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DEVELOPMENT AND EVALUATION OF TASTE MASKED SUSPENSION OF PROKINETIC AGENT BY USING ION EXCHANGE RESIN

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ABSTRACT: In the present work the attempt was made to prepare taste masked suspension of Itopride hydrochloride using a simple rapid and cost effective method like complexation with ion exchange resin for taste masking that may acceptable to the industries. Itopride hydrochloride is a novel prokinetic agent it is used in treatments of gastro esophageal reflux disease, it is a highly bitter drug and not suitable for pediatric patients hence taste masking of drug was required. In the present work an attempt has been made to mask the taste, by employing complexation with various ion-exchange resins like doshion P 542, Tulsion 344, Indion 234, Indion 204, Kyron T 114 and to formulate in to a suspension. The prepared suspensions were evaluated for taste, drug content, particle size, viscosity, sedimentation volume, drug release and accelerated stability studies. Among the various resins, Kyron T 114 was found mask the drug satisfactorily. The developed formulation was an additional advantage like simplification of manufacturing procedure and is economical. The drug release studies showed that complete drug was released within 20 min. The manufacturing procedure was found to be reproducible and formulations were stable after one month of accelerated stability studies.

KEYWORDS: Itopride HCl, Doshion P 542, Tulsion 344, Indion 234, Kyron T 114, Taste masked suspension.

INTRODUCTION

A pharmaceutical suspension is a course dispersion in which insoluble solid particles are dispersed in a liquid medium. The particles have diameters for the most part greater than 0.1µm and some of the particles are observed under the microscope to exhibit Brownian movement if the dispersion has a low viscosity. Suspensions contribute to pharmacy and medicine by supplying insoluble and often substances in a form for the application of dermatological materials to the skin and sometimes to the mucous membranes and for the parenteral administration of insoluble drugs. Itopride hydrochloride is a prokinetic agent, it is useful in treatment of gastro esophageal reflux disease (GERD) & this drug is bitter in taste which is major concern in pediatrics and geriatric.

Taste Masking by Ion-Exchange Resins[1,2,3]: 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.)Drug can be bound to the resin by either repeated exposure of the resin to the drug in a chromate graphic column or by prolonged contact of resin with the drug solution. Drugs are attached to the oppositely charged resin substrate, forming insoluble adsorbates or resinates through weak ionic bonding so that dissociation of the drug-resin complex does not occur under the salivary pH conditions. This suitably masks the unpleasant taste and odour of drugs. Drug release from the resin depends on the properties of the resin and the ionic environment within the GIT. Drug molecules attached

to the resin are released by exchanging with appropriately charged ions in the GIT, followed by diffusion of free drug molecule out of the resins.

MATERIALS AND METHODS

Itopride Hcl was obtained as gift sample from Micro lab Hosur; all different resins were procured from ion exchange india pvt.ltd. And other ingredients and chemicals were used from laboratory grade.

Formulation of Itopride HCl Suspension With different resins[5].

All the ingredients were weighed individually.

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 Itopride hydrochloride 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 sugar was dissolved in specified quantity of boiled water and filtered.weighed quantities of Sorbitol, Glycerine, Xanthane gum, Xween-80 Aspartame, Methyl paraben, Propyl paraben, were added in sugar solution under stirring.

Mixing of DR complex with Syrup: The drug resin complex (mother liquor) obtained was added in to sugar solution under stirring.

Weighed quantities of coloring & flavoring agents were added in above solution & stirred for 10 min. The volume of suspension was made up to required quantity by using purified water.

Evaluation of Itopride HCl Suspension

Determination of sedimentation volume (F)[5,6,7]: 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 14^{th} day was considered as final volume of sediment (H_u). 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.

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

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. Results were shown in table 2.

Determination of Viscosity[10,11]: 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. Results were shown in table 2.

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

Assay of suspension[10,11]: 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 258 nm in U.V. Spectrophotometer & compared with standard and then % drug content was calculated. Results were shown in table 2.

Taste Evaluation[10,11]: Bitter taste was evaluated based on human bitter taste recognized by volunteers. The study protocol was explained and written consent was obtained from volunteers. Suspension equivalent to 50 mg of Itopride HCl was held in the mouth for 15seconds by each volunteer, the bitterness level was compared with formulation S1. Results were shown in table 2.

In-Vitro drug release[12,13]: *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 $\pm$ 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 258 nm using 0.1 N HCL as blank. The cumulative percentage drug release was calculated. This test was carried out only for final batch. Results were shown in table 3.

Particle size Analysis[10,11]: The size was measured using an optical microscope (Labomed CX RIII, Ambala, India), 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.Results were shown in table 4.

Accelerated Stability Study[14]: Itopride suspension was packed in 60 ml glass bottle. The packed bottles were placed in stability chamber maintained at 40 ± 2 °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 color, Assay, viscosity, any bad odor & pH). Results were shown in table 5.

RESULTS AND DISCUSSION

Table 1: Composition of Itopride HCl Suspension With different resins

Name of ingredient	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11
Complex Preparation											
Itopride hydrochloride	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg
Doshion P 542	-	100 mg	150 mg	-	-	-	-	-	-	-	-
Tulsion 344	-	-	-	100mg	150mg	-	-	-	-	-	-
Indion 234	-	-	-	-	-	100mg	150mg	-	-	-	-
Indion 204	-	-	-	-	-	-	-	100mg	150mg	-	-
Kyron T 114	-	-	-	-	-	-	-	-	-	100mg	150mg
Water	2.5 ml	2.5 ml	2.5ml	2.5 ml	2.5 ml	2.5ml	2.5 ml	2.5 ml	2.5ml	2.5 ml	2.5 ml
Syrup Preparation											
Sucrose	2.496 gm	2.496 gm	2.496 gm	2.496 gm	2.496 gm	2.496 gm	2.496 gm	2.496 gm	2.496 gm	2.496 gm	2.496 gm
Sorbitol solution 70%	458 mg	458 mg	458 mg	458 mg	458 mg	458 mg	458 mg	458 mg	458 mg	458 mg	458 mg
Glycerine	498 mg	498 mg	498 mg	498 mg	498 mg	498 mg	498 mg	498 mg	498 mg	498 mg	498 mg
Xanthan gum	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Tween-80	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Methyl paraben	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Propyl paraben	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
Aspartame	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg
Candy flavor	0.13ml	0.13ml	0.13ml	0.13ml	0.13ml	0.13ml	0.13ml	0.13ml	0.13ml	0.13ml	0.13ml
Quinoline yellow color	0.1 mg	0.1 mg	0.1 mg	0.1 mg	0.1 mg	0.1 mg	0.1 mg	0.1 mg	0.1 mg	0.1 mg	0.1 mg
Purified water up to	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml

Table 2: Evaluation parameters of Itopride HCl Suspension With different resins

Parameters	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11
Color	**Yellow**										
Viscosity (cps)	74.1	3400	3560	3920	3920	3650	3820	3810	3830	4180	4230
pH	4.34	5.54	5.60	5.57	5.60	5.70	5.63	5.58	5.62	5.68	5.60
Sedimentation volume (F)	**Sedimentation volume (F) were found to be 1 for all formulations**										
Assay %	101.1	76.2	77.7	71.1	75.0	57.4	66.8	98.4	91.7	97.5	99.9
Taste	Very bitter	Slight bitter	Less bitter	Less bitter	Less bitter	after taste bitter	Less bitter	After taste bitter	less bitter	Not bitter	Not Bitter

Formulation S1 was only for taste comparison hence it was not containing any resin. Formulation S2, S3 were prepared by using Doshion P 542 resin. Prototype formulation of itopride formulated (S2, S3,) with Doshion P 542 in the ratio of 1:2, 1:3 respectively. Prototype formulation of itopride formulated (S4, S5) with Tulsion 344 in the ratio of 1:2, 1:3 respectively. Prototype formulation of itopride formulated (S5, S7) with Indion 234 in the ratio of 1:2, 1:3 respectively. Prototype formulation of itopride formulated (S8, S9) with Indion 204 in the ratio of 1:2, 1:3 respectively. Prototype formulation of itopride formulated (S10, S11) with Kyron T 114 in the ratio of 1:2, 1:3 respectively. All the formulations were rejected since the bitterness was not masked and also the assay was found very less in S1 to S9 except S10 and S11

All physical properties of the suspension of all the formulation were found satisfactory but the assay & taste were not satisfactory as per requirement. Hence, further uses of all resins were discontinued except Kyron T114. All physical properties of the suspension of S10 and S11 were found satisfactory. The assay & taste of S11 was found satisfactory as per requirement. Hence, formulation S11 was taken as optimized formulation of suspension.

Optimized formula:

From all 10 batches of formulations prepared with different resin in different concentration, S11 (1:3, drug: Kyron T 114) showed good taste masking as compared to other formulations. The physical parameters of S11 were found satisfactorily & comply with official specification. Hence, S11 was considered as optimized formula for preparation of taste masked Itopride suspension using ion exchange resin.

Dissolution profile of optimized formulation S11[12,13]:

The dissolution of S11 was determined using *The United States Pharmacopoeia* (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 50 rpm that trial was studied. Dissolution was carried out up 45 minute and samples were taken after 5, 10, 15, 20, 30, and 45min. For S11 results of % drug release was shown in Table 3. Itopride release from the developed formulations has been observed & it was found that resin was not retard the release of drug from suspension.

Table 3: In-vitro cumulative % drug release profile of optimized batch S11

Time of sampling in minutes	*Cumulative % drug release AM ± SD
5	96 ± 0.5
10	97 ± 1.5
15	100 ± 1
20	101 ± 1
30	101 ± 1.5
45	101 ± 2

***Each value was an average of six determinations**

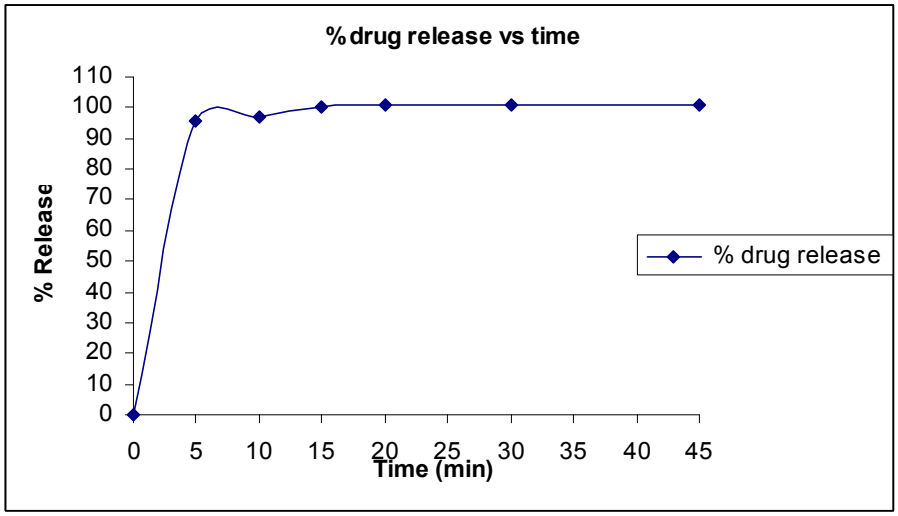

Figure 1: in vitro release of Itopride Hcl from optimised batch S11

Particle size analysis of optimized formula: As described in methodology the particle size of final formula S11, was measured microscopically. The mean particle size of trial 11 was shoun in table 4. Kyron T-114 is highly porous, and even though insoluble in water, it is capable of hydration.

Table 4: Particle size analysis of optimized formula S11

Batch no.	Particle size
Non swollen Kyron T114	30 ± 5
Swollen Kyron T114	42 ± 7
Formulation S11	53 ± 8

Aparticle size analysisof S11 suggest that resin is producing a swollen porous network structure that is capable of allowing the drug molecules to permeate /diffuse inside and also get complexed with the resin. Fig 2 & 3 shows the photomicrograph of non swollen and swollen Kyron T 114 particles in distilled water while Fig 4 shows the photomicrograph of suspension particle.

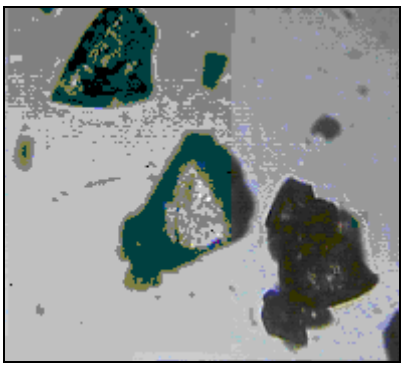

Figure 2 : Photomicrograph of non swollen Kyron T 114

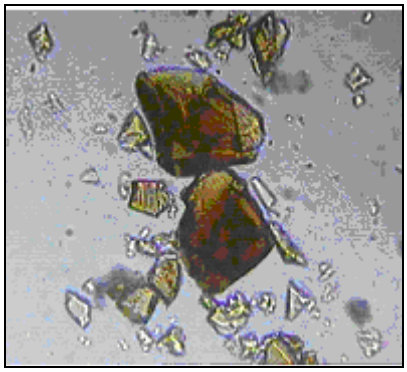

Figure 3 : Photomicrograph of swollen Kyron T 114

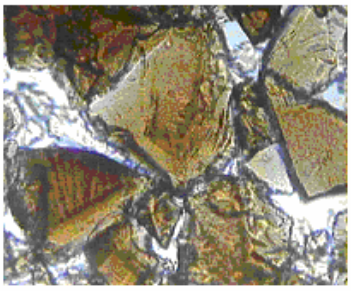

Figure 4 : Photomicrograph of prepared suspension S11

Accelerated Stability Study[14]: Suspension of S11 was kept for accelerated stability study at 40 ± 2 °C and 75 ± 5% RH for 1 month in stability chamber. After a period of one month, the samples were observed for any change in physical parameters. It was observed that any change in color. It was also noted that suspension was free of any kind of bad odor.

Results obtained from the Evaluation after stability studies are shown in Table 5.

Table 5: Evaluation Parameters after Stability Study of Itopride HCl Suspension S11

Evaluation Parameters	Initial	After 1 month
Color	Yellow	Yellow
Viscosity (cps)	4230	4120
pH	5.60	5.59
Sedimentation volume	1	1
Assay %	99.9	99.3
Taste	Not bitter	Not bitter

CONCLUSIONS

Complexation with ion exchange resin is a simple and cost effective technique for taste masking. Complexation of drug and resin was done by stirring them together for 3-4 hr in aqueous media. Taste masked suspension of Itopride hydrochloride (S10, S11) were successfully prepared using Kyron T 114 as ion exchange resin by complexation method. Suspensions were evaluated for Particle size, viscosity, in vitro drug release, sedimentation volume, Assay and taste evaluation. The taste of final trial was found totally masked & acceptable for the pediatric & geriatric patients. Itopride release from the developed formulations has been observed & it was found that resin was not retard the release of drug from suspension. Suspension of formulation S11 complies with quality control tests. Developed formulation S11 was found stable after the period of one month. It can be concluded that Kyron T 114 has a maximum ability to mask the bitter taste of Itopride satisfactorily.

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