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Taste masking of oral pregabalin liquid preparation by using ion exchange resins

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***Abstract*---**The purpose of this study was to use cation exchange resins to mask Pregabalin's unpleasant taste. Dowex-50, a crosslinked polystyrene backbone, was employed. DRCs were synthesised in batches with drug-to-resin ratios of 1:1, 1:2, and 1:3. The optimal drug-to-resin ratio as well as the time required for maximum complexation were discovered. In this work, an attempt was made to develop a taste-masked Pregabalin solution using a simple, rapid, and cost-effective flavour masking approach, such as complexation among ion exchange resin, that could be acceptable to industries. To mask the flavour, researchers used a combination of ion-exchange resins such as doshion P 542, Tulsion 344, Indion 234, Indion 204, and Kyron T 114, as well as formulation into a solution. The generated suspensions were tested for taste, drug content, particle size, viscosity, sedimentation volume, drug release, and accelerated stability. Kyron T 114 has been shown to effectively disguise the drug among the various resins. The newly developed formulation also has the benefit of simplifying the manufacturing process and being cost-effective. According to drug release studies, the entire medicament was released within 20 minutes. After a month of accelerated stability tests, the production process was proven to be repeatable and the formulas were stable.

***Keywords*---**taste masked suspension, pregabalin, dowex-50, ion-exchange resins.

Introduction

When creating a formulation for youngsters and the elderly, the administration of an oral medicine with a bitter taste and a tolerable level of palatability has always been a worry. As a result, taste masking has emerged as a viable tool for increasing patient compliance [1]. Flavors, sweeteners, and amino acids, as well as a variety of other processes like lipophilic vehicles, coating, inclusion complexation, ion exchange, effervescent agents, rheological modification, solid dispersion system, group variation and prodrug perspective, freeze drying Process, wet spherical agglomeration method, and continuous multipurpose melt technology [2-5], can be used to mask taste. A pharmaceutical suspension is a dispersion of insoluble solid particles in a liquid medium. In the final segment, the particles have sizes higher than 0.1mm, and only a handful of them are visible under a microscope to indicate Brownian movement if the dispersion is viscous. Suspensions aid pharmacy and medicine by delivering insoluble and often materials in a state that can be utilised to apply dermatological chemicals to the skin and, in some situations, the mucous membrane, as well as to administer insoluble drugs via parenteral administration [6-16].

Ion-Exchange Resins mask the taste

Ion-exchange resins (IERs) are high-molecular-weight polymers with cationic and anionic functional groups (most common polymeric network is a copolymer of styrene and divinylbezene.) Repeated exposure to the drug in a chromate graphic column or extended contact with the drug solution can bond the drug to the resin. By weak ionic bonding, drugs attach to the oppositely charged resin substrate and form insoluble adsorbates or resinates, preventing the drug-resin complex from dissolving under salivary pH conditions. This successfully masks the drug's unpleasant flavour and odour. Drug release is influenced by resin properties and the ionic environment within the GIT. Drug molecules bound to the resin are released by exchanging with suitably charged ions in the GIT, followed by diffusion of free drug molecules out of the resins [17-19].

By binding to the 2 subunits of the voltage-dependent calcium channel in the central nervous system, pregabalin reduces calcium influx into nerve terminals. Pregabalin also inhibits the release of glutamate and noradrenaline, two neurotransmitters. Pregabalin raises GABA levels in neurons by increasing glutamic acid decarboxylase activity in a dose-dependent manner. Pregabalin is a chemical compound with the formula (S)-3-(aminomethyl)-5-methylhexanoic acid. Pregabalin is used to treat neuropathic pain in diabetic peripheral neuropathy, postherpetic neuralgia, supplementary therapy for adult patients with partial onset seizures, and fibromyalgia.

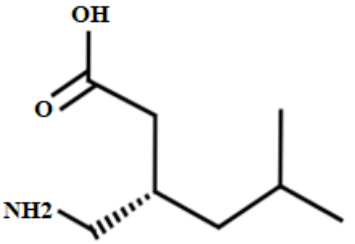


Fig. 1. Structure of Pregabalin

Material and Methods

Material

Sigma Aldrich provided the pregabalin. Dowex-50 was used, which has cross connected polystyrene backbones. Ion exchange India Pvt. Ltd. provided all of the different resins. The rest of the chemicals and reagents were of analytical quality.

Method

Formulation of Pregabalin Suspension with different resins

All the ingredients were weighed individually.

Preparation of drug resin complex

A weighed amount of resin was mixed with prescribed amounts of water in a clean beaker for 15 minutes. Pregabalin was added to the resin solution in a weighed amount and swirled continuously for 4-5 hours. The liquid obtained after stirring was collected and employed in the suspension preparation process.

Preparation of syrup base

A specific amount of sugar was weighed and dissolved in hot water before being filtered. Under stirring, weighed amounts of Sorbitol, Glycerine, Xanthane gum, Xween-80 Aspartame, Methyl paraben, and Propyl paraben were added to the sugar solution.

Mixing of DR complex with Syrup

The drug resin complex (mother liquor) was obtained and mixed into the sugar solution. Colouring and flavouring chemicals were added in weighed amounts to the aforesaid solution and swirled for 10 minutes. Purified water was used to get the suspension volume up to the desired level.

Evaluation of Pregabalin Suspension
Determination of sedimentation volume

The physical stability of the formed suspensions was assessed by estimating the sedimentation volume. In a 50 ml stopped graduated measuring cylinder, 50 ml of suspension was taken. By turning upside down three times, the suspension was widely dispersed. After allowing the suspension to settle for three minutes, the volume of sediment was measured. This is the initial sediment volume (H0). For 14 days, the cylinder was left alone. The volume of sediment measured at 1 hour and 14 days was deemed the final volume (Hu). The suspensions' redispesibility was tested by turning the stoppered cylinder upside down until no sediment remained at the bottom.

Sedimentation Volume (F) = Hu/H0

The sedimentation volume might range from less than one to more than one. The final height of the solid phase after settling is determined by the solid concentration and particle size. F should be at least 0.9 for 1 hour to get an acceptable suspension, however a longer interval was desired for our purposes. Table 2 shows the results.

Viscosity Determination

Viscosity is an important factor in suspension. A Brookfield synchrolectic viscometer is used to determine. 15 mL of suspension is placed in a 25 mL glass beaker, and the viscometer is placed on a stand such that its bob is entirely immersed in the suspension. Turn on the viscometer and run it until the signal changes from red to green. The viscosity of suspension was measured using spindle no. 1. Table 2 shows the results.

pH

A pH metre was used to determine the pH of the suspension.

Assay of suspension

In a 100 ml volumetric flask, 10 ml of suspension was placed and the volume was increased to 100 ml with 0.1 N HCL. 15 minutes of sonication Fill a 200 ml volumetric flask halfway with 2 ml solution, then top up with 0.1 N HCL and filter. In a UV Spectrophotometer, absorbance was measured at a wavelength particular wavelength, compared to a standard, and percent drug content was determined. Table 2 shows the results.

Taste Evaluation

Bitter taste was assessed using participants' perceptions of human bitter taste. The study procedure was described to volunteers, and they signed a consent form. Each participant held a suspension containing 50 mg of pregabalin in their mouth for 15 seconds, and the bitterness level was compared to formulation P1. Table 2 shows the results.

In-Vitro drug release

The suspension was drug released in vitro utilising a USP class II dissolution device (paddle type). The dissolution media, 500ml 0.1N HCL, was added to the dissolution flask at 37 + 0.5 oC and 50 revolutions per minute. Each bucket of the dissolution device received 5 mL of suspension. The machine was left running for 45 minutes. Using an auto sampler, 10 ml samples were taken every 5, 10, 15, 20, 30, and 45 minutes. During the sampling process, samples were filtered through a 10 m filter that was connected to the auto sampler. Every time, the fresh dissolving medium was replaced with the same amount of sample. The collected samples were diluted appropriately with 0.1N HCL and examined at a specified wavelength with 0.1 N HCL as a blank. The total drug release percentage was computed. Only the final batch was subjected to this test. Table 3 shows the results.

Particle size Analysis

The mean particle size was obtained by measuring the size of 200 particles with the use of a calibrated ocular micrometre (Labomed CX RIII, Ambala, India). The microscope stage was mounted on the slide containing suspension particles, and the diameter of at least 100 particles was measured using a calibrated optical micrometre. Resin and suspension photomicrographs (10 x magnifications) were taken. Table 4 shows the results.

Accelerated Stability Study

A 60 mL glass bottle was used to store the pregabalin suspension. For one month, the packed bottles were kept in a stability chamber at 40 + 2 oC and 75 + 5 percent RH. After one month, the samples were removed and examined for changes in the physical parameter (i.e., change in color, Assay, viscosity, any bad odour and pH). Table 5 shows the results.

Result and Discussion

Drug–excipient interactions study
Fourier-transform infrared spectroscopy (FTIR)

FTIR spectrum of Pregabalin was shown in following Fig. revealed characteristic peaks representing the presence of functional groups claim by its chemical structure. From this we can consider that the Pregabalin was of pure quality.

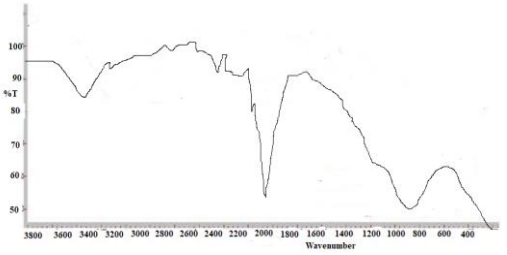


Fig. FTIR Spectra of Pregabalin

After interpretation of FT-IR Spectrum of Drug, it was concluded that all the characteristic peaks corresponding to the functional group present in the molecular structure of Pregabalin were found within the reference range and confirming its identity.

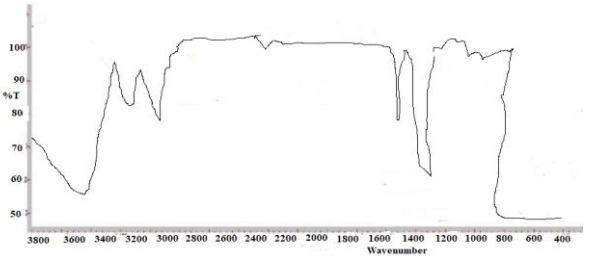


Fig. FTIR Spectra of Dowex -50

After interpretation of FT-IR Spectrum of polymer, it was concluded that all the characteristic peaks corresponding to the functional group present in molecular structure of Dowex-50 were found within the reference range, confirming its identity.

Table
Evaluation parameters of Pregabalin Suspension With different resins

Parameters	P1	P2	P3	P4	P5
Colour	Orange	Orange	Orange	Orange	Orange
Viscosity	76.5	3500	3870	3908	3667
pH	5.87	5.98	4.98	5.76	5.55
Sedimentation volume (F)	1	1	1	1	1
Assay %	99.76	75.34	78.98	65.56	59.87
Taste	Less bitter	Not bitter	Very bitter	Slight bitter	Less bitter

Optimized formula

In comparison to the other formulations, P5 showed good taste masking from all 5 batches of formulations generated with various resin in varied concentrations. P5's physical properties were judged to be satisfactory and meet official specifications. As a result, P5 was chosen as the best formula for making taste-masked Pregabalin with ion exchange resin.

Dissolution profile of optimized formulation

The dissolution of P5 was measured using the USP XXIV dissolution testing device II (paddle method). The dissolution test was carried out using 900 ml of 0.1 N HCl at 37 0.5°C and 50 rpm during the trial. After 45 minutes of dissolution, samples were obtained at 5, 10, 15, 20, 30, and 45 minutes. Table shows the percent medication release results for P5. The release of pregabalin from the

developed formulations was studied, and it was discovered that the resin did not slow the release of the medication from suspension.

Table
In-vitro cumulative % drug release profile of optimized batch P5

Time of sampling in minutes	Cumulative % drug release
5	95.09 %
10	97.67 %
15	97.99%
20	98.56%
30	99.23%
45	100.78%

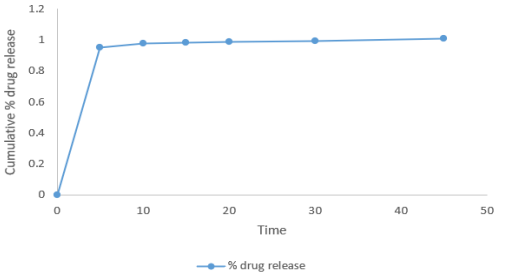


Figure: In-vitro drug release of Pregabalin from optimised batch P5

Particle size analysis of optimized formula

As described in methodology the particle size of final formula P5, was measured microscopically.

Table
Particle size analysis of optimized formula P5

Batch no.	Particle size
Non swollen Kyron T 114	32±6
Swollen Kyron T114	45±9
Formulation P5	58±3

Gravimetric swelling percentage

Gravimetric swelling percentage of pure resin, NNSC is given in Table and the trend in their variation with percentage composition of NNSC is shown in Fig.

Table
Gravimetric swelling (%) of resins

Sample	% of NNSC in resin (w/w)	Gravimetric swelling percentage
Pregabalin	0	93.59
A	10	96.78
B	20	98.23
C	30	97.01
D	40	97.89
E	50	98.43
NNSC	100	99.56

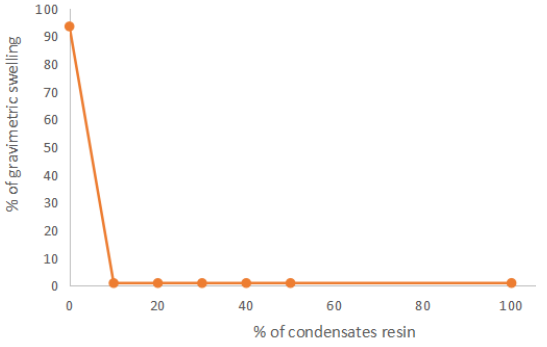


Fig. Gravimetric swelling

A detailed examination of the data in Table reveals a consistent increase in gravimetric swelling percentage of the condensates as the percentage (w/w) composition of NNSC increases up to 30% in the condensates. Furthermore, because the samples are macro reticular with non-gel holes, the values are not particularly high. When compared to pure resin, GSC has a swelling capacity of only 99.56 percent (PFR). The swelling capacity of the sample is considerably reduced when pure resin is blended with even 50% NNSC. As a result, PFR could be combined with up to 30% w/w NNSC without compromising its properties.

Attritional breaking

The percentage of Attritional breaking for pure resin PFR, SC and condensates (A, B, C, D and E) are presented in Table and their variation with the percentage composition of condensates is illustrated in Figure.

Table
Percentage of Attritional breaking

Sample	% of NNSC in resin (w/w)	% of Attritional breaking
Pregabalin	0	43.87
A	10	46.56
B	20	45.65
C	30	49.87
D	40	52.74
E	50	65.76
NNSC	100	74.89

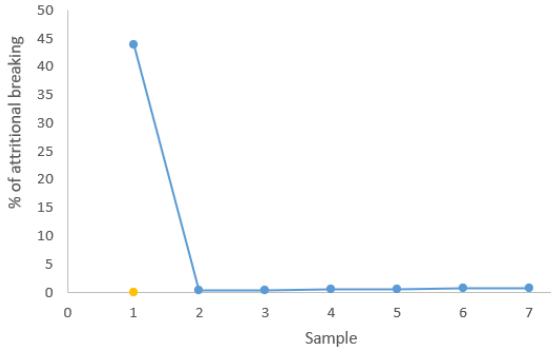


Fig. Attritional breaking

According to the table, 30% of condensates resin has the lowest percentage of Attritional breaking compared to pure resin (PFR), and the values increase as the (w/w) percentage composition of NNSC in the condensates increases. It has been determined that the resin and composites are mechanically stable, with good stability up to 30% (w/w) substitution. This means that the parent percent of Attritional breaking resin (PFR) might be substituted up to 30% (w/w) without compromising the parent resin's properties.

Thermal Stability

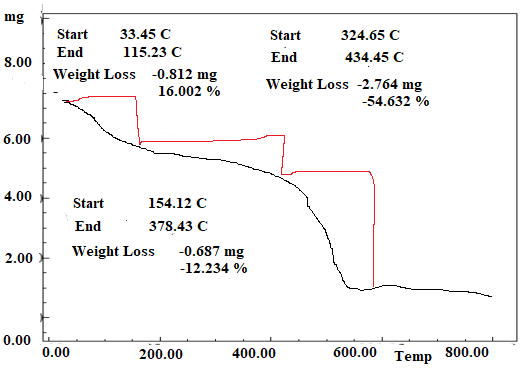


Fig. TGA for pure drug

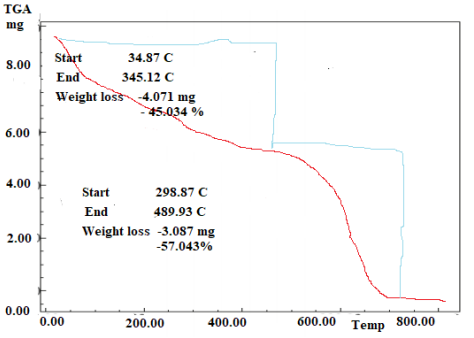


Fig. TGA for 30% condensate resin

The TGA curves in Figs. show that there is only a little (6%) weight loss for both PFR and condensate resin, which is made by mixing PFR with 30% (w/w) NNSC at 900 C. This is due to PFR absorbing moisture (water molecules) and condensing with 30% (w/w) NNSC. There is a 20 percent weight loss in PFR and an 18 percent weight loss in condensate with a 30 percent (w/w) NNSC between 50 and 900 C. Up to 4500 C, there is a 57 percent weight loss in PFR and up to 3400 C, there is a 31 percent weight loss in condensate with 30 percent (w/w) NNSC. This is most likely owing to the materials' breakdown.

Scanning Electron Microscopy (SEM)

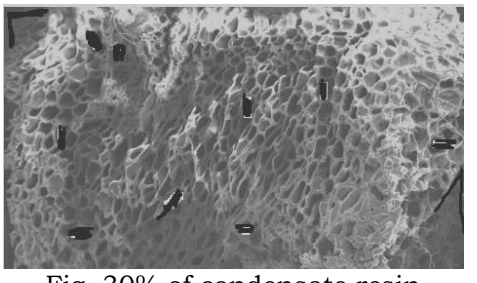


Fig. 30% of condensate resin

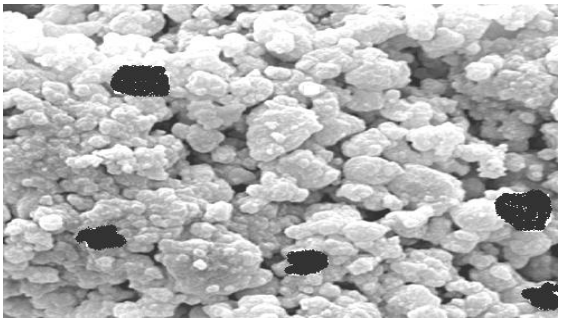
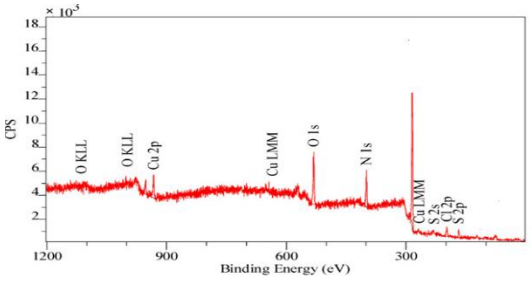


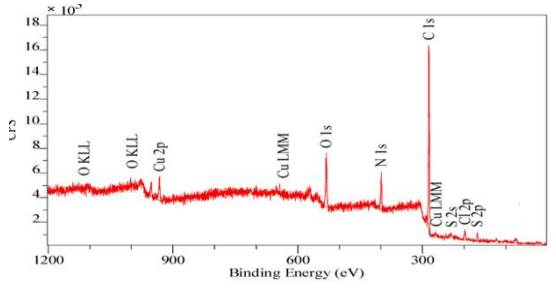
Fig. Pure Pregabalin

The high macroporous carbon derived from the reservoir in which the Phenol-formaldehyde sulphonic acid particles are deposited. As a result, when 30 percent (w/w) NNSC is added to condensate, the pore diameter reduces. In comparison to pure NNSC, condensate resin containing 30% (w/w) NNSC Nelumbo nucifera (NN) charcoal exhibits good mechanical stability and low Attritional breakdown. Increasing the amount (percent w/w) of NNSC in PFR, on the other hand, reduces the stability of the three-dimensional network in the polymeric matrix. As a result, from 30% condensate resin to original pure resin, mechanical stability and density drop (PFR).

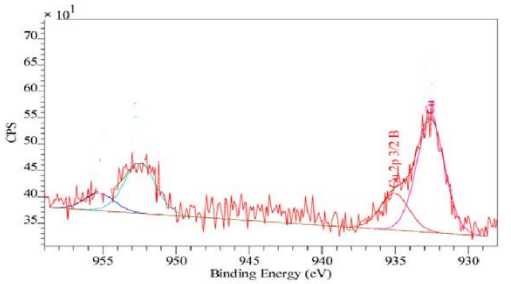
X-ray diffraction study



XPS spectrum obtained in a wide range of binding energy made for the Dowex 50 before the sorption process



XPS spectrum obtained in a wide range of binding energy made for the Dowex 50 after the Cu(II) sorption



XPS spectrum obtained in a wide range of binding energy made for the Dowex 50 With Pregabalin sorption

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