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TASTE MASKING AND FORMULATION OF ONDANSETRON HCl SR SUSPENSION USING ION EXCHANGE RESIN AND COATING TECHNIQUE

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ABSTRACT

The purpose of this research was to mask the taste of Ondansetron HCl and to formulate SR (Sustained Release) suspension. Ondansetron HCl is an antiemetic drug used to treat and prevent Chemotherapy induces nausea and vomiting in cancer, post operative treatment, pregnancy, cyclic vomiting syndrome and gastroenteritis. The bitter taste, shorter half-life and frequent administration of drug reduce patient compliance, to overcome this problem, taste masking was done by complexing drug with Ion Exchange Resins (IER) Indion 244 and Amberlite 69 (1:1, 1:2 and 1:3) by batch method followed by coating with Acrycoat E100-40 (AC) (5-15% v/v) by conventional pan coater.

Drug-resin complex (Resinate) and coated resinate (CR) was characterized by drug content, DSC, *in vitro* dissolution and *in vitro* taste evaluation. *In-vitro* taste evaluation showed that bitter sensation was after 1 min. CR showed up to 80 % of drug was release within 8 hr, where as Resinate showed 70 % of drug release within 6 hr and pure drug showed more than 90 % within 2hr. respectively. Finally suspension was formulated and evaluated. Thus, results conclusively demonstrated successful masking of Ondansetron HCl taste and sustained release.

KEY WORDS:

Acrycoat E100-40 (AC), Amberlite 69, Coating, Coated Resinate (CR), Drug-resin complex (Resinate), Indion 244, Ion Exchange Resins (IER), Ondansetron HCl, Sustained Release (SR)

INTRODUCTION

IER have received significant interest from pharmaceutical scientists because

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of their versatile properties as drug delivery vehicles. Several IER have been developed for immediate release, SR and controlled release. They are used in several formulations for taste masking purpose too, so the study was design to mask the taste of Ondansetron HCl and sustain its release by using IER approach. (IV)
Coating of Resinates provides better control over the drug release because of presence of rate controlling membrane.
The absorption of the drug from CR is a consequence of the entry of the counter ions into the CR and release of drug ions from Resinate by the ion exchange process and diffusion of drug ions through the membrane into the dissolution medium.
A most important disadvantage of SR systems is dose dumping which may increase risk of toxicity. IER offer better drug retaining properties and prevention of dose dumping. The polymeric (physical) and ionic (Chemical) properties of IER will release the drugs more uniformly than that of simple matrices.

MATERIALS AND METHODS

Ondansetron HCl, (FDC Ltd. Aurangabad.), Indion 244, (Ion Exchange India Ltd. Mumbai.), Amberlite 69, (Wockhardt research Center, Aurangabad), Acrycoat E100-40 (Coral Pharma Chem., Ahemdabad.) were obtained as gift samples.

Calibration curve by UV Spectrophotometer:

The UV spectrophotometric method was selected for the estimation of Ondansetron HCl which showed absorbance at λ max 310 nm as shown in (figure 1).

Selection and Preliminary Evaluation of Resin:

Selection of resin was done depending on the percent of the drug bound to the resin. Primary complexation study was carried out using two type of resin Amberlite 69 and Indion 244 in the ratio of drug: resin 1:1 and 1:2 respectively. Then the selected resins were evaluated for particle size, Water absorption time**,** Depending on the result of the primary study further research work were done with Indion 244. (II)

Purification, Pretreatment and activation of resin:

Resin was purified by using methyl alcohol to remove impurities. The purified resin was washed with deionised water and filtered. Resin was pretreated and activated alternately with 1N HCl and1N NaOH (each 100ml) rewashed with deionized water until neutral pH is obtained. (V)

Formulation of Drug resin complex

In a beaker containing 25 ml of deionized water add accurately weighed drug and activated resin in 1:1, 1:2, and 1:3 ratio and stirred for 24hr then filtered it, residue was then washed with 75 ml of deionized water. To know the drug-loading efficiency,

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unbound drug was estimated at 310 nm from the filtrate. (IX)

Determination of Resinate drug content (X)

In 100 ml 0.2 M HCl solution, 100 mg of resinates were added and was sonicated for 15 minutes. Then it was filtered through Whatman filter paper (No.42) and the absorbance of filtrate was measured by UV-visible spectrophotometer at 310 nm.

Differential Scanning Calorimeter (DSC)
DSC (Shimadzu/DSC-60) equipped with intra cooler and refrigerated cooling system was used to analyses the thermal behavior of pure Ondansetron HCl, and Resinate. Air was purged at 50 ml/min through cooling unit. Thermal behavior of hermetically sealed samples heated at 10^0C/min and heating was performed from 0^0C to 500^0C was recorded in the form of diffractogram.

Drug Release from Resinate:
USP type I dissolution test apparatus (Electrolab TDT) was used to determine *invitro* drug release from resinate. Accurately weighed resinate equivalent to 100 mg of drug and subjected to dissolution studies in triplicate in 900ml of 0.1 N HCl for 2 hrs. and remaining 6 hrs. in pH 7.2 buffer maintained at 37±2 ^{o}C and stirred by basket at 100 rpm. After every time interval , 5 ml of Sample was withdrawn from the rotating filtration assembly and analyzed at 310 nm maintaining sink condition and time required for complete drug release was noted and was compared with Pure Ondansetron HCl as shown in (figure 5a).

Coating of Resinate: (III)
Particle size of resinate was very small for coating purpose as such small particles cannot withstand with the pressure of the coating pump , so to increase the particle size the granules of the resinate were prepared by kneading method.

Granules preparation for coating:
Granules for coating were prepared by kneading method using HPMC 5 % w/w as binder and where dried at 50 ^{0} C. Granules prepared were coated with AC for preventing the drug release from resinate after reconstitution of the suspension in the water. Coating solution of AC was prepared as per the formula (Table-5).

Coating procedure:
The granules obtained upon kneading were coated with coating solution in Pharma R & D coater. The coating parameters followed are mentioned in (Table -6)

Evaluation of coated resinates (CR): (III)

Determination of percent coating polymer:
100mg of CR granules were weighed accurately and washed three times with 10ml portion of acetone in order to remove polymer coating then the

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resinates were dried at 60^0C for 12 hr. After drying it was accurately weighed .The percent of coating polymer calculated as equation 1

$$\% \text{ Coating polymer} = \frac{\text{CR granules initial wt.} - \text{CR granules dried wt.}}{\text{CR granules initial wt.}} \times 100 \quad \text{eq.(1)}$$

Drug content of CR:
100 mg of CR were taken and triturated finely then, 100 ml of 0.2 M HCl was added and sonicated for 15 minutes, it was filtered through Whatman filter paper (No.42) and the absorbance of filtrate was measured at 310 nm in triplicate.

Drug leaching from CR:
100mg of resinate and CR was placed in an amber coloured bottled with 30 ml of distilled water and kept for 5 days. Each day, a clear supernatant was withdrawn and absorbance of drug leached in distilled water was determined at 310 nm . The result obtained is as per (Table -9)

Taste Evaluation (I and IV)
Evaluation of taste was done in two parts
Determination of threshold bitterness concentration
Various concentrations (10-50 µg /ml) of drug were prepared in phosphate buffer pH 6.7. Mouth was rinsed with buffer solution and then, l0 ml of most dilute solution was tasted by swirling it in the mouth mainly near the base of the tongue for 30 seconds. If the bitter sensation was no longer felt in the mouth after 30 seconds, the solution was spat out and waited for 1 minute to ascertain whether this is due to delayed sensitivity. Then mouth was rinsed with safe drinking water. The threshold bitter concentration is the lowest concentration at which a material continues to provoke a bitter sensation after 30 seconds. After the first series of tests, mouth was rinsed thoroughly with safe drinking water until no bitter sensation remained. Interval of at least 10 minutes was observed between two tests.

***In-vitro* evaluation of bitter taste of resinates:**
An accurately weighed (4 mg drug equivalent) resinate and 10 ml of pH 6.7 phosphate buffer (0.1 M) was taken in series of volumetric flask and stirred at 50 rpm. The stirring was stopped at different time intervals such as 0,10, 30,60 and 120 sec., dispersion was filtered, and the concentration of Ondansetron HCl in filtered resinate was determined. Time for resinate to achieve drug concentration corresponding to threshold bitterness in 10 ml phosphate buffer was recorded.

Formulation of Ondansteron HCl oral suspension for reconstitution purpose:
As per the literature survey suspending agents and other ingredient were selected and Ondansteron HCl oral suspension for reconstitution purpose was formulated as per (Table-10)

RESULT & DISCUSSION

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The standard curve of Ondansetron HCl was constructed in distilled using JascoV-630 UV- visible spectrophotometer. Excellent linearity, precision and reproducibility were obtained in the range 2 µg/ml to 15 µg/ml. Standard calibration was plotted as (figure 1)

Selection of Resin:

Selection of resin was done depending on the percent of the drug bound to the resin. Amberlite 69 and Indion 244 ,were selected for study, both where stirred for drug loading in 1:1 and 1:2 and the result were as per (Table -1).

From the result Indion 244 showed more loading capacity as Indion 244(≤ 0.15mm) is having smaller particle size than Amberlite 69 (0.150-0.160mm) The water uptake of Indion 244 was found to be 60 min whereas Amberlite 69 showed 45min. Loading capacity of Indion 244 is a function of exchange of H^+ ions in the resin with ions in solution. [(x)]

Drug content of Resinate:

Ondansteron HCl is absorbed in the GI tract, so the drug content was studied at pH 2.8 (0.2 M HCl) sonicated for 15 minutes which showed drug was released within 15 minutes and release was increased as the (drug: resin) ratio was increased that is 1:1, 1:2 and 1:3 ratio shows 72.27% ,76.65% and 78.20 % drug content as per (Table-2)

DSC study of Resinate, Ondansteron HCl and Indion 244:

The thermal behavior of the pure drug shows sharp endothermic peak at 192°C corresponding to melting (figure -2) and Indion 244 thermogram shows a broad endothermic peak and then slowly heat is evolved showing broad exothermic peak near 220° C (figure-3) while in physical mixture of drug retain both characteristic of drug as well as resin only slight shift take place in endothermic and exothermic peak of drug and resin respectively. The melting of pure drug peak is shifted towards 189° C and exothermic peak is shifted towards 225 ° C (figure-4a) the thus indicate that the drug and resin does not form any chemical complex but act as a physical mixture only. (Figure-4b) indicates different nature compared to DSC of Drug and Resin .It indicates board endothermic peak at 270° C and the drug peak at 190° C is missing this clearly indicate that a complex is formed which placed between drug and resin peak which shows some sort of amorphous nature .[(VII)]

***In-vitro* Drug Release from resinate:**

Dissolution studies of resinate showed that drug release was more than 70 % within 6 hr .where as Pure Ondansteron HCl enclosed in capsule more than 90 % within 2hr. respectively. (figure-5a)

Evaluation of CR with AC:

Evaluation of CR with AC was carried for nature of complex, drug content, coating %, particle size and *in vitro* drug release the result obtained are as per (Table-7 and 8). The *invitro* result had shown the decrease in the release of the drug from the CR when dissolved at pH-6.8 and pH- 2 respectively. The release

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of the drug is retarded from 88% to 80%for AC 5%- AC15% respectively. (figure -5c).

Taste evaluation:

Determination of threshold bitterness concentration

Most of the volunteers reported the threshold bitterness at 40 µg/ ml.

Time for attainment of threshold bitterness concentration *invitro* of Resinate:

The time for achievement of threshold bitterness concentration *invitro* in buffer of salivary pH showed that the drug may not get released in saliva to attain threshold bitterness concentrations thereby masking the bitter taste satisfactorily.

Evaluation of Suspension after reconstitution organoleptic evaluation

Formulation was evaluated for the Appearance, flavor and taste. They were found to pleasant in appearance and acceptable as far as taste was concerned and other evaluation parameter are as per (Table-11)

CONCULSIONS:

Formulated Ondansetron HCl SR suspension using IER and coating technique showed sustained release of drug and its taste masking was also done successfully which may increase patient compliance and may reduce the dosing frequency. Indion 244 IER can be used for both taste masking and SR. AC coating controlled release as well as drug leaching after reconstitution of suspension. Formulated reconstituted suspension shown good organoleptic properties, viscosity, resuspendibility and SR properties.

ACKNOWLEDGMENT:

The authors are highly thankful FDC Ltd. Aurangabad, Ion Exchange India Ltd. Mumbai, Wockhardt research Center, Aurangabad and Coral Pharma Chem, Ahemdabad for providing drug, resin and polymers.

Table 1: Selection of resin

Sr. no.	Resin	Drug-Resin ratio	%drug loading ± SD (n=3)
1.	Amberlite 69	1:1	24.65±0.20
2.		1:2	26.74±0.15
3.	Indion 244	1:1	26.33±0.94
4.		1:2	29.19±0.19

Table 2: Drug content of resinate

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Sr. no.	Drug-Resin Ratio	% drug content ±SD(n=3)
1.	1:1	72.27 ± 0.15
2.	1:2	76.65 ± 0.64
3.	1:3	78.20 ± 0.25

Table 3: Determination of Threshold Bitterness Concentration

Concentration of drug(µg/ml) / No. of candidate	10	20	30	40	50
1	0	0	1	1	2
2	0	0	1	1	2
3	0	0	0	1	2
4	0	0	0	1	2
5	0	0	0	1	2
6	0	0	0	1	2

Table 4: Time for Attainment of Threshold Bitterness Concentration in- vitro of Drug resin complex

Sr. no.	Time	Concentration of drug (µg/ml)± SD (n =5)
1	0	23.15 ± 1.25
2	10	26.15 ± 1.45
3	30	32.11 ± 1.34
4	60	49.43 ± 0.91
5	120	72.65 ± 1.54

Table 5 : Formula for Coating Solution.

Sr. No.	Ingredients	Quantity		
1	AC	05% (v/v)	10% (v/v)	20% (v/v)
2	Talc	0.25(gm)	0.25(gm)	0.25(gm)
3	IPA+Acetone	q. s.100	q. s.100	q. s.100

Table 6: Parameters for Coating Procedure.

Sr. No.	Parameter	Observation
1	Pump speed	2 rpm
2	Drying temperature	60ºC
3	Speed of the pan	25 rpm
4	Pressure	2 bar kg/cm^2

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Table 7 : Coating of resinate by Acrycoat E100-40. (AC)

Test	Observation		
	5%AC	10% AC	15 % AC
Nature	Free flowing	Free flowing	Cohesive, lumpy
Drug content (%w/w)	74.94	72.23	70.26
Coating (%w/w)	4.59	9.86	15
Particle size(µm)	62-165	75-170	82-190

Table 8 : Comparative *In-vitro* Drug Release Profile of coated resinate with 5% AC, 10 %, AC 15% AC.

Sr No.	Time (hr.)	*In vitro* drug release of AC± SD(n=3)		
		5%	10%	15%
1	0.5	8.591±0.33	7.96±0.19	6.731±0.13
2	1	12.661±0.20	10.969±0.20	9.419±0.20
3	2	18.051±0.27	15.052±0.15	12.348±0.39
4	3	39.776±0.34	32.089±0.13	24.44±0.27
5	4	56.648±0.32	49.134±0.13	33.917±0.32
6	5	69.562±0.36	58.585±0.20	43.532±0.19
7	6	78.041±0.20	69.68±0.46	50.49±0.40
8	7	81.19±0.13	82.267±0.34	66.79±0.20
9	8	88.936±0.20	85.572±0.13	80.639±0.20

Table 9 : Drug leaching study of complexes with AC

Sr.no.	Day	Drug Leached Avg. % ± SD(n=3)	
		AC	Resinate
1	1	4 ±0.16	12 ±0.14
2	2	6 ±0.15	35 ±0.16
3	3	16 ±0.42	65 ±0.13
4	4	18 ±0.51	72 ±0.16
5	5	20 ±0.31	86 ±0.13

Table 10: Formulae for each 5ml Ondansetron HCL oral suspension

Sr. No.	Ingredients	Quantity
1	Ondansetron HCL	4mg
2	Na CMC	0.5%
3	Sucrose	30%
4	Methyl Paraben	0.18%

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5	Propyl Paraben	0.02%
6	Peppermint flavor(ml)	0.25%

Table 11 : Evaluation of Suspension after reconstitution

Sr.no.	Test	Observation
1	Appearance	Uniform
2	Taste	Sweet, palatable
3	Flavour and Aroma	Peppermint
4	Mouthfeel	Viscous
5	pH	6.8
6	Viscosity(cps)	146
7	Separation ratio	0.42
8	Redispersibility	+++
9	% in-vitro drug release	70.92

Figure 1: Calibration curve of ODH

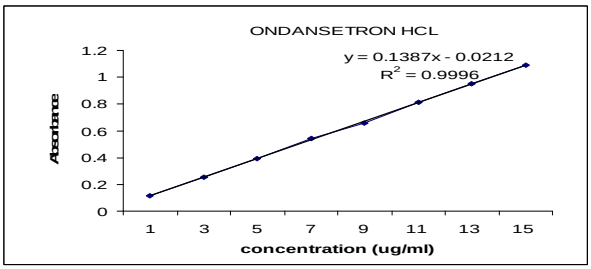

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Figure 2: DSC of Drug

Figure 3: DSC of Indion 244

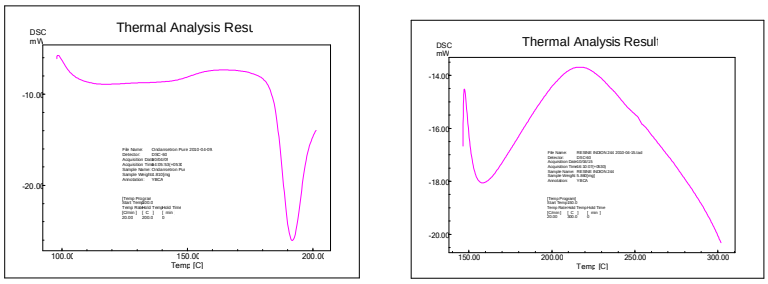


Figure 4a: DSC of Physical mixture (drug+ Indion 244) and **Figure 4b** Resinate

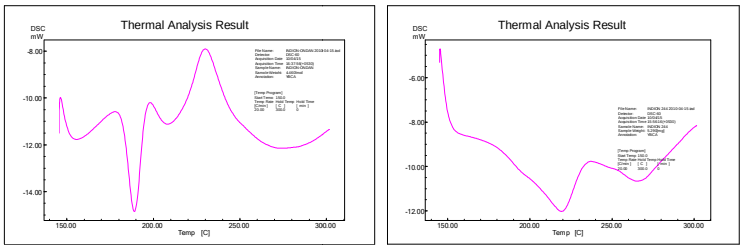


Figure 5a: Comparison of *invitro* Drug Release Profile of Conventional Ondansteron HCl, **Figure 5b:** Drug Resinate and **Figure 5c** CR Suspension.

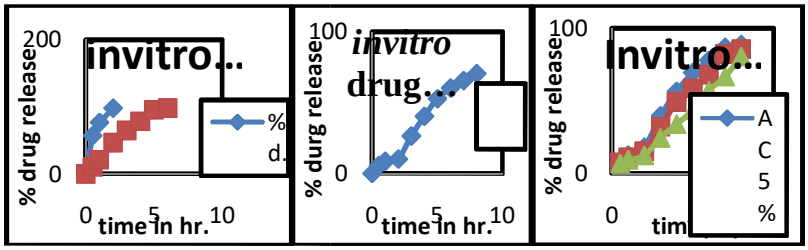
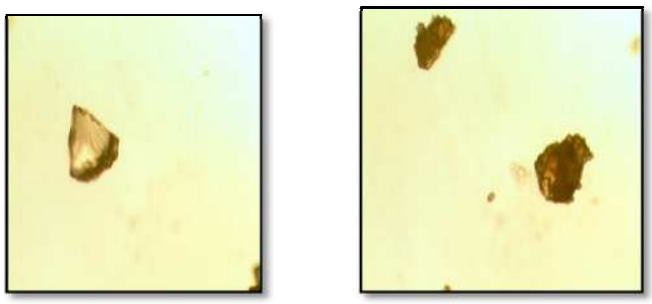


Figure 6. Photo. of Uncoated Resin and CR particle



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