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RESEARCH ARTICLE
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TASTE MASKING OF BITTER DRUG USING ION EXCHANGE RESINS

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Abstract:
The objective of present research work was to masking the bitter taste of Levamisole HCl with strong cation exchange resin i.e Tulsion 343. The complex formation of drug with Tulsion 343 was carried out using batch method to block the functional group responsible for causing bitter taste.
FTIR spectra, X-RD spectra, DSC analysis, and decomplexation studies shows evidences of complex formation. Drug release from drug: resin complex was obtained at salivary pH (6.8) and gastric pH (1.2). Accelerated stability study (AST) on drug: resin complexes were performed by keeping sample of complexes at 40° C for period of 1 month.
The efficient drug loading was evident in batch process using Tulsion-343 with a drug: resin ratios 1:1, 1:1.5, and 1:2 (% w/w). Drug release from selected drug: resin complex at salivary pH was insufficient to impart bitter taste. Drug release has no significant effect using different media at same pH: salivary pH (phosphate buffer pH 6.8 and simulated salivary fluid) and at gastric pH (0.1 N HCl and simulated gastric fluid). Drug: resin complexes were found stable at elevated temperature.
Depending upon percent complexation, release study at different pH, Levamisole Hydrochloride: Tulsion-343 complex of ratio 1:1 (%w/w) was gives good results.

Keywords: Taste Masking, IER, Drug-Resin Complex

INTRODUCTION:

"Consumer satisfaction**"** is the buzzword of current millennium and the moment to achieve it has already begun in the pharmaceutical industry. Taste, smell, texture and after taste are important factors in the development of dosage forms and also in product preference. Good flavor and texture are found to significantly affect the sale of the product i.e. it's commercial success. Undesirable taste is one of the important formulation problems encountered with most of the drugs. [1] "Worst the taste of the medication, the better the cure" was once the prevailing attitude. Today this trend has changed and great importance is given to the organoleptic characteristics of pharmaceutical products i.e. mainly appearance, odor and taste. [2]

"Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist." The ideal solution to taste masking of bitter substances is the discovery of a universal inhibitor of all bitter tasting substances that does not affect the other taste modalities such as sweetness. But to date there is no single substance that acts as the universal inhibitor of bitter taste. [3]
Pharmaceutical companies are commercially motivated to invest time, money and resources in developing palatable, pleasant tasting products because good tasting products:

- Enhance patient compliance
- Provide a competitive advantage when a therapeutic category is crowded with similar products e.g. anti-infective category etc.
- Provide brand recognition to combat private-label competition.

In the pharmaceutical industry, taste-masking science broadly covers physiological and physiochemical approaches to prevent Active Pharmaceutical Ingredient (API) or drugs from interacting with taste buds; thereby eliminating or reducing negative sensory response. Physiological approaches consist of inhibiting or modifying an API-mediated bitterness response by incorporating agents into a pharmaceutical formulation. Agents like sodium chloride, phosphatidic acid and peppermint flavor are known to inhibit bitterness by selected API molecules via a mechanism that takes place at the bitterness receptors in the taste buds[4].

The advantage of ion-exchange materials for taste masking is their ability to bind and exchange charged drug molecules. In general, for taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of the drug. Sometimes strong cation exchange resins are also used for taste masking purpose. The nature of the drug-resin complex formed is such that the average pH of 6.7 and cation concentration of about 40 meq/L in the saliva are not able to break the drug resin complex but it is weak enough to be broken down in the acidic environment of the stomach[5, 6, 7].

Ion exchange resins (IER) have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery vehicles[8,9,10].
Levamisole is a synthetic imidazothiazole derivative that has been widely used in treatment of worm infestations in both humans and animals. As an anthelmintic, it probably works by targeting the nematode nicotinergic acetylcholine receptor.

MATERIAL AND METHODS:

Levamisole HCl was gift sample from Cipla Pharmaceuticals Ltd. Mumbai. Ion Exchange Resins (IER) was obtained as gift sample from Thermax, Pune. All other chemicals/solvents were of analytical grade.

METHODOLOGY:

Preparation of Drug – Resin complex[12]:

Ion exchange resin was weighed accurately. The ion exchange resin was allowed to swell by stirring in 20 ml of water for 30 min, using a magnetic stirrer. After 30 min, the accurately weighed quantity of drug was added in slurry of resin during stirring. The resultant mixture of drug and ion exchange resin was stirred for 1 hour. The solution was filtered off and the filtrate was analyzed for drug complexed with each of the ion exchange resin. The residue was washed with water and air-dried.
Solid complexes of the ion exchange resin with drug were prepared in various ratios, keeping the quantity of drug constant, as indicated in following table no.1

Table No. 1: Ratio of Drug: resin selected for complexation

Resins	Tulsion 343
Ratios of Drug: Resin (%w/w)	1:1
	1:1.5
	1:2

Percent drug complexed:

The percent drug complexed with the ion exchange resin was determined by analyzing the filtrate, after appropriate dilution with distilled water. The filtrate was analyzed by Shimadzu UV-250 1PC

double beam spectrophotometer at λ max 213 nm. The reported values of percent complexation are average values of three readings and shown in table no. 2

Release Rate Study of complexes at mouth pH:

The release of the drug from the ratio of the drug: resin complex was studied at the pH of mouth (pH 6.8) and in Simulated Salivary Fluid (SSF) to determine the amount of the drug that would be released in mouth during the administration of formulation. The bitterness of the taste is related with the amount of drug released in the mouth. Levamisole HCl (plain drug) was used as a control to study its rate of release at the pH of mouth.

Solid drug: resin complex equivalent to 50 mg of drug was subjected to release rate study. The complex was accurately weighed and added to 5ml phosphate buffer pH 6.8 I.P. and SSF. Aliquot was withdrawn after 1 min. The sample was filtered through whatmann filter paper. The absorbance was measured at 214 nm. Drug concentration in the sample was determined from the standard curve of the drug in PO_4 Buffer (pH 6.8). The results shown in table no. 3

Release rate study at the gastric pH:

The release rate of the drug from each of the ratio of the drug: resin complex was studied at the gastric pH i.e in 0.1 N HCl and in Simulated Gastric Fluid (SGF) to determine the amount of drug that would be released in the stomach after administration of formulation.

Solid drug: resin complex equivalent to 50 mg of drug was weighed accurately and subjected to release rate study using USP dissolution test apparatus I (Model: Tablet Dissolution Test Apparatus, Lab India). Levamisole hydrochloride was used as control and subjected to release rate study by weighing 50 mg of it. 10 ml of the aliquot were withdrawn at different time intervals as per requirement and replacement was made each time with 10 ml of fresh dissolution medium. Each of the 10 ml sample was filtered through Whatmann filter paper. 1 ml of the filtrate was taken and was diluted upto 10 ml. The drug concentration in the sample was determined from the standard curve of the drug in 0.1N HCl at 213.4 nm. The results shown in figure no. 1 and figure no. 2.

Characterization of Drug: Resin Complex

Assay of Drug: Resin Complexes:

A complex equivalent to 50 mg was accurately weighed, in that 10 ml of 1 N HCl was added to break the drug: resin complex. This was stirred on magnetic stirrer for 2 hr. Solution was filtered and dilutions were made. Absorbance was measured at 214 nm using UV-Spectrophotometer. The data obtained is shown in table no 4

Differential Scanning Calorimetry (DSC):

A Mettler Toledo differential scanning calorimeter (DSC Q100v9.4Build287, Mettler Toledo, Greifensee, Switzerland) equipped with an intracooler and a refrigerated cooling system was used to analyze the thermal behavior of Levamisole Hydrochloride, Tulsion-343 and drug: resin complex of Levamisole HCl: Tulsion-343. Indium standard was used to calibrate the DSC temperature. The thermal behavior of hermetically sealed samples (5-10 mg) heated at 20°C/min is shown in figure no. 3.

FT-IR Spectroscopy:

FT-IR spectrum of the Drug, Tulsion-343, Drug: Tulsion-343 (1:1) was recorded on Shimadzu 8400-S Type FT-IR Spectrophotometer using chloroform & the spectra were recorded over the wave number 4000 to 400 cm^{-1}. The spectrum of the Drug: Tulsion-343 (1:1) is shown in figure no. 04

X-ray diffractometry:

X-ray powder diffractometry was carried out to investigate the effect of complexation process on crystallinity of drug. Powder x-ray diffractometry were carried out using a Phillips-PW-1050 scanner with filter Ni, Cu K∝ radiation, voltage 40 kV and a current of 20 mA. The scanning rate employed

was 1°/min over the 5° to 50° diffraction angle (22) range. The X-RD patterns of drug powder, resin (Tulsion 343) and drug resin complex were recorded. The XRD patterns of drug resin complex were given in figure no. 5

Accelerated Stability Study:

Accelerated stability study was conducted, to find out the stability of Levamisole Hydrochloride: Tulsion-343 (1:1) at 40^{O} C.

For Accelerated stability study, 1gm of the solid drug: resin complex (1:1) (packed in aluminum foil) was kept at 40^{0}C in oven for a period of 2 months. Along with drug: resin complex, 1.0 gm of plain drug (Levamisole Hydrochloride) sample was also kept for above-mentioned temperatures for 1 month. After 1 month samples were eluted in 1 N HCl for decomplexation and diluted suitably with 1N HCl and residual degradation was estimated using UV-Spectrophotometer. The data obtained is shown in table no. 6 and figure no. 6

RESULT:

Drug – Resin complexation:

Levamisole hydrochloride shows good complexation with Tulsion-343, from the table of percent complexation, it is clearly seen that the drug is complexing with the strong resins even when the ratio of drug: resin is increased.

Table No. 2: Percent drug complexed in various ratios of strong ion exchange resin

Ratio Drug: resin(% w /w)	**% Drug complexed**
	Tulsion-343
TYPE	Strong acid cation exchange resin (H^+)
1:1	97.41 ± 1.178
1:1.5	90.89 ± 1.391
1:2	95.45 ± 0.955

Release Rate Study of complexes:

- **At mouth pH:**

From the result, we can say that as the quantity of resin increases, release at salivary pH decreases. Strong resin show negligible release in salivary pH after 60 sec.

Table No. 3: Release Rate Study of complexes at mouth pH

Ratio of Drug: Resin	**% Drug release at salivary pH 6.8 (PO_4 Buffer)**	**% Drug release at salivary pH (simulated salivary fluid)**
	Drug: T 343	
1:1	3.67 ± 0.168	3.77 ± 0.115
1:1.5	3.53 ± 0.120	3.35 ± 0.221
1:2	2.41 ± 0.156	2.43 ± 0.355
Pure Drug	92.86 ± 0.7186	94.47 ± 0.941

- **At the gastric pH:**

From the data of release of drug from complexes at gastric pH in different dissolution media, the release of complexed drug follows first order release kinetics in both medias. As the quantity of resin increases, release rate constant decreases. This means that as the ratio of the resins is increased release is sustained.

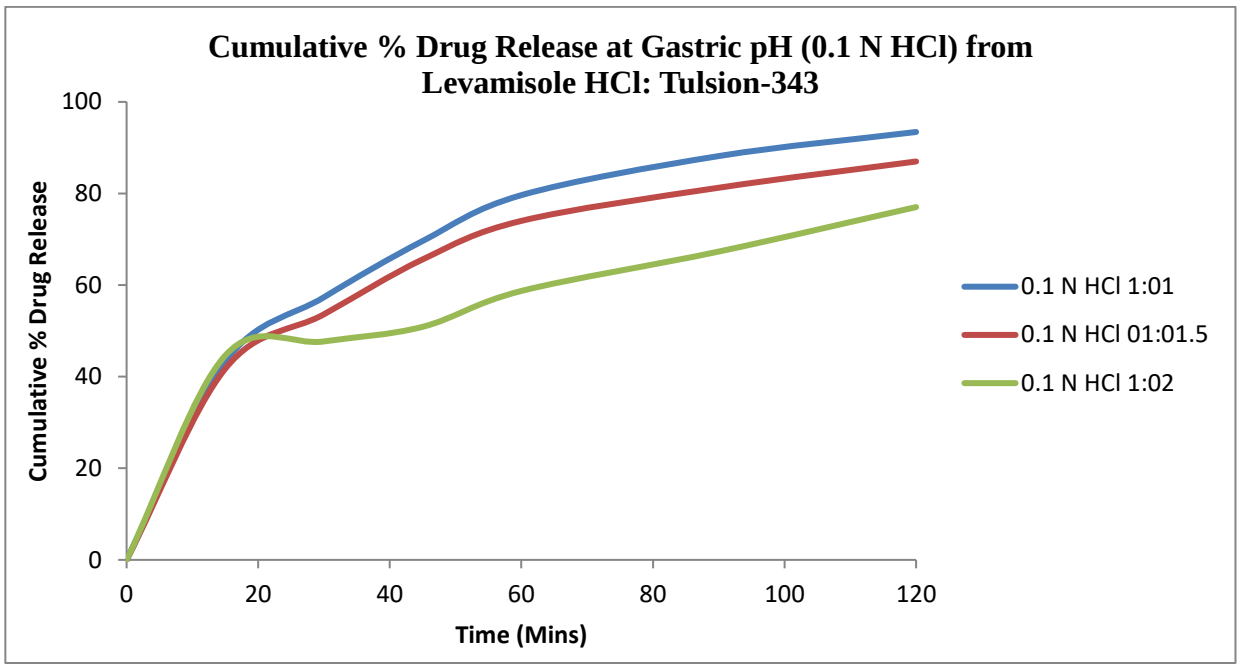

Figure No. 1: Percent cumulative release from at Gastric pH (0.1N HCl) Levamisole hydrochloride -Tulsion 343 complexes

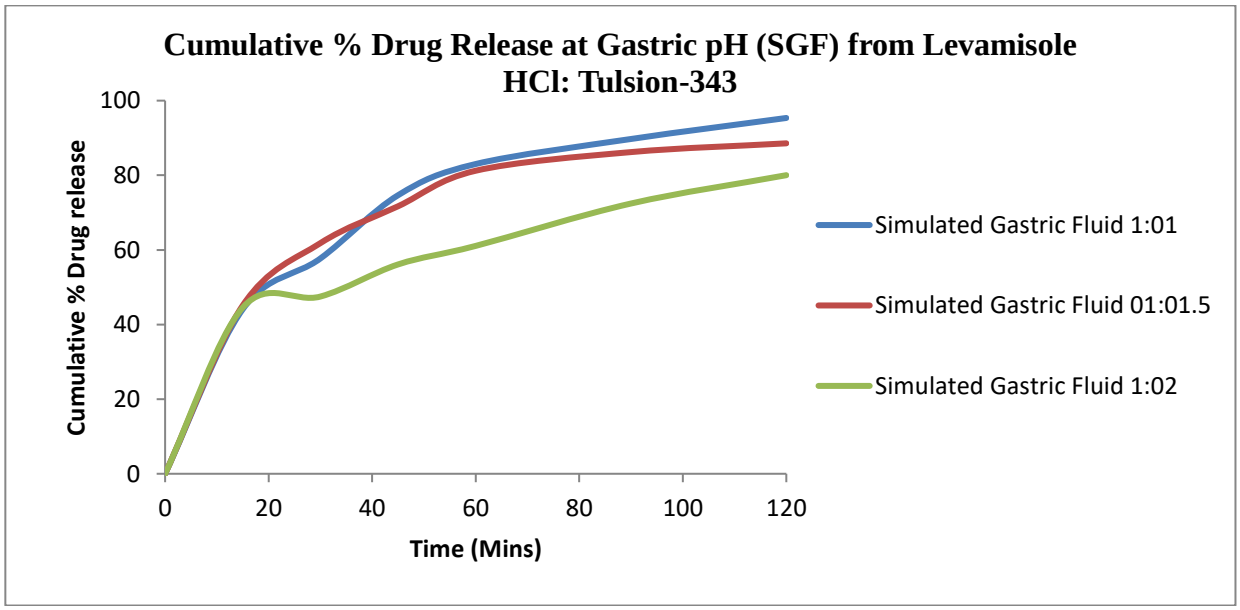

Figure No. 2: Percent cumulative release from at Gastric pH (SGF) Levamisole hydrochloride - Tulsion 343 complexes

Characterization of Drug: Resin Complex

Assay of Drug: Resin Complexes:

From the data of Assay of Drug: Resin Complexes, it is clear that as the quantity of resin increases, release rate constant decreases

Table No 4: Percent Drug content of drug: resin complexes

Ratio of drug: resin (% w/w)	Percent Drug content
	Tulsion-343
1:1	99.34 ± 0.955
1:1.5	98.54 ± 0.701
1:2	97.07 ± 0.542

Differential Scanning Calorimetry (DSC):

DSC Thermogram of the drug shows sharp endothermic peak at 233ºC, indicating melting point of the drug. On the other hand, no peak was observed over the range of 140 º C -240 º C in the DSC curves of resin and complex.

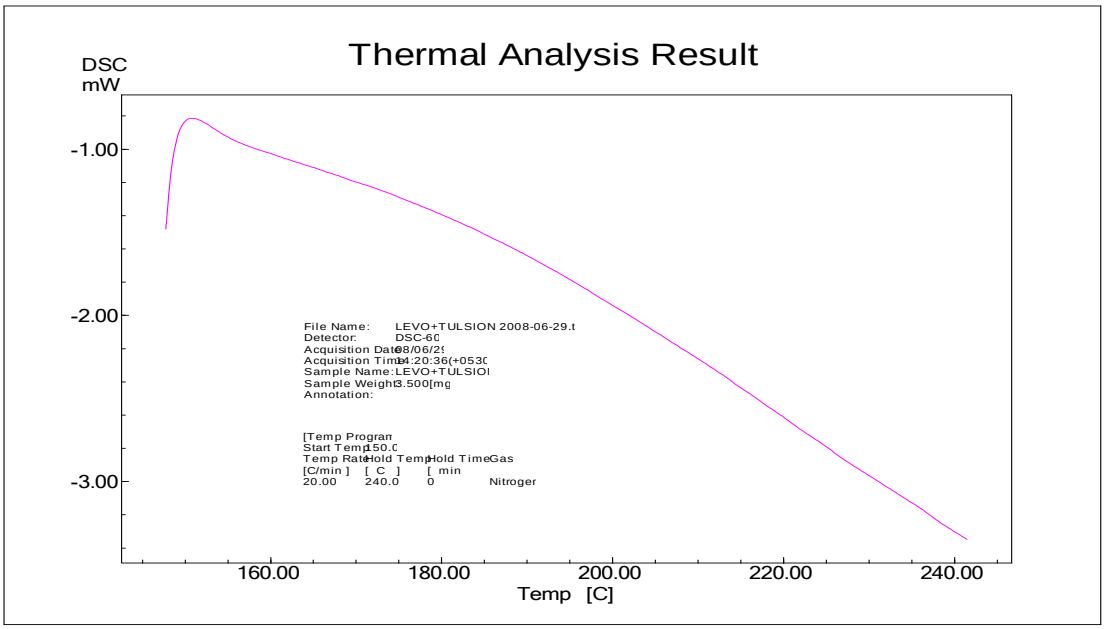

Figure 3: DSC curve of complex of drug: resin

FT-IR Spectroscopy:

The FTIR spectra of the complex exhibit significant difference in the characteristic spectrum of the Levamisole HCl, revealing modification in the drug environment. As shown in the figure, Levamisole Hydrochloride shows the peak of C=N Stretching at 1573 cm^{-1}**,** C-N Stretching at 1217.12 $cm^{-1}$and C-S Stretching at 634.60. In the case of complex the peak of C=N Stretching is suppressed and shifted to 1545 cm^{-1}, which suggest that due to the complexation new bond with resin is formed at that site.

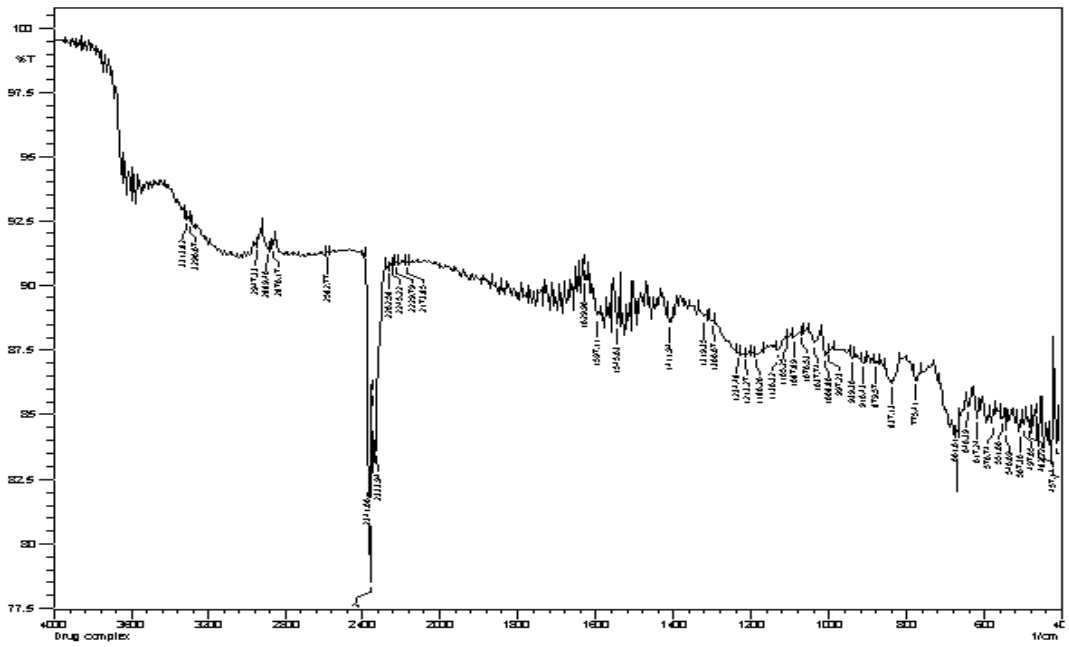

Figure No.4: FTIR of Levamisole HCl: Tulsion-343 (1:1) Complex

Table No. 5: FT- IR spectral analysis of Levamisole HCl: Tulsion-343 (1:1)

IR Spectrums (cm^{-1})	Assignments
2947.33 (3000-2850)	C – H stretching
1629.90 (1630-1850)	C = C Stretching
1300.07 (1600 - 1300)	C = C ring stretch
1545.03 (1650-1550)	C=N Stretching
1130.32 (1120-1160)	Sulphonate stretching

X-RD Spectra:

X-ray powder diffraction studies were performed to examine the crystallinity and provide further evidence of complex formation. The analysis of X-ray powder diffraction patterns is powerful and very well assessed method for the characterization of complexes in the solid state. Significantly different X-ray diffraction patterns are to be expected if complex is formed, since crystal structure will change. The X-ray powder diffraction pattern confirms the crystalline nature of Levamisole Hydrochloride that is evident from the number of sharp and intense peaks obtained for drug. The X-ray powder diffraction patterns of resin showed diffused peaks. Only diffused peaks were observed in the diffraction patterns of the complex regardless of presence of drug. According to the data from X-ray powder diffraction patterns, the molecular state of the pure drug was crystalline and that of the resin was amorphous can be said. The molecular state of the pure drug was changed from crystalline to amorphous in the drug: resin complex. The X-ray powder diffraction patterns showed the formation of complex of drug within the resin.

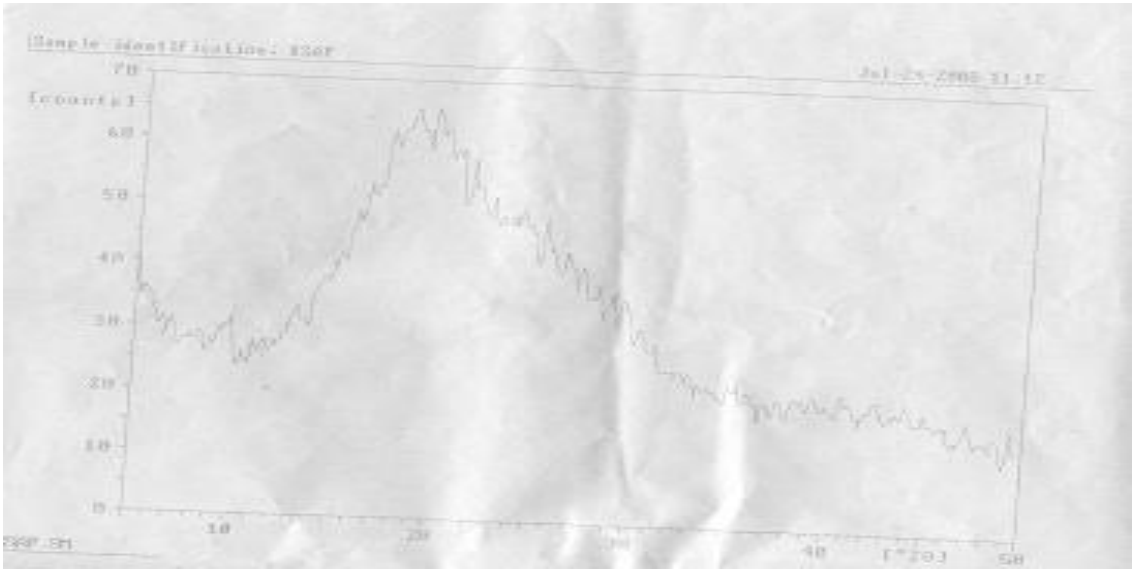

Figure No. 5: X-RD Spectra of Levamisole HCl: T-343 (1:1)

Accelerated Stability Study:

Accelerated stability study at 40 ^{0} C temperature showed that drug – resin complex of Levamisole Hydrochloride with Tulsion – 343 (1:1) was stable at the end of 30 days.

Table No. 6: Wavelength maxima (λ max) for Levamisole (plain drug) and Levamisole: Tulsion-343 complexes at 40^{0}C

DRUG: RESIN COMPLEX	PARAMETERS	TIME IN MONTHS	
		0 (INITIAL)	1
1:1	Appearance	Cream colour	Cream colour
	Wavelength maxima (nm)	214	213.4
	Drug content	98.34 ± 0.955	96.68 ± 0.468

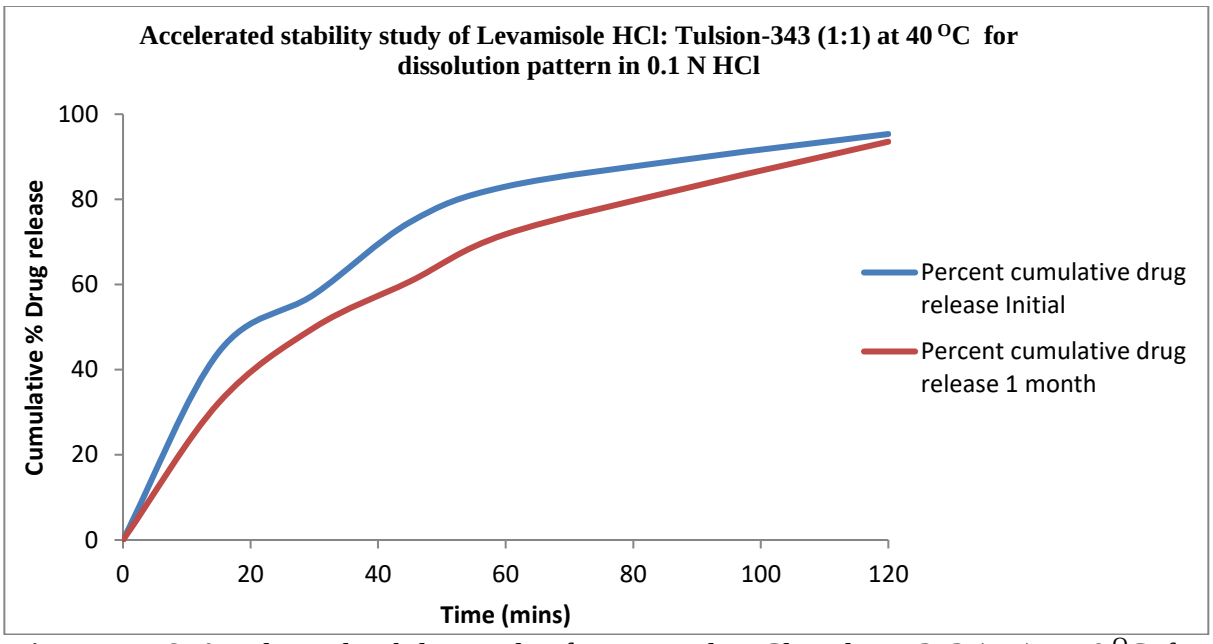

Figure No. 6: Accelerated stability study of Levamisole HCl: Tulsion-343 (1:1) at 40 ^{O}C for dissolution pattern in 0.1 N HCl

CONCLUSION:

The efficient taste masking was obtained from drug–resin a complex for better patient compliance. Use of strong cation exchange resin offers superior method for preparing taste-masked substrates of Levamisole Hydrochloride. A result obtained in this work shows that drug-resin complexes effectively masked bitter taste of Levamisole Hydrochloride. Thus, the "patient friendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and non cooperative patients, will be successfully formulated using this technology.

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