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EFFECT OF PROCESS VARIABLES ON COMPLEXATION OF BITTER DRUG USING ION EXCHANGE RESINS

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Abstract:

Donepezil Hydrochloride is a reversible inhibitor of the enzyme acetyl cholinesterase and used as an Alzheimer's disease, but due to bitterness it has poor patient compliance. Strong and weak cation-exchange resins were used to block the functional group responsible for causing bitter taste by forming resinates of drug.

An attempt was made to form drug-resin complexes of different ratios with various cation exchange resins like Indion-234, Indion-234, and Indion 254. Effect of variables was studied on percentage complexation of drug like type of process, time of complexation, time of swelling, temperature, activation media, pH, and concentration of loading solution and mode of complexation. Drug-resin complexes were characterized by DSC and FTIR study. Resinates of different ratios were subjected to sensory evaluation for taste by ranking method. Release of drug from each complex was studied at the pH of saliva (6.8) and at the gastric pH (1.2) to determine amount of the drug that would be released during the administration of formulation. Stability of drug-resin complexes was studied by carrying out AST at elevated temperatures. Amount of drug released from complex was about 5% at salivary pH and 95% at gastric pH.Drug: Indion-234 (1:3 w/w) complex showed good complexation. Drug-resin complex shows negligible decomplexation of resinate at salivary pH and maximum at gastric pH.

Keywords: *Taste Masking, IER, Drug-Resin Complex, SSF, SGF.*

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INTRODUCTION:

Since four decades after the appearance of spansule, a new era has started in modern therapeutics. One of the attractive methods for oral drug delivery systems preferably is the use of ion exchange resins as carriers for such systems [1]. Various formulations have been examined for the development of taste-masked oral pharmaceuticals in recent years. Especially many efforts have been made in the development of oral fast-disintegrating tablets and dry syrup and liquid products, which can inhibit bitter taste, for use in oral dosage forms for a wide array of drugs taken by infants or elderly patients [2].

Administration of a drug orally having bitter and obnoxious taste with acceptable level of palatability is a challenge to the pharmacist in the present world, especially in pediatric and geriatric formulation. Thus taste masking in the present day pharmaceutical industry has become a potential tool to improve patient compliance and commercial success of the product [3].

"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 [5-7].

Ion exchange resins (IER) have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery vehicles [8-10].

Donepezil Hydrochloride is a reversible inhibitor of the enzyme acetyl cholinesterase and used as an Alzheimer's disease, but due to bitterness it has poor patient compliance. Strong and weak cation-exchange resins were used to block the functional group responsible for causing bitter taste by forming resinates of drug.

MATERIAL AND METHODS:

Donepezil Hydrochloride was gift sample from Lupin Pharmaceuticals Ltd. Indore. Ion Exchange Resins (IER) was obtained as gift sample from Ion Exchange Ltd., Mumbai. 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 1: Ratio of Drug: resin selected for complexation

Resins	Indion 234
Ratios of Drug: Resin (%w/w)	1:1
	1:2
	1:3

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 229.6 nm. The reported values of percent complexation are average values of three readings and shown in table no. 2

Effect of Batch and Column process on percent drug complexation:
Batch process
In this process, 100 mg Donepezil HCl of was added in a beaker containing 300 mg of activated resin slurry and stirred for one hour on magnetic stirrer. The mixture was filtered and residue was washed with distilled water. Percent complexation of drug with resin was estimated at **229.6 nm** using UV-Spectrophotometer. Data obtained is as shown in table no 3.

Column process
In this process, a glass column (1.4-cm inner diameter, 20-cm length) plugged with cotton was packed with 300 mg of activated resin by gently tapping. The 50 ml of distilled water maintained in the column was drained after 30 minutes. Aqueous drug solution (50 ml as per ratio), added in small portions on top of column by using separating funnel. Column was left to equilibrate for 120 minutes. The solution was drained, and drug: resin complex was washed with distilled water. Percent complexation of drug with resin was estimated at **229.6 nm.** Data obtained is as shown in table no. 3.

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. Donepzil 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 229.6 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. 4

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). Donepzil 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 229.6 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 229 nm using UV-Spectrophotometer. The data obtained is shown in table no 5

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 Donepzil Hydrochloride, Indion-234 and drug: resin complex of Donepzil HCl: Indion-234. 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, Indion-234, Drug: Indion-234 (1:3) 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: Indion-234 (1:3) is shown in figure no. 04

Accelerated Stability Study:
Accelerated stability study was conducted, to find out the stability of Donepzil Hydrochloride: Indion-234 (1:3) at 40^{O} C.

For Accelerated stability study, 1gm of the solid drug: resin complex (1:3) (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 (Donepzil 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.

RESULTS:

Drug – Resin complexation:
Donepzil hydrochloride shows good complexation with Indion-234, from the table of percent complexation, it is clearly seen that the drug is complexing with the weak resins even when the ratio of drug: resin is increased.

Table 2: Percent drug complexed in various ratios of weak cation ion exchange resin

Ratio Drug: resin (% w /w)	% Drug complexed
	Indion-234
TYPE	weak cation exchange resin
1:1	90.00±0.46
1:2	94.45±0.61
1:3	95.61±0.64

Effect of Batch and Column process on percent drug complexation:

Table 3: Effect of Batch and Column process on % drug complexation

Resin	% Drug complexation of drug: resin (1:3)	
	Batch Process	Column Process
Indion-234	96.24±1.16	65.49±0.52

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. Weak resin show negligible release in salivary pH after 60 sec.

Table 4: 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: Indion 234	
1:1	5.204±0.263	9.368±0.260
1:2	4.440±0.338	8.317±0.722
1:3	1.196±0.198	6.356±0.205
Pure Drug	98.305±0.633	99.833±0.664

- **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.

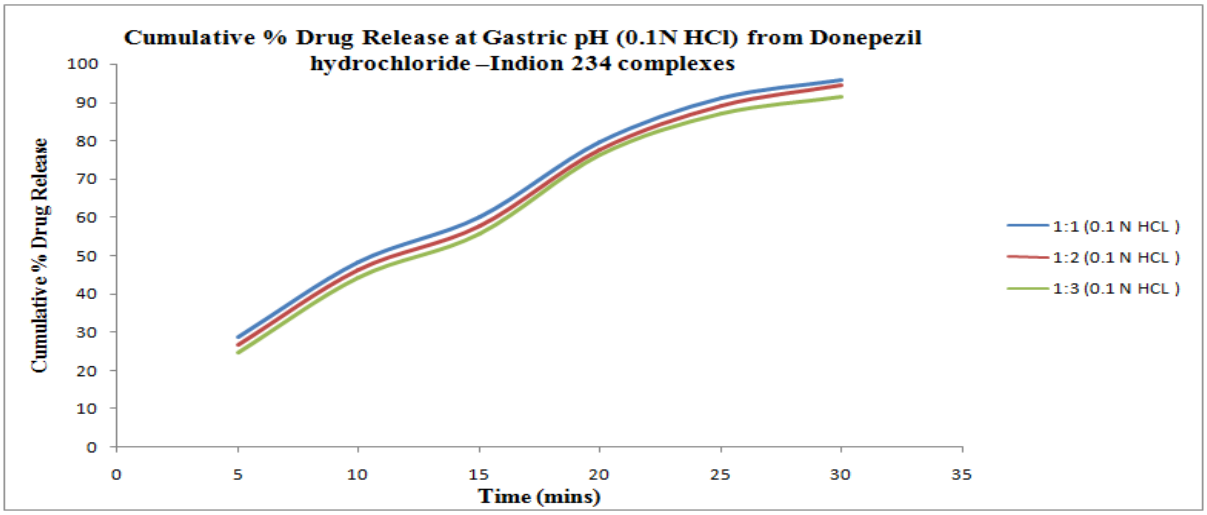

Fig. 1: Percent cumulative release from at Gastric pH (0.1N HCl) Donepzil hydrochloride – Indion 234 complexes

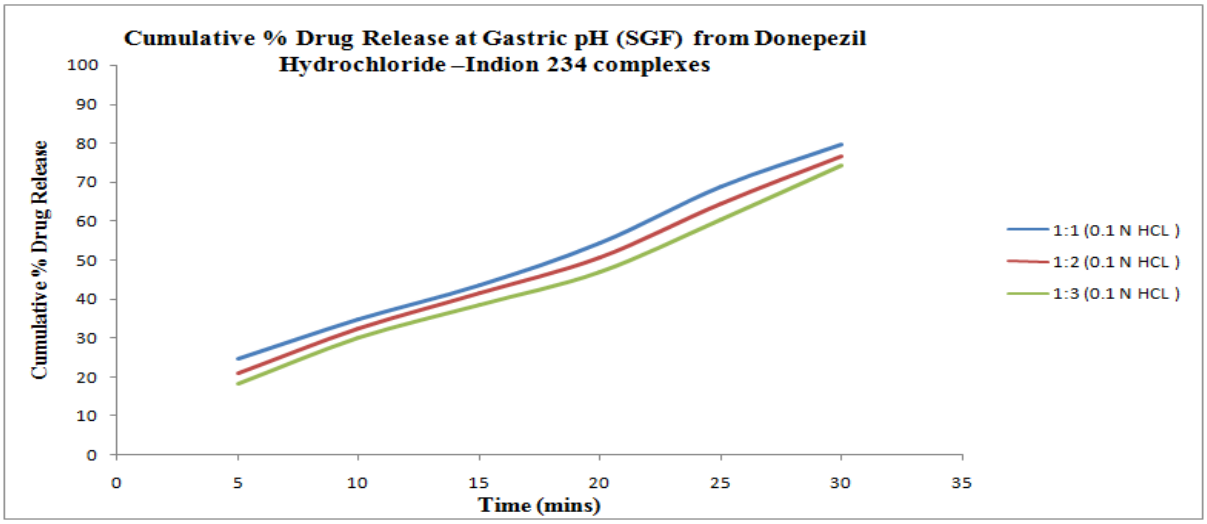

Fig. 2: Percent cumulative release from at Gastric pH (SGF) Donepzil hydrochloride – Indion 234 complexes

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 5: Percent Drug content of drug: resin complexes

Ratio of drug: resin (% w/w)	Percent Drug content
	Indion-234
1:1	99.292±0136
1:2	98.793±0.129
1:3	97.242±0.128

Differential Scanning Calorimetry (DSC):

DSC Thermogram of the plain drug shows sharp endothermic peak at 212ºC, indicating melting point of the drug. But due to complexation with resin this peak gets suppressed, became broad at 455.8^{O}C.

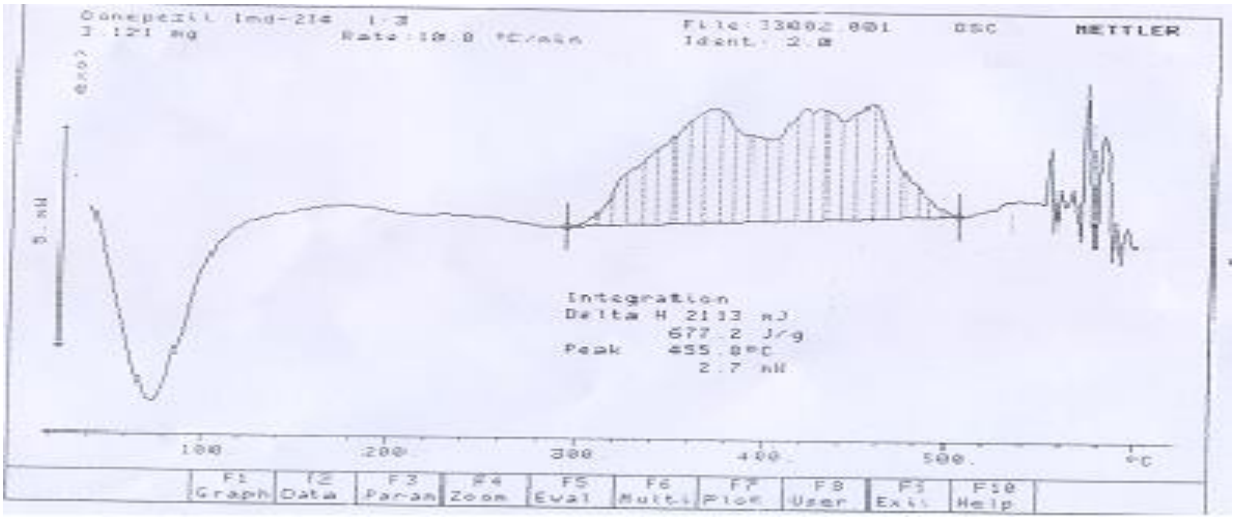

Fig. 3: DSC curve of complex of drug: resin

FT-IR Spectroscopy:

The FTIR spectra of the complex exhibit significant difference in the characteristic spectrum of the Donepzil HCl, revealing modification in the drug environment. In the FTIR Spectra of plain drug, Donepzil 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 2564 cm^{-1}, which suggest that due to the complexation new bond with resin is formed at that site.

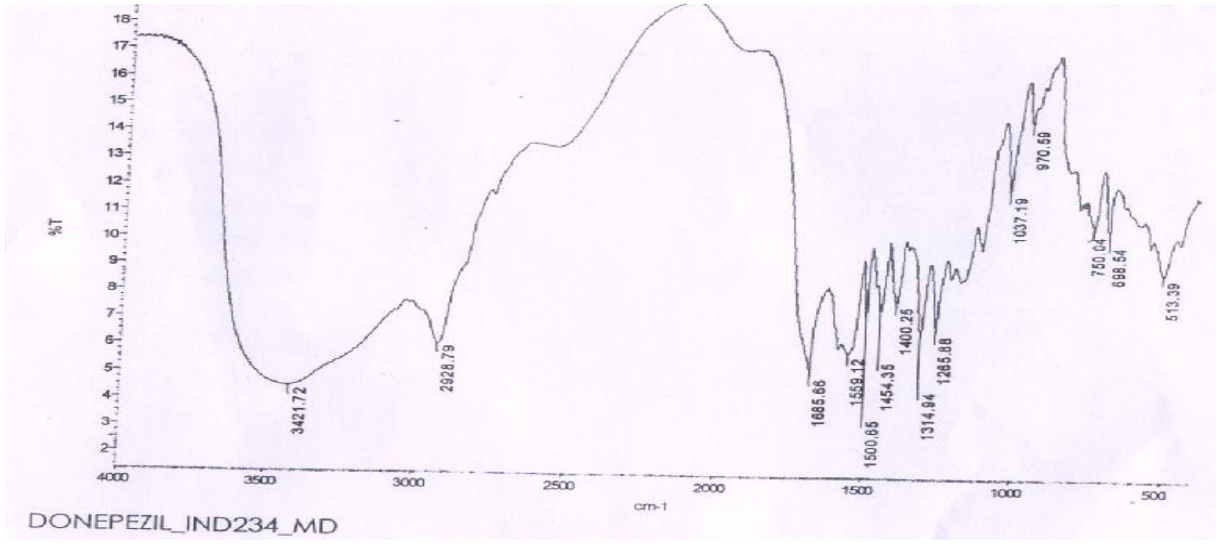

Fig.4: FTIR of Donepzil HCl: Indion-234 (1:1) Complex

Accelerated Stability Study:
Accelerated stability study at 40 ^{0}C temperature showed that drug – resin complex of Donepzil Hydrochloride with Indion – 234 (1:3) was stable at the end of 30 days.

Table 6: Wavelength maxima (λ max) for Donepzil (plain drug) and Donepzil: Indion-234 complexes at 40^{0}C

DRUG: RESIN COMPLEX	PARAMETERS	TIME IN MONTHS	
		0 (INITIAL)	1
1:3	Appearance	Cream colour	Cream colour
	Wavelength maxima (nm)	229.8	229
	Drug content	99.34 ± 0.955	97.68 ± 0.468

CONCLUSION:

Percent drug complexed is dependant on the type of resin and also on ratio of drug: resin. Drug shows good complexation with weak cation-exchange resin. Batch process is better for complexation as compared to column process. Drug release depends on type and ratio of resin. Drug release at salivary pH is very less. DSC and FTIR study gives evidence of complex formation. AST revealed that drug is stable in complex. Drug –Indion 234 complex.

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