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Formulation Of Sustained Release Ondansetron HCl Pediatric Suspension Using Ion Exchange Resin

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Abstract: Ondansetron Hydrochloride (ODH) is 5-HT3 receptor antagonists and is used for pediatric formulation. It is an antiemetic drug given in treatment of nausea and vomiting. The bitter taste of the drug and having shorter half-life and needed frequent administration which reduces patient compliance. Hence, need was felt to deliver ODH to the patients, once a day to improve the patient compliance of drug.So in the work undertaken, an attempt was made to sustain the release and to mask the taste of the ODH using ion exchange resin approach.

Method used was complexation with ion exchange resin (Indion 244). The drug resin complex (DRC) was prepared by conventional batch method and microencapsulated with Eudragit RS 100 and ethylcellulose. The complex product was characterized by IR, DSC, drug content, *in vitro* dissolution and micrometric properties. The taste evaluation was done by an *in-vitro* and panel method.

Drug release of complex showed that release was more than 70 % within 6 hr .where as Pure ODH enclosed in capsule more than 90 % within 2hr. respectively. The release of the drug is retarded from 62% to 48% for EC5%-20% and 58% to 45% for EU5%-20% and bitter sensation after 60 s.

Thus it can be concluded that release of Ondansetron HCL is sustained and its taste can be masked using ion exchange resin complexation method.

Key words: Ondansetron HCL, Ion Exchange Resins, Indion 244, Taste masking, suspension.

INTRODUCTION

Pediatric oral formulations can be quite scientifically challenging to develop and the prerequisites for both a measurable dosage form and to administer based upon body-weight, and also sustaining the drug release and taste-masking are two of the challenges unique for pediatric oral formulations.[1] During last two decades many approaches are successfully used for developing Sustained release dosage form of adults. Literature survey reveals development of Sustained release dosage form in pediatric segment is not much exploited, so the study was design to develop oral sustained release suspension of ODH by using IER approaches.

A major drawback of controlled or sustained release systems is dose dumping, resulting in increased risk of toxicity. Ion exchange resins offer better drug retaining properties and prevention of dose dumping. The polymeric (physical) and ionic (Chemical) properties of ion exchange resin 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.) and Eudragit RS 100 (Evonik Degussa India Pvt. Ltd., Mumbai.) were obtained as gift samples. Ondansetron HCL was analyzed by using JASCO-

V630-UV/Visible spectrophotometer at λ-max 310 nm.

Formulation of Drug resin complex[2]

100 mg of activated resin was placed in a beaker containing 25 ml of deionized water and accurately weighed Ondansetron HCL (as per 1:1, 1:2, and 1:3, drug: resin ratio) was added and stirred for 24hr. The mixture was filtered and residue was washed with 75 ml of deionized water. Unbound drug in filtrate was estimated at 310 nm and drug-loading efficiency was calculated.

Characterization of resinate:

Determination of drug content [3]

100 mg of complex were taken and triturated finely. To this, 100 ml of aqueous acid having pH 2.8 (0.2 M HCL) was added and sonicated for 15 minutes. Then the solution was filtered through whatman filter paper no 42 and the absorbance of filtrate were measured by UV-visible spectrophotometer at 310 nm.

Infra Red spectroscopy

Infrared spectra of drug, Indion 244 and complex was obtained using Fourier-transform infrared (FTIR) spectroscopy (Jasco 4100 Plus Toekyo, Japan).Drug was mixed with potassium bromide (KBr) , and the spectra were recorded over the wave number 4000 to 400 cm−1. The spectra were comparatively analyzed as **per (Figure 1).**

Differential Scanning Calorimeter

Differential scanning calorimeter (specification.) equipped with intra cooler and refrigerated cooling system was used to analyses the thermal behavior of pure ODH, and DRC. Indium standard was used to calibrate DSC temperature. 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[4]

Accurately weighed resinate equivalent to 100 mg of drug and subjected to dissolution studies in triplicate in USP type I dissolution test apparatus (Electrolab TDT) in 900ml of 0.1 N HCL (for first 2 hrs.) and for remaining 6 hrs. in pH 7.2 buffer maintained at 37±2 ^{o}C and stirred by basket at 100 rpm. Every time, 5 ml of Sample was withdrawn from the rotating filtration assembly and analyzed spectrophotometrically at 310 nm. Same amount of fresh respective medium that is 0.1 N HCL or pH 7.2 buffer was used to replace the sample withdrawn and time required for complete drug release was noted and was compared with Pure ODH enclosed in capsule as shown in (**figure 6).**

Microencapsulation of drug resinate (MDR)[4]

To retard the further drug release the resinate particles were coated with ethylcellulose (5-20% w/w) and Eudragit RS-100 (5-20%w/w).microencapsulation was carried out by solvent evaporation technique. Drug-resinate (1gm) was stirred with polymer solution for 2hr. the solvent cyclohexane was evaporated by continuous stirring on a heating magnetic stirrer, the stirring rate was increase as the viscosity of the solution was increase .The product was filter and dried at 37 ^{0}C and evaluated for drug content uniformity, similarly same process was followed using Eudragit RS-100 as a polymer and using dichloromethane and chloroform as a solvent.

Taste Evaluation [5, 6]

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.

Determinations of micromeritic properties[7]

Evaluation parameters like bulk density, tap density, angle of repose and Carr's index of resinates were determined using methods reported (**Table 6).**

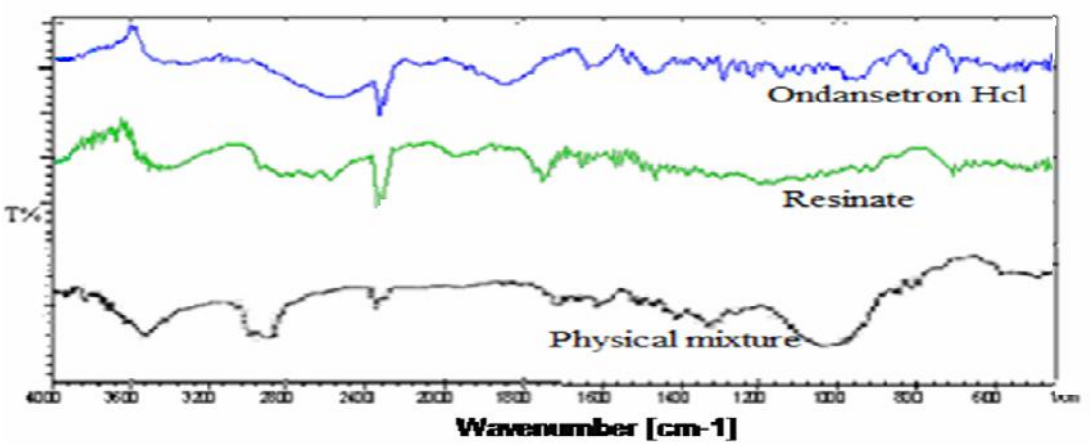

Figure 1: FTIR spectra of pure drug ODH, DRC and PM.

RESULT & DISCUSSION

Drug Entrapment/drug content:

ODH is absorbed throughout the GI tract, so the drug content was studied at pH 2.8 (0.2 M HCl) sonicated for 15 minutes and showed ODH 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.

FTIR Spectroscopic Studies:

The overlain FTIR spectra of pure drug ODH, DRC and PM are shown in (figure8.10). The FTIR spectrum of pure drug has showed N-H stretching at 2941.03 cm^{-1}, C-N stretching at 1278cm^{-1}, C-O stretching at 1612.38 cm^{-1}, C-H stretching at 3010.01 cm^{-1}, and C=C stretching at 1639.38 cm^{-1}.The FTIR spectra of DRC showed C-N stretching at 1278cm^{-1}, C-O stretching at 1612.38 cm^{-1}, C-H stretching at 3010.01 cm^{-1}, and C=C stretching at 1639.38 cm^{-1}. The spectra of PM showed that C-N stretching at 1278cm^{-1}, C-O stretching at 1612.38 cm^{-1}, C-H stretching at 3010.01 cm^{-1}, and C=C stretching at 1639.38 cm^{-1}.

The complexation of ODH with Indion-244 in DRC was confirmed by loss of N-H stretching at 2941.03 cm^{-1}, and same was observed for PM. The loss of N-H stretching might have been due to the complexation of Indion 244 with quaternary nitrogen of ODH. Where do to electrostatic bonding with resin active site it get masked. From the FTIR spectrum of ODH, DRC, and PM it can be concluded that chemical integrity of ODH was preserved.

DSC study of DRC, ODH and Indion 244:

The thermal behavior of the pure drug shows sharp endothermic peak at 192°C corresponding to melting. As shown in figure (2) and Indion 244 thermogram shows a broad endothermic peak and then slowly heat is evolved showing broad exothermic peak near 220° C as shown in 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 as shown in figure (4) the thus indicate that the drug and resin does not form any chemical complex but act as a physical mixture only. Figure (5) 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 .

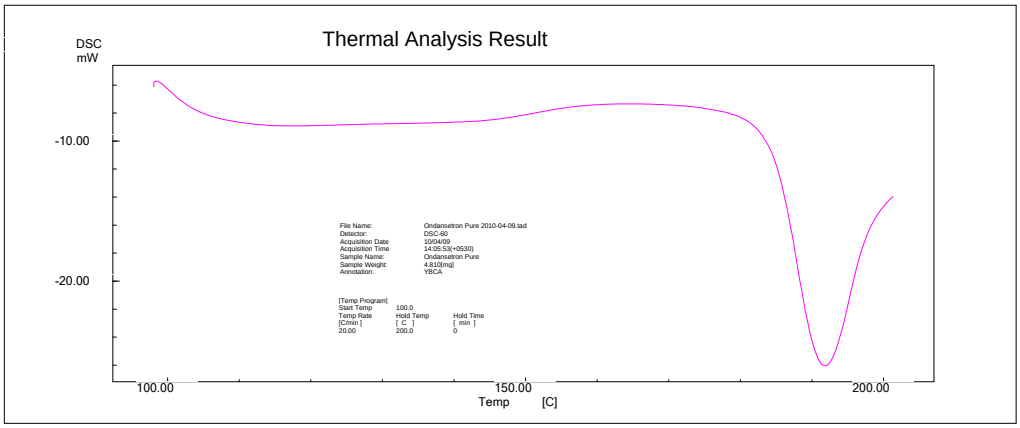

Figure 2: DSC thermogram of Drug (ODH)

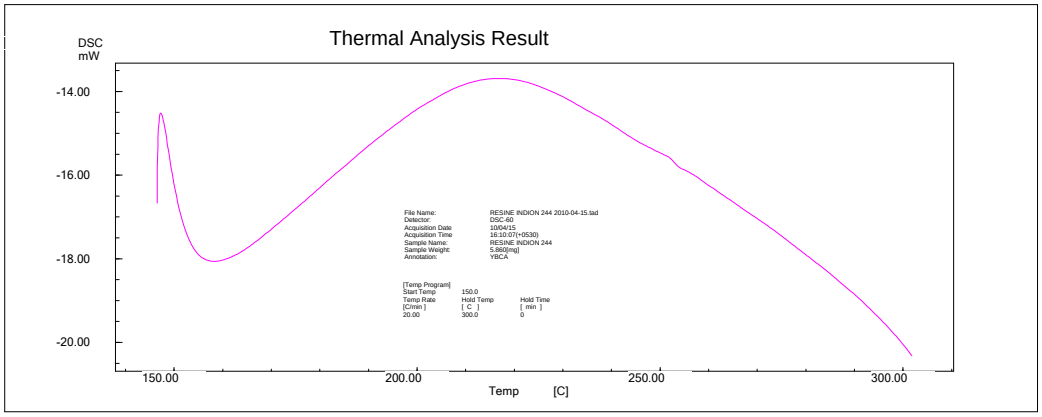

Figure 3: DSC thermogram of Resin(Indion 244)

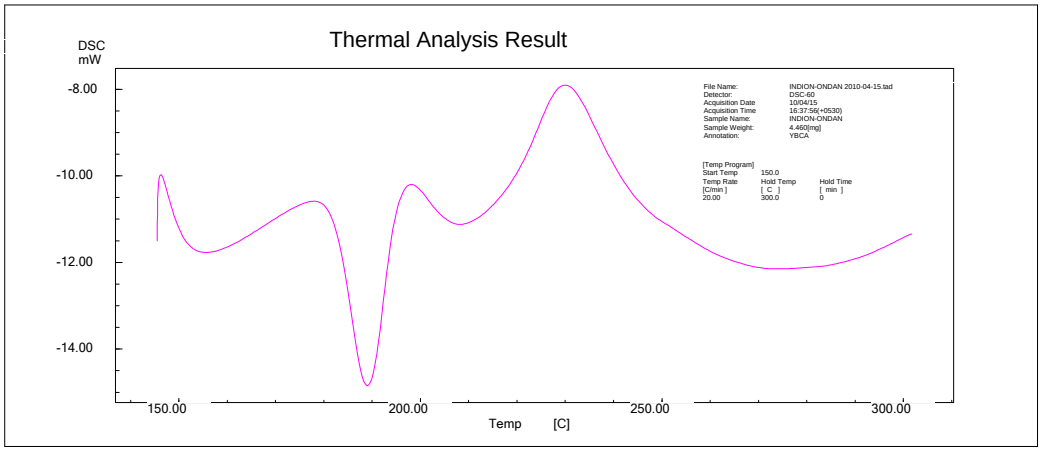

Figure 4: DSC thermogram of Physical mixture (ODH + Indion 244)

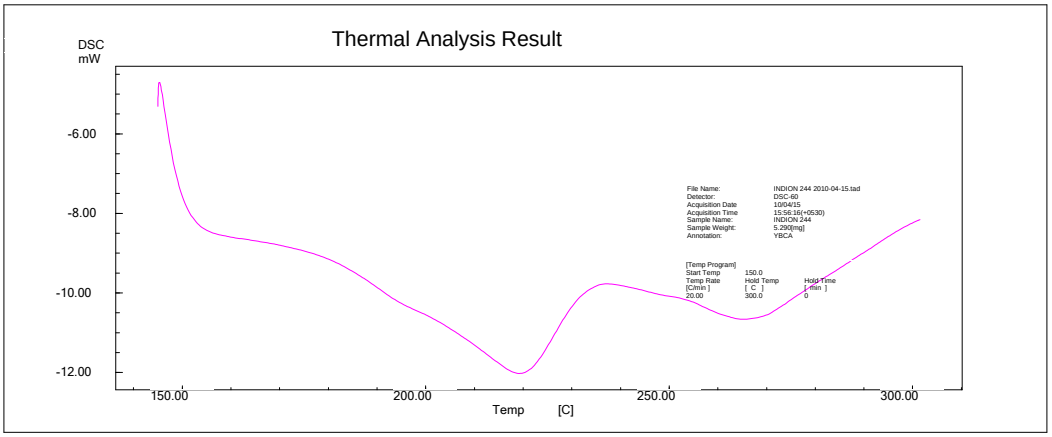

Figure 5: DSC thermogram of resinate(ODH + Indion 244)

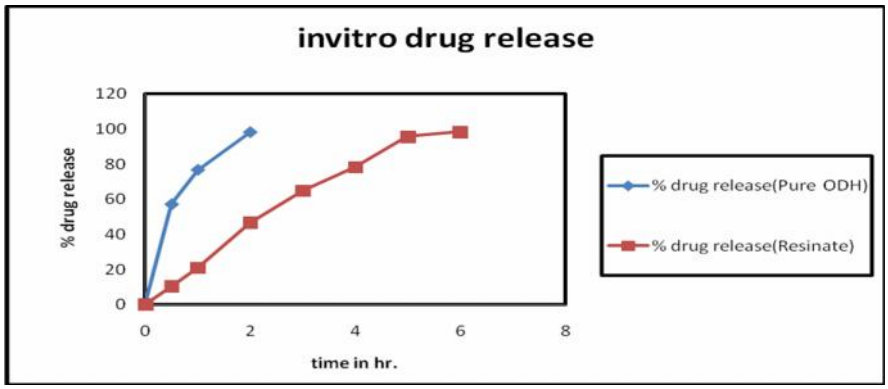

Figure 6: Comparison of *invitro* Drug Release Profile of Conventional ODH and Drug Resinate.

***In-vitro* Drug Release:**

The DRC prepared by loading method was subjected to dissolution studies in 0.1N HCL (for first 2 hour) and for remaining 6 hours in pH 7.2 buffer using USP 23 Type I apparatus at 100 rpm and 37^0 C which showed that drug release was more than 70 % within 6 hr .where as Pure ODH enclosed in capsule more than 90 % within 2hr. respectively,as shown in (figure 6).

Evaluation of microencapsulated drug resinate (MDR)

The MDR prepared using different concentration of polymer ethylcellulose (EC) and Eudragit RS100 (EU) by solvent evaporation method and was subjected to dissolution studies in 0.1N HCL (for first 2 hour) and for remaining 6 hours in pH 2 buffer using USP 23 Type I apparatus at 100 rpm and 37^0 C which showed that drug as per following tables.

Table 1: Comparative *In-vitro* Drug Release Profile of microencapsulated resinate with5%-20% EC.

Sr No.	Time (hr.)	Avg. *In vitro* drug release of EC ± SD (n=3)			
		5%	10%	15%	20 %
1	1	11.013 ±0.26	10.451±0.15	9.326±0.13	9.206±0.13
2	2	13.799 ±0.22	11.244±0.20	10.373±0.20	9.897±0.13
3	3	16.125 ±0.20	12.474±0.33	11.209±0.39	10.428±0.07
4	4	25.426 ±0.30	21.755±0.5	21.651±0.33	19.524±0.46
5	5	36.033 ±0.13	30.612±0.15	29.901±0.74	20.71±0.27
6	6	44.448 ±0.27	41.636±0.19	38.51±0.27	35.048±0.23
7	7	56.413 ±0.27	49.843±0.07	46.190±0.34	40.993±0.20
8	8	62.994 ±0.26	56.11±0.42	53.017±0.08	48.484±0.20

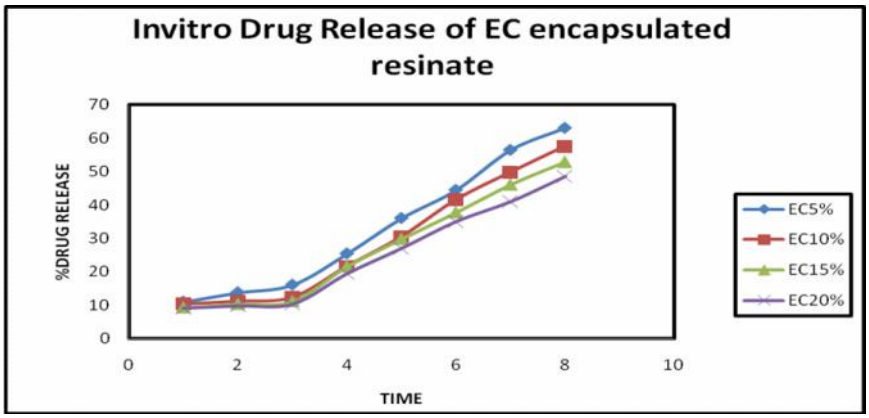

Figure 7: *Invitro* Drug Release Profile of EC microencapsulated resinate

Table 2: Comparative *Invitro* Drug Release Profile of microencapsulated resinate with 5%-20% EU.

Sr No.	Time (hr.)	Avg. *In vitro* drug release of EU ± SD(n=3)			
		5%	10%	15%	20 %
1	1	9.716±0.26	9.326±0.13	9.197±0.12	8.375±0.61
2	2	12.494±0.22	11.627±0.15	9.810±0.07	9.113±0.13
3	3	15.548±0.13	13.465±0.26	10.599±0.13	10.029±0.41
4	4	22.683±0.45	22.319±0.27	19.048±0.33	18.129±0.33
5	5	32.280±0.42	30.400±0.13	26.766±0.15	25.581±0.27
6	6	43.227±0.27	40.472±0.27	35.217±0.27	33.896±0.26
7	7	54.753±0.40	49.387±0.42	42.936±0.52	40.397±0.68
8	8	58.729±0.19	54.718±0.42	50.697±0.27	45.852±0.20

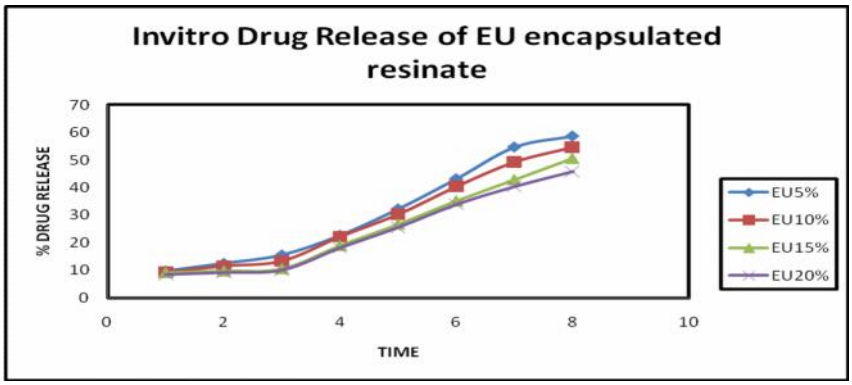

Figure 8 : *invitro* Drug Release Profile of EU microencapsulated resinate.

The above observation from the (table 1 and 2) and (figure 7 and 8) shows that as the concentration of the polymer increases the release of the drug from the MDR decreases. The release of the drug is retarded from 62% to 48% for EC5%-EC20% and 58% to 45% for EU5%-20%. The other evaluation parameter of the MDR are as per following (table 3).which showed nature, drug content ,particle size and coating percentage.

Table 3: Evaluation of EC and EU microencapsulated resinates:

Test	Observation							
	5%EC	**10%EC**	**15%EC**	**20%EC**	**5%EU**	**10% EU**	**15% EU**	**20% EU**
Nature	Free flowing	Free flowing	Cohesive, lumpy	Cohesive, lumpy	Free flowing	Free flowing	Cohesive , lumpy	Cohesive, lumpy
Drug content	74.94	72.23	70.26	68.57	76.54	74.63	72.91	69.92
Coating (%w/w)	4.59	9.86	15	19.92	4.59	9.86	14.98	19.92
Particle size(µm)	59-160	65-170	95-180	98-190	62-160	72-170	85-180	93-190

Taste evaluation taste masked products:

Evaluation of taste was done in two parts.

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 Drug resin complex:

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.

Micromeritic Properties:

Depending on the evaluation result of EC and EU. Microencapsulated drug resinate (MDR) of EC and EU 10% was taken for further studies as more than 10% retard the release further but it forms the lumps and cohesive in nature therefore, they were not used.

Table 4: Determination of Threshold Bitterness Concentration

No. of candidate	Concentration of drug(µg/ml)				
	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 5: 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 6: Micromeritic Properties of Drug resin complex, EU 10% and EC10%

Sr. No.	Property	Observation	
		EC 10%	**EU 10%**
1	Bulk density	0.2645g/ml	0.2677 g/ml
2	Tap density	0.2821g/ml	0.2863 g/ml
3	Angle of repose	34.35	35.42
4	Carr's index	6.22 %	6.34 %

Formulation of suspension for reconstitution purpose:

Selection of suspending agent:

Viscosity Measurement:

Formulation C has been selected for final formulation because it shows appropriate viscosity with acceptable separation ratio and redispersibility.

Resuspendability:

Resuspendability of suspension was expressed in terms of number of shakes (produced by hard shaking) required to redisperse. Number of shakes required for each suspension and nature of settled layer of suspension were shown in (Table 8). Formulation C shows fewer strokes to redisperse the settled layer so it has been selected for final formulation.

Form the result obtained table 7 and 8, batch C is used for formulation of suspension and evaluated further.

Evaluation of Suspension after reconstitution[8]

Organoleptic evaluation:

Formulations were 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 the (table 9).

Table 7: Viscosity Measurement of Different Suspending Agents

Formulation	rpm	Suspending agent			Viscosity (cps)
		MCC(w/v)	**N a CMC** (w/v)	**Gaur Gum** (w/v)	
A	50	1%	-	-	55
B	50	2%	-	-	120.9
C	50	-	0.25%	-	30.2
D	50	-	0.5%	-	45.1
E	50	-	1%	-	62.2
F	50	-	-	0.5%	842
G	50	-	-	1%	1699

Table 8: Resuspendability of Suspending Medium

Sr. No.	Suspending medium	No. of Strokes	Separation ratio	Nature sediment
A	1% MCC + 30% Sugar	17	0.72	Non caking
B	2% MCC + 30% Sugar	22	0.78	Non caking
C	0.25% Na CMC+30%Sugar	07	0.41	Non caking
D	0.5% Na CMC + 30% Sugar	10	0.53	Non caking
E	1 % Na CMC + 30% Sugar	25	0.65	Non caking
F	0.5% Guar Gum+30% Sugar	15	0.72	Non caking
G	1 % Guar Gum + 30% Sugar	26	0.88	Non caking

Table 9: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

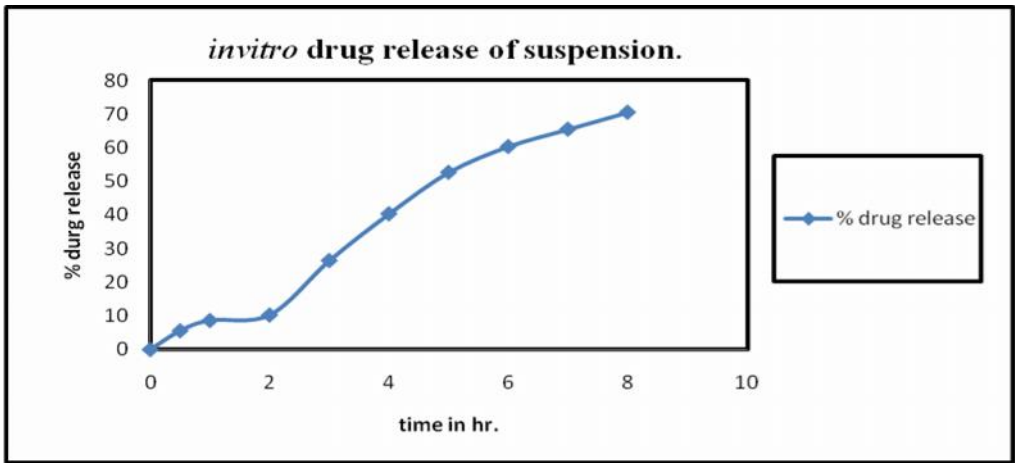

Figure 9: *in-vitro* Drug Release Profile of Suspension.

***In-vitro* drug release of suspension:**

5ml of suspension was removed from bottle and dissolution was carried out as mentioned previously. Suspension showed not more than 72 percent of drug release within 8 hr.

CONCULSIONS:

Formulated Sustained Release Suspension restricts the release of ODH which may reduce the dosing frequency. Indion 244 Ion exchange resin may be used for both taste masking and Sustained Release of drug. Na CMC was giving better suspending property as compared to Gaur gum and MCC. The Formulated suspension was having good organoleptic properties, viscocity, resuspendibility and Sustained Release properties.

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