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Taste masked oral formulation of Ambroxol Hydrochloride using Ion Exchange Resin.

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ABSTRACT

In the present research work attempt was to formulate tasteless complexes of Ambroxol hydrochloride using cation exchange resins and to evaluate molecular properties of drug complexes. Tulsion 343 that contained crosslinkedpolyacrylic backbone was used. The drug loading onto ion-exchange resin was optimized for mixing time, activation, effect of pH, mode of mixing, ratio of drug to resin, and temperature. Drug resin complexes (DRC) were evaluated for taste masking and characterized by x-ray diffraction study and infrared spectroscopy.Ambroxol hydrochloride is a potent mucolytic agent capable of inducing bronchial secretion. It is used in the treatment of asthma, bronchitis and cough.It is a highly bitter drug and not suitable for pediatric patients hence taste masking of drug was required. Ambroxol hydrochloride-Tulsion 343 complex of ratio 1:0.7% w/w was developed into suspension formulation using different suspending agents with varying concentration and was evaluated for sedimentation volume, pH, drug content and viscosity. The prepared suspensions were evaluated for taste, drug content, particle size, viscosity, sedimentation volume, drug release. The results showed that Ambroxol Hydrochloride was successfully taste masked,showed easy redispersibility and more than 80% drug release within 45 minutes and when compared with marketed preparation.

Key words: Tulsion 343, Drug-resinate complex, Taste masking, Suspension

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INTRODUCTION

Convenience of administration and patient compliance has gained significant importance in the design of dosage forms. Recently, more stress is laid down on the development of an organoleptically elegant and patient-friendly drug delivery system for pediatric and geriatric patients[1-2]More than 50% of the pharmaceutical products are orally administered for several reasons, and undesirable taste is one of the important formulation problems encountered with such oral product taste of a pharmaceuticalproduct is an important parameter for governing compliance. Thus, taste masking of oral pharmaceuticals has become an important tool to improve patient compliance and the quality of treatment especially in pediatrics and geriatrics. Therefore, formulationof taste masked products is a challenge to the pharmacists . Ion exchange resins have been increasingly used as taste masking agent[3]. The complex of cationic drug and strong cation exchange resin does not break at the pH of saliva i.e. 6-7 with cation concentration of 40 meq/l, thereby imparting no bitter taste in the mouth.[6-7]Ambroxol Hydrochloride is a potent mucolytic agent capable of inducing bronchial secretion. It is used in the treatment of asthma, bronchitis and cough. It works to decrease mucus viscosity by altering its structure. With respect to preparations, such as cold and cough syrups, the bitterness of the preparation leads to lack of patient compliance. It will be much advantageous to present such drug in suspension form. It is extremely bitter in taste and should be masked to formulate it in a palatable form.The purpose of this research was to formulate tasteless complexes of Ambroxol Hydrochloride with Tulsion 343 and attempt was made to develop patient friendly dosage for i.e. taste masked suspension.

MATERIALS AND METHODS

Ambroxol Hydrochloride was a gift sample from Cipla Limited (Mumbai, India). Tulsion 343 was obtained from Thermax (Pune, India). All other chemicals and reagents used were of high analytical grade.

Preparation of drug resin complex (Resinate)

Resinates were prepared by batch method. An accurately weighed amount of drug (100 mg) was dissolved in 100 ml of distilled water. Then ion exchange resin (100 mg) was added and stirred on a magnetic stirrer for 180 min. Resinate thus formed was filtered with whatman filter paper and washed with deionised water to remove any uncomplexed drug. Unbound drug was estimated spectrophotometrically at 244.4 nmand the drug loading efficiency was evaluated

Determination of drug content in the resinate

Accurately weighed 100 mg drug equivalent resinate was added to 100 ml of 0.1N HCl and stirred for 90 minutes. Then the suspension was filtered, further dilutions were made & the drug content was determined at 244.2 nm using 0.1N HCl as a blank.

Optimization of Ambroxol Hydrochloride -Tulsion 343 resin complexation

The drug loading on to resin was optimized for various parameters such as mixing time, activation, effect of pH, ratio of drug: resin and effect of temperature.

Optimization for mixing time and activation of resin on drug loading

Separate batches of Tulsion 343 were soaked in 100 ml of distilled water in a beaker and about 100 mg of drug was added and stirred for 15,30,45,60 and 240 minutes and the drug content was determined as mentioned previously. For optimization of activation, resins were washed with distilled water and subsequently with1N HCl. The resins were rewashed with water until neutral pH was reached. Resinates were prepared by dissolving 100 mg of acid-activated resin in 100ml distilled water containing 100 mg of drug and stirred for 90 minutes and drug content was determined. Similarly, alkali activation of resin was performed, replacing 1N HCl with 1 N NaOH.

Effect of pH, mode of mixing, ratio of drug: resin and temperature on drug loading

For optimization of pH, 100 mg of drug was added to 100 mg of activated resins in 100 ml of distilled water. The pHs of solutions were adjusted to 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5 and 6.0and stirred for 90 minutes and the drug content was determined. For optimization of mode of mixing, rotary shaker and magnetic stirrer were used. Activated resin (100 mg) in100 ml of distilled water and about 100 mg of drug. The pH was adjusted at 3 and drug content was determined. For ratio of drug:resin, three batches were prepared containing drug-resin in the ratio of 1:1, 1:0.5,1:0.7,1:0.8, 1:0.9. The pH was maintained at 3.The solution was stirred for 90minutes. For optimization of temperature, 100 mg of drug was added to 140 mg of activated resins in 100 ml of distilled water. The pH was maintained at 3 and was stirred at 30^0C, 35^0C, 40^0C, 45^0C, 50^0C, 60^0C and the drug content was determined.

Characterization of resinate

A MettlerToledo differential scanning calorimeter (DSC) 821 (Mettler Toledo, Greifensee, Switzerland) equipped with an intracoolerand a refrigerated cooling system was used to analyze the thermal behavior of Ambroxol Hydrochloride and drug resin complexes (DRC). Indium standard was used to calibrate the DSC temperature. Nitrogen was purged at 50mL/min and 100mL/min through cooling unit. The thermal behavior of hermetically sealed samples (5-10 mg) heated at 20°C/min.

Taste evaluation of solid drug: resin complex

Drug resin complex (1:0.7) was subjected to sensory evaluation by a panel of six members using time intensity method[9]. Sample equivalent to 16 mg of drug (dose of drug) was held in mouth for 10 seconds. Bitterness was recorded instantly and then after 2,10, and60 seconds. The evaluation was performed by classifying bitter taste into five scores ,score 0: no bitter taste is sensed, 1: acceptable bitterness, 2: slightly bitter, 3: moderately bitter, 4: strongly bitter.These volunteers were instructed not to swallow the granules, which were placed on the tongue. They were instructed to thoroughly gargle their mouth with distilled water after the completion of test. Results are revealed inTable5

In vitro release studies from resinate

The release rate of the Ambroxol Hydrochloride from resinate was studied at the gastric pH, to determine the amount of drug that would be released in the stomach after administration of formulation. Solid drug: resin equivalent to 100 mg of drug was weighed accurately and subjected to *in vitro* dissolution studies using USP type II apparatus (paddle type) at 100 rpm with temperature of 37^0C ± 5^0C. Dissolution was carried in 900 ml simulated gastric fluid for 90 minutes. 5 ml of aliquots were withdrawn at different time intervals of 5, 10, 20, 30, 45, 60 and 90 minutes and replacement was made each time with 5 ml of fresh dissolution medium. The samples withdrawn were diluted to 50 ml with buffer and filtered through Whatman filter paper no. 41. The filtered samples were analyzed at 244.4 nm

Formulation development

Solid drug: resin complex (ratio 1:0.7) of Ambroxol Hydrochloride and Tulsion 343 ion exchange resin was developed into oral suspension formulation. Different formulations were attempted using different suspending agents as shown in Table 4.

Evaluation of formulation

The formulation of solid drug: resin complex was evaluated for pH, viscosity, sedimentation volume, density and drug content. The rheological properties of all the formulation like viscosity, type of flow system, shear thinning index (ST index) and thixotropic index (Thix index) were determined by Brook Field viscometer (LVDV-IIUCP, cone and plate) model.

Taste Evaluation of oral Taste Masked Suspension

10 mL samples of each formulation and marketed formulation(with flavors) containing 30mg of Ambroxol Hydrochloride were subjected to sensory evaluation by a panel of six members using time intensity method . Samples were placed on tongue for 10 seconds bitterness levels were

recorded instantly and then at the end of 1 minutes and 2 minutes, bitterness levels were again noted and recorded and compared with commercial product.Results shown in Table:5 Figure.3

In-vitro release of suspension

Dissolution studies of above samples were performed using USPXXIII apparatus type 2. Suspension equivalent to 30 mg of the drug were added to the dissolution medium (500 ml 0.1N HCl at a temperature of 370C ± 0.50C), which was stirred with a rotating paddle at 50 rpm. At suitable time intervals, 10 ml samples were withdrawn, filtered (0.22 µm), diluted and analyzed at 244.2 nm using UV spectrophotometer.Figure.4

RESULTS AND DISCUSSION

Optimization of Ambroxol hydrochloride: Tulsion-343 resin complexation Ambroxol Hydrochloride was loaded on ion exchange resin by batch process. Complexation is essentially a process of diffusion of ions between the resin and surrounding drug solution. As reaction is an equilibrium phenomenon, maximum efficacy is best achieved in batch process. The equilibrium ion exchange in solution occurs stoichiometrically and hence is affected by stirring time. 60 minutes mixing time was optimized.(Table:1) Highest drug binding on resin was achieved when activated with 1N HCl. as after activation with acid treatment, the exchangeable ion on the resin is H^+. Relative selectivity of H^+ is least than other ionic form and therefore it increases percent complexation.

Therefore acid activated resin is used for preparation of complex. As pH increases above 5, percentage of drug loading decreases. This may be due as fraction of Ambroxol Hydrochloride protonation decreases as the pH increases and reduces the interaction with the resin The pH of the solution affects both solubility and the degree of ionization of drug and resin. The drug-loading efficiency for a drug-resin ratio of batch process was found to be highest in 1:0.8 ratio.It is due to the fact that, increase in the amount of resin increases the amount of drug adsorbed from the solution. Maximum drug loading on the resin occurs at a temperature of 30^0C; a maximum of 89.702±0.265% wt/wt for Tulsion 343. Increase in temperature above 30^0Cdid not further increase the percentage drug loading.Increased temperature during complexation increases ionization of drug and resin.

Higher temperatures tend to increase the diffusion rate of ions by decreasing the thickness of exhaustive exchange zone. Also at increased temperature, swelling of resin takes place. Due to swelling ionic sites are open for exchange of counter ions.

Table 1: Effect of stirring time on Ambroxol Hydrochloride–Tulsion-343 complex

Stirring (Time in Minutes)	%complexed
15	79.872±0.322%
30	87.191±0.390%
45	88.085±0.195%
60	89.915±0.255%
90	89.412±0.351%,
240	90.012±0.245%

Evidence of complex formation

Differential scanning calorimetry of the plain drug showed a sharp endothermic peak at 243.0C whereas the solid: drug resin complex of Ambroxol Hydrochloride with Tulsion 343 ion exchange resins did not show any peak in the DSC graph indicating the complete complexation of the drug with Tulsion-343, as shown in figure.1

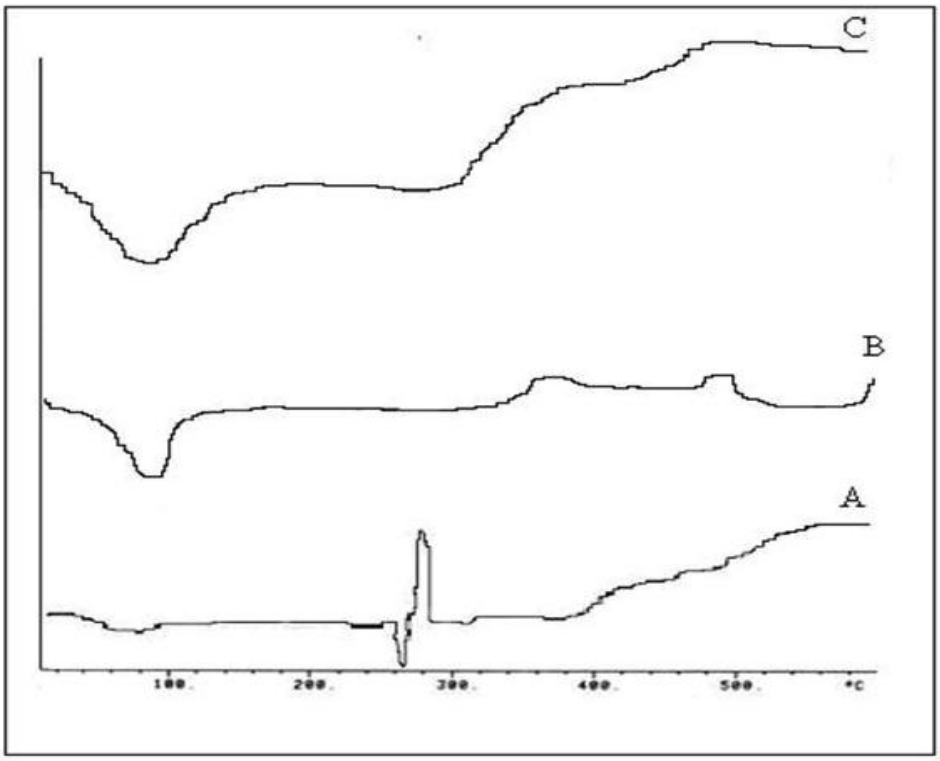

Figure-1:DSC thermogram of a) Ambroxol hydrochloride b) Tulsion-343 c) Drug-resinate

The X-ray diffraction pattern confirms the crystalline nature of Ambroxol Hydrochloride that is evident from the number of sharp and intense diffraction peaks obtained for drug.Only diffused peaks were observed in the diffraction pattern for the complex regardless of presence of drug. According to the data from XRPD, the molecular state of pure drug was crystalline and that of the resin was amorphous. The molecular state of the drug prepared as drug-resin complex was changed from the crystalline to the amorphous.

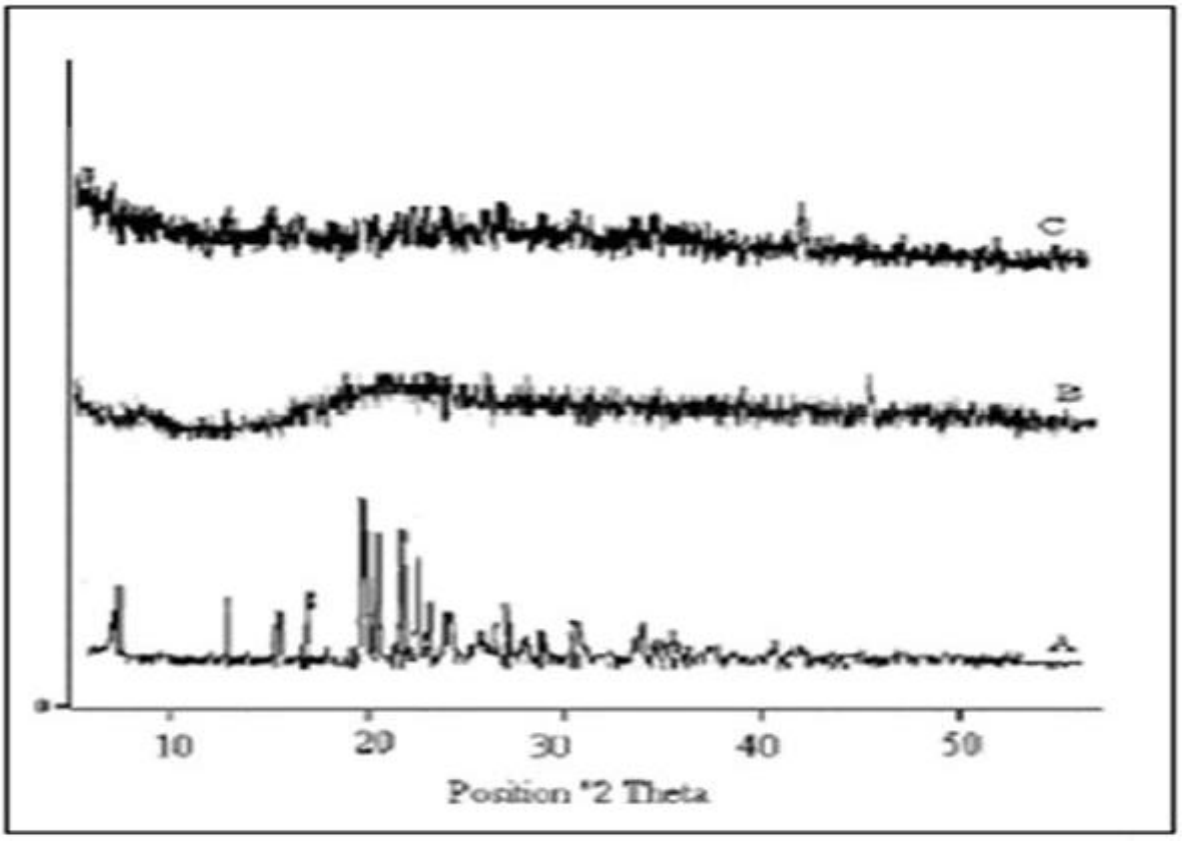

Figure-2 XRPD of a) Ambroxol hydrochloride b) Tulsion-343 c) Drug-resinate

Panel evaluation of taste

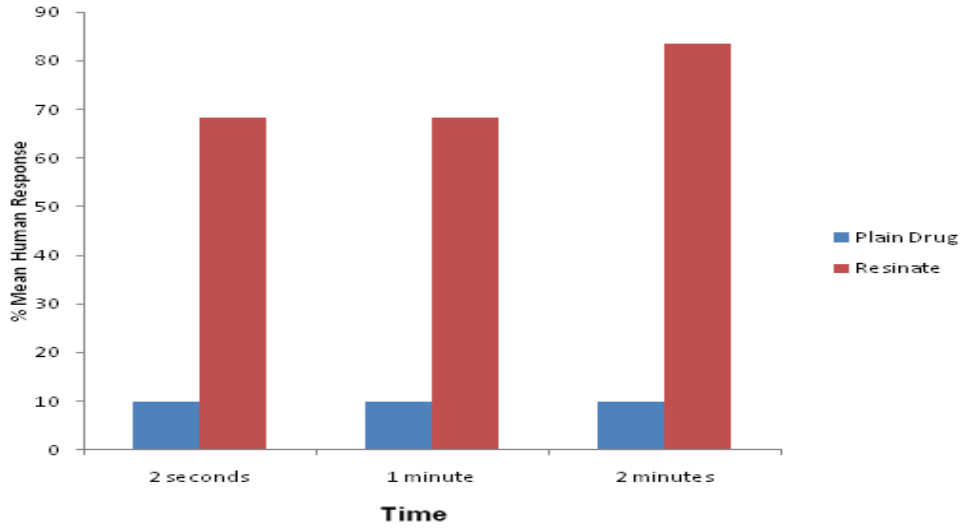

Figure-3: Taste Evaluation Graph of DRC

Panel of 6 members using time intensity method determined the threshold bitterness value.[9] Taste evaluation in volunteers confirmed that the taste of drug was masked by complexing with Tulsion 343 resin. The majority of the volunteers found the drug resin complex to be tasteless and agreeable as shown in Table 2.and Figure:4

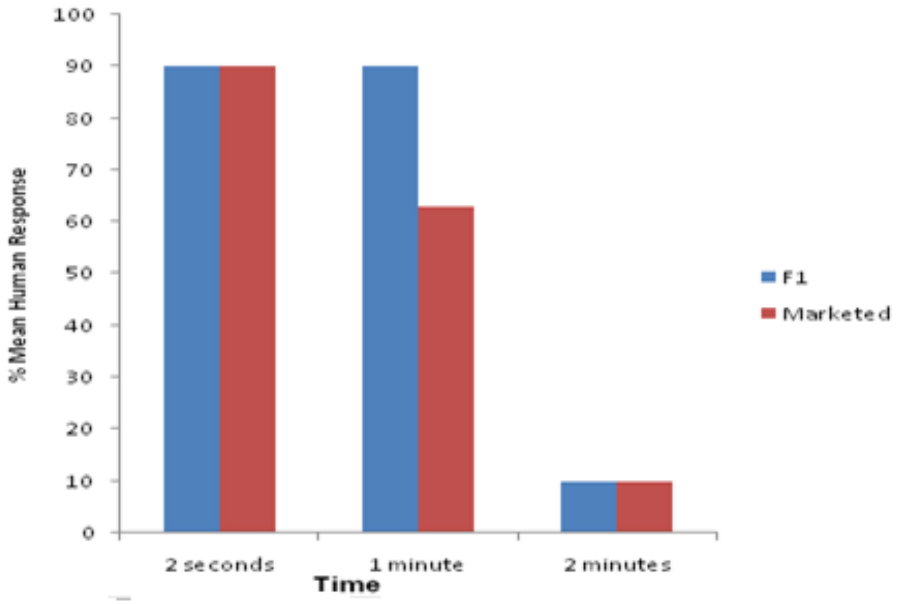

Figure-4Taste Evaluation Graph of F1 Formulation and Marketed

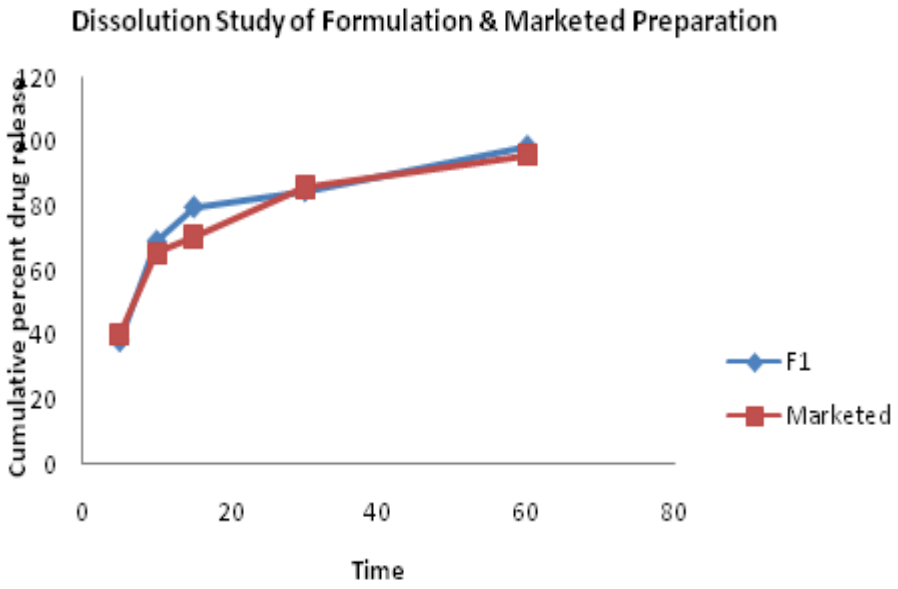

Figure-5: Dissolution Profile of F1 and Marketed Formulation

Formulation development

DRC was formulated into suspension formulation. Since drug resin complex are insoluble in all solvents (including water) and they show release only in ionic environment. Therefore drug resin complex was formulated into aqueous suspension formulation. Drug-Tulsion 343 complex (1:0.7) was selected for formulation.

Evaluation of formulation

The result revealed that, viscosity of allformulations was showing pseudo plastic behavior because as shear increases, viscosity decreases. Sedimentation volume values indicated that all

formulations behave like flocculated suspension cellulose).Drug content of all formulations was found to be in the range of 99-104% and pH of all formulations was in the range of 3.5-4.5 as shown in Table 3. All formulations have particle size ranging from 32-42 micron with span factor ranging from 1.987-2.157 .Formulation F1 Showed comparable drug release with that of marketed formulation.

Table 2: The drug-loading efficiency for a drug-resin ratio of batchprocess for Tulsion 343.

Ratio of Drug:Resin	Drug-Loading Efficiency
1:0.7	93.228±0.585%w/w
1:0.8	96.043±0.959% w/w
1:0.9	96.716±0.383 % w/w

Table 3: The percentage drug loading with inactivated resin, treated with acid and alkali.

Treatment	Percentage Drug Loading
Inactivated resin	88.956±0.485%,w/w
Treated with acid	92.016±0.154% w/w
Treated with alkali	84.429±0.862 %w/w

Table 4: Different Formulation of Ambroxol Hydrochloride–Tulsion-343 complex

Ingredients	Quantity of ingredients			
	F1	F2	F3	F4
Drug :Resin complex(1:0.7)	Equivalent to 30 mg	Equivalent to 30 mg	Equivalent to 30 mg	Equivalent to 30 mg
Guar gum	40 %	----	----	----
Veegum	----	40 %	----	----
Xanthan gum	----	---	40%	----
Methyl cellulose	----	-----	----	40%
Propylene glycol	0.5%	0.5%	0.5%	0.5%
Sugar	5%	5%	5%	5%
Methyl Paraben	0.5%	0.5%	0.5%	0.5%
Propyl Paraben	0.25%	0.25%	0.25%	0.25%
Flavour	q.s	q.s	q.s	q.s
Water	q.s to 100 %	q.s to 100 %	q.s to 100 %	q.s to 100 %

Table 5: Result of Taste Evaluation Study of AmbroxolHydrochloride Resinate.

Volunteers	Bitterness level					
	PlainDrug			Resinate		
	2 sec	10sec	60sec	2 sec	10 sec	60sec
1	4	4	4	1	0	0
2	4	4	4	0	1	0
3	4	4	4	0	0	0
4	4	4	4	0	0	0
5	4	4	4	1	0	2
6	4	4	4	0	0	0
Mean Human Response	10	10	10	68.33	68.33	83.33

Score: 4=0-20%; 3 =20-40%; 2=40-60%; 1=60-80%; 0=80-100%

Table 6: Evaluation of Suspension Formulation

Evaluation parameter	F1	F2	F3	F4
pH	3.9	4.05	4.2	3.65
Density	1.051	1.288	1.095	1.245
Sedimentation volume	0.54	0.92	0.88	0.79
Particle size(µm)	32.04	39.11	32.60	41.07
Span	1.987	1.764	2.083	2.157
Percent drug content	99.738±0.512	99.794±2.927	100.177±1.79	103.324±0.67
Viscosity (cps)	74.0	66.5	63.2	55.5
Shear thinning index	1.79	1.13	1.56	1.23
Thixotropic index	1.56	1.03	1.42	1.06
Type of system	Pseudoplastic	Pseudoplastic	Pseudoplastic	Pseudoplastic

Table 7: Result of Taste Evaluation Study of Ambroxol Hydrochloride Formulations

Score: 4=0-20%;3 =20-40%; 2=40-60%; 1=60-80%;0=80-100%

Volunteers	Bitterness level					
	PlainDrug			Resinate		
	2 sec	10sec	60sec	2 sec	10 sec	60sec
1	0	0	0	3	4	4
2	0	0	0	2	4	4
3	0	0	0	0	4	4
4	0	0	0	1	4	4
5	0	0	0	1	4	4
6	0	0	0	1	4	4
Mean Human Response	90	90	90	70	10	10

CONCLUSION:

For better taste masking effective techniques are being developed constantly in the pharmaceutical industry. For taste masking & formulation ion exchange resins are best suited in comparison to other methods of taste masking as well as this method is also economical. Reported methods prove that ion exchange resins play an important role in taste masking.Presently the use of type of ion exchange resins depends on the nature of the drug, thus the use of Tulsion-343 offers good taste masking of Ambroxol Hydrochloride and its formulation into suspension could be useful in patients such as paediatric, geriatric, bedridden or mentally disabled, who may face difficulty in swallowing.

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