suspension was carried out in 0.1N HCl. The formulation S7 has a good % drug Content. (Table 3)

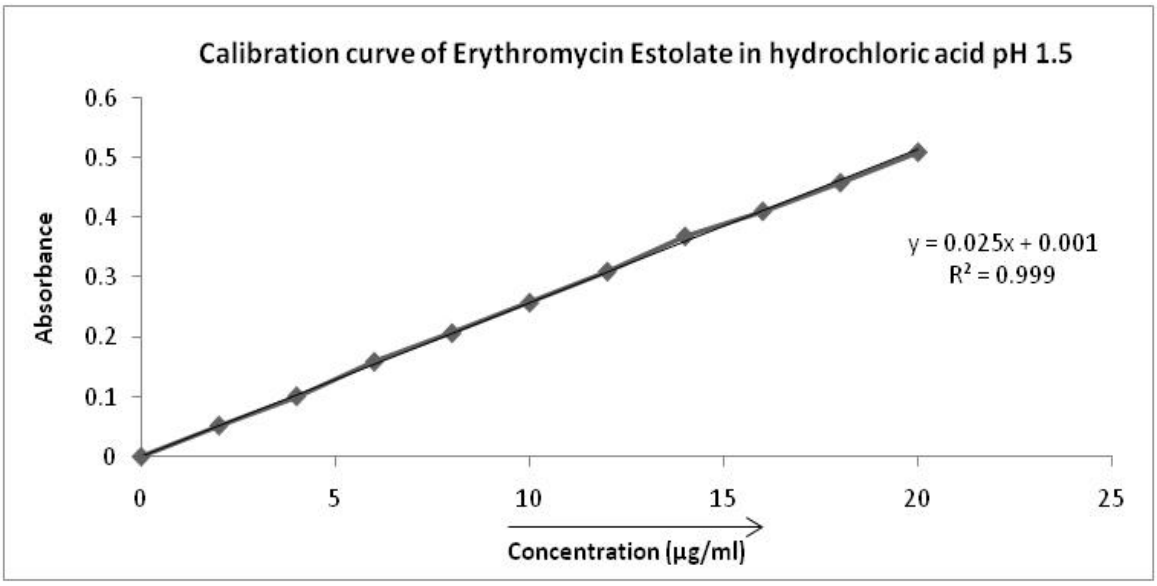

Figure 1: Calibration curve of pure drug in hydrochloric acid pH 1.5

Table 2: Organoleptic Evaluations

Formulation code	Colour	Taste	Odour
S1		Bitter	
S2		Bitter	
S3	*O*	Slightly bitter	*B S*
S4	*R*	Not Bitter	*U C*
S5	*A*	Bitter	*T O*
S6	*N*	Slightly bitter	*T T*
S7	*G*	Not Bitter	*E C*
S8	*E*	Slightly bitter	*R H*
S9		Slightly bitter	
S10		Not Bitter	

Table 3: Evaluations of suspension

Formulation Code	*Average Particle Size(µm)*	*Viscosity(cps)*	*pHof Suspension*	*Assay (cumulative % drug release)*
S1	357	74.1	3.54	76.6
S2	360	569	3.59	98.24
S3	367	632	3.66	98.98
S4	380	665	3.70	99.97
S5	345	695	3.90	97.98
S6	365	704	3.96	98.25
S7	395	726	4.11	98.67
S8	365	630	4.26	97.69
S9	378	641	4.35	98.63
S10	369	698	5.0	99.96

Table 4: *In-Vitro* drug release of Suspension

Time (min.)	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
0	0	0	0	0	0	0	0	0	0	0
5	23±0.3	25±0.5	22±0.7	20±0.9	21±0.6	23±0.6	34±1.0	25±0.9	26±0.9	24±0.9
10	34±0.7	36±0.7	33.5±0.09	31±0.6	32±0.3	34±0.9	45±0.5	36±0.3	36.5±0.07	35±0.8
15	45±0.9	46.5±0.09	54±0.9	43±0.7	44±0.4	44.6±0.05	66.5±0.09	47.5±0.07	47±0.02	46±0.7
20	55.5±0.08	58±0.8	66±0.5	55±1.0	65±0.9	56±0.9	77±0.8	58±0.9	68±0.5	58±0.9
30	66±1.2	79±1.2	77±0.8	67±1.2	76±0.9	68±1.0	88±1.2	69±1.8	79±1.4	79±1.6
45	78±2	85±2	89±1.2	88±2.0	89±1.8	82±1.2	93±2	89±2	89.5±2	87±2
60	91±1.2	92±1.2	94±2	97±1.2	93±1.6	95±2	98.1±0.06	94±1.6	95±1.6	97±1.9

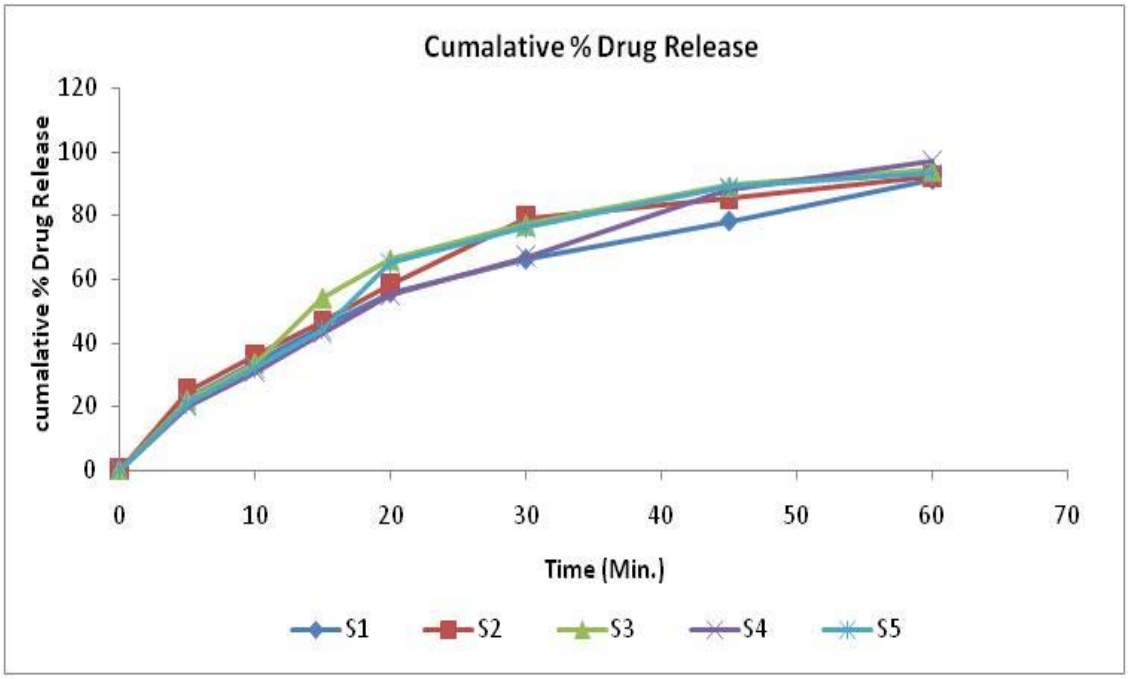

Figure 2: *In-Vitro* drug release of Suspension (S1-S5)

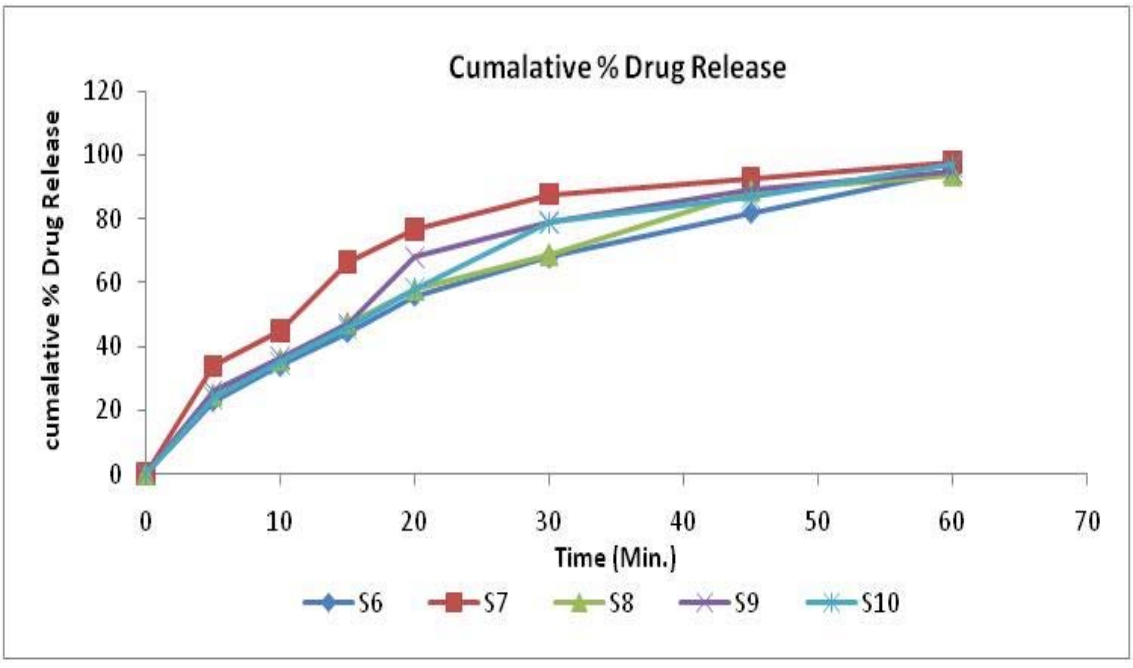

Figure 3: *In-Vitro* drug release of Suspension (S6-S10)

Taste Evaluation

In Taste of the formulation is the lifeline in these investigations as taste masked suspension is formed and taste masking is only evaluated by the taste evaluation. Taste evaluation carried out on volunteer's shows that the formulation S7 has been most palatable formulation in all the prepared formulation.

Now, from the above discussions we can conclude the S7 is optimized Taste masked Formulation. This shows that the Kyron –T-114 in 3:1 with the drug is most suitable resin to prepare the Tasked masked Suspension of Erythromycin Estolate. Therefore carried out the accelerated stability studies for Formulation S7 Table.

Accelerated stability study of S7 revealed that prepared formulation can remain intact for a long period of time without major changes in assay, viscosity and sedimentation volume. It was found that formulation remained palatable without any appearance of degradation in assay result (Table 6).

It was observed that with a increase in ratio of resin the drug release form the suspension is also increased. The release showed by formulations in 1hr (Table 4) The suspension S7 has the highest drug release which can be easily revealed in plot (Fig.2 and 3). The Drug in ratio 1:3 with the kyron –t-114 has highest release from the suspension.

Table 5: Accelerated Stability Study of S7 Formulation

Evaluation Parameters	Initial	After 1 month
Color	Orange	Orange
Viscosity (cps)	726	724
pH	4.11	4.09
Sedimentation volume	1	1
Assay %	98.67	98.65
Taste	Not Bitter	Not Bitter
Particle Size	395	395

CONCLUSION

Oral suspensions of bitter drug Erythromycin Estolate using Ion Exchange technique had good palatable taste and optimum parameters were successfully formulated which may be useful for children and elderly patients. On the basis of results obtained from executed experiments it can be concluded that, the preformulation studies like pH, melting point, solubility and UV-analysis of Erythromycin Estolate were complied with British Pharmacopoeia standards. The FTIR Spectra revealed that, there was no interaction between Resins and drug (Figure 1). Resins used were compatible with Erythromycin Estolate. Kyron –T-114 is better resin in masking the taste of bitter Erythromycin Estolate in comparison to Indion-204 and Doshion –P-542.In the further evaluation, it was revealed that kyron –T-114 is most effective in optimize ratio of 1:3 with the drug. On the basis of Particle size, pH, Assay, viscosity, *in vitro* release studies and Taste evaluation, S7 was selected as an optimized formulation of Taste Masked suspension. The S7 formulation can remain intact for a long period of time without major changes in assay, viscosity and sedimentation volume. It was found that formulation remained palatable without any appearance of degradation in assay result.

In conclusion, it is possible to formulate taste mask suspension of bitter drug viz. Erythromycin Estolate by Ion Exchange method.

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