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Formulation and evaluation of oral dispersible tablets of vibegron

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Abstract
In the present work, taste masking of Vibegron was carried out by using strong cation exchange resin tulsion 344. These taste-masked complexes were further formulated into the Oro dispersible tablet by the direct compression method using Ac-Di-Sol and Avicel as a super disintegrant. Vibegron is used in treating OAB symptom. This thesis has described the production of a taste masked dosage form from initial determination of threshold bitterness concentration of the pure drug through to the development of a final taste masked prototype formulation. An attempt has been made in the current work to use cation exchange resins (Indion 234 and Tulsion-344) which is used in the long drug therapy of AIDS and drug Vibegron used to treat over active bladder, a common problem in geriatric patients. It was found that the taste masked 1:2 ratio of LMV: HP-β-CD inclusion complex increases the bulk of final ODT blend (above 1000 mg) which is not feasible for formulation of ODTs. So in this study the ODTs of LMV: HP-β-CD inclusion complex (1:1 ratio) showing acceptable bitterness in human taste panel studies was used in formulation of ODTs. In all formulations, the dispersion produced was soft (without grittiness) with a good mouth feel, and the bitter taste was fully masked. *In vitro* drug release profile of all optimized ODT formulations showed around 90% of drugs release within 10 to 15 minutes in acidic buffer (pH 1.2), implying that the drug will be absorbed fast, increasing the chances of bioavailability. A three-month stability analysis was carried out. For the optimized formulations, there was no noticeable difference in disintegration time, hardness, friability, or drug content.

Keywords: Vibegron, super disintegrant, orodispersible

Introduction
Oral is the most preferred route of drug administration, but is not suitable for the patients with dysphagia. To overcome this problem or dispersible tablets is one of the famous technological innovations in the contract manufacturing and pharmaceutical field. Taste masking and taste assessment are the two main factors taken into consideration while formulating ODTs as they disintegrate and/ or dissolves in oral cavity. Taste masking in addition is related to patient compliance. Patient compliance is particularly important in pediatrics, geriatric and long drug therapy patients.

An ODT is a drug dosage form available for a small variety of over-the-counter (OTC) and prescription drugs (4). ODT disintegrates and/ or dissolves rapidly in the mouth without the need for water, which makes it suitable during traveling without immediate access to water. Since swallowing the saliva containing the dissolved or dispersed medication, the drug is consumed normally. Any drugs in ODT are showing fast onset of action and improved bioavailability as compared to same drugs in traditional tablet dosage form. This is due to ODTs pregastric absorption. ODT is also the best formulation option for drugs with a first-pass effect.

Methods
Formulation of ODTs of Vibegron- Tulsion 344Complex
170 mg tablet was prepared by using drug-resin complex equivalent to 25mg of Vibegron. Microcrystalline cellulose (Avicel PH 101) and mannitol were used as diluents and croscarmellose as super disintegrant. Aspartame, strawberry flavor, menthol, aerosil were mixed at the end and three formulations *viz*. F1 to F3 of Vibegron: Tulsion 344 complex were prepared by using Croscarmellose sodium in 6.0%, 8.0%, and 10.0% concentration.

Results and Discussion

Taste masking assessment of drug-polymer complexes

Sensory Test for Determination of Threshold Bitterness Concentration for Vibegron Six healthy human volunteers (of age group 20-25 years) held 10 ml of most dilute solution of Vibegron from 25, 50, 75, 100, 200, 225, and 250 µg/ml prepared in Phosphate Buffer pH 6.8, in their mouths for 10 seconds and washed their mouth with 50 ml distilled water. The bitterness threshold concentration was judged by considering opinion of volunteers.

Table 1: Sensory Test for Determination of Threshold Bitterness Concentration for Vibegron

No. of volunteer	Concentration (µg/ml)						
	25	50	75	100	125	150	200
1	0	0	0	0	1	2	3
2	0	0	0	0	1	2	3
3	0	0	0	1	1	2	4
4	0	0	0	0	2	2	3
5	0	0	0	0	1	2	3
6	0	0	0	0	2	2	3

In vitro taste masking evaluation of Vibegron: tulsion 344 (1:1) complex

Table 2: *In vitro* taste masking evaluation of Vibegron: tulsion 344 (1:1 complex in phosphate buffer pH 6.8

Time (sec.)	Concentration (µg/ml)			
	1	2	3	Average
30	52.65	53.56	53.75	53.32
60	64.57	63.96	64.78	64.51
120	80.64	81.12	80.75	80.83

Threshold Bitterness Concentration for Vibegron was found to be 100 µg/ml *in vitro* release of Vibegron from DRC was 80.83 g/ml below threshold bitterness concentration i.e., 100 g/ml up to time period of 120 seconds.

In vivo Taste Evaluation of Vibegron: Tulsion 344 (1:1) complex

Panel of 10 members using time intensity method determined bitterness value. From this data it was observed that up to 5 minutes, all volunteers have experienced no bitter taste with Vibegron, which is complexes with Tulsion 344 in 1:2 ratio. Volunteers rated that (1:2) drug: Tulsion 344 as tasteless and agreeable. For both variables, descriptive statistics such as mean and standard deviation were computed. INSTAT programme was used to perform a paired t test. Value $p<0.05$ has been considered as statistically significant level.

Table 3: *In vivo* taste evaluation of Vibegron: Tulsion 344 (1:1) complex

Volunteers	Bitterness level after taste masking					
	10 sec	1 min	2 min	5 min	10 min	15 min
1	0	0	0	0	0	0
2	0	0	0	0	0	1
3	0	0	0	0	0	0
4	0	0	0	0	1	1
5	0	0	0	0	0	0
6	0	0	0	0	1	1
7	0	0	0	0	0	0
8	0	0	0	0	0	1
9	0	0	0	0	0	1
10	0	0	0	0	0	0

Table 4: Volunteers Opinion Test for Vibegron Before and After Taste Masking

Time (seconds)	Before taste masking Mean ± SD	After taste masking Mean ± SD
10	2.3***± 0.58	0
60	3.3***± 0.48	0
120	3.4***±0.51	0
300	3.8***±0.42	0
600	3.8***±0.32	0.2***±0.63
900	4.0***± 0.0	0.5***± 0.84

Determination of Drug Content in the Drug-Polymer Complex

Drug content of Vibegron: tulsion 344 (1:2) complex

Resinate so prepared by the batch process, was evaluated for the drug content. Amount of resinate containing 25 mg of Vibegron was stirred with 50ml of acidic buffer (pH 1.2) till the entire drug was leached out. Then the Suspension was filtered and further dilutions were made. The drug content was noted spectrometric ally at 251nm using acidic buffer (pH 1.2) as blank.

Table 5: Drug content of Vibegron: tulsion 344 (1:2) complex

Name of Complex	Theoretical Conc. (mg)	Practical Conc. (mg)	% Drug Content
Vibegron: Tulsion 344 (1:2)	25	24.73 ± 0.11	98.92

Drug content of LMV: Indion 234 (1:1.5) complex

The resinate prepared (containing 10 mg of LMV) was subjected for evaluation of drug content and the data obtained is shown in Table 7. It was observed that the practical concentration obtained was 9.91 ± 0.043 mg, which was almost 99.1% of theoretical concentration that is 10 mg.

Table 6: Drug content of Vibegron: tulsion 344 (1:15) complex

Name of Complex	Theoretical Conc. (mg)	Practical Conc. (mg)	% Drug Content
Lamivudine: Indion 234	10	9.91 ± 0.043	99.1%

Evaluation of Oro dispersible tablets

Pre-Compression Studies

The directly compressible tablet blends were evaluated for pre-compression studies to determine their flow and compressibility (86).

Table 7: Micromeritic Properties of tablet blends containing optimized drug: polymer complexes (n= 3)

Property	Vibegron: Tulsion 344
Carr's Index (%)	12.8 ±1.34
Bulk Density (g/ml)	0.7843 ± 0.94
Angle of Repose (0)	27.540± 0.13

Post-Compression Studies

Table 8: Evaluation of ODTs of Vibegron: Tulsion 344 Complex

Test	F1	F2	F3
Weight variation test	170.0±1.4	170.4±1.2	170.2±1.6
Hardness (Kg/cm2)	3.5±0.09	3.75±0.08	4.00±0.10
Friability (%)	0.84	0.80	0.72
Drug content (%)	100.8±0.20	100.6±0.56	99.90±0.10
Wetting time (Seconds)	45±1.00	37±1.53	30±2.00
Mouth feel	-	-	-
In vivo disintegration time (Seconds)	57±1.97	48±1.86	30±1.37
In vitro dispersion time (Seconds)	42±1.00	38±2.00	25±1.53

In vitro release profile of formulated tablets:

Dissolution test of tablets was performed using acidic buffer pH 1.2 with USP dissolution type II apparatus at 100 rpm and 37 ± 0.50C temperatures. Test sample (5 ml) was withdrawn at a particular time interval and replaced with fresh dissolution media maintained at 37 ± 0.50C. The test sample was filtered through membrane filter having size 0.45 µm and analyzed using UV spectrophotometer at λmax values. This test was performed on successive three tablets and mean ± SD calculated.

Table 9: Dissolution data for formulation F1 to F3

Time (Min)	F1	F2	F3
0	0	0	0
1	11.06 ± 0.70	16.31 ± 0.61	27.56 ± 0.54
2	18.37 ± 0.91	25.90 ± 1.01	41.99 ± 0.95
3	20.72 ± 1.28	35.54 ± 1.24	58.76 ± 1.31
4	24.58 ± 1.54	43.74 ± 1.34	67.36 ± 1.54
5	31.47 ± 1.61	48.48 ± 1.51	77.75 ± 1.37
6	41.89 ± 1.34	64.49 ± 1.31	87.42 ± 1.67
7	48.87 ± 1.47	73.09 ± 2.03	100.9 ± 1.84
8	57.39 ± 1.34	86.74 ± 2.61	-
9	67.70 ± 1.41	100.9 ± 2.87	-
10	77.57 ± 2.04	-	-
11	92.99 ± 2.14	-	-
12	99.74 ± 2.24	-	-
13	100.6 ± 1.84	-	-

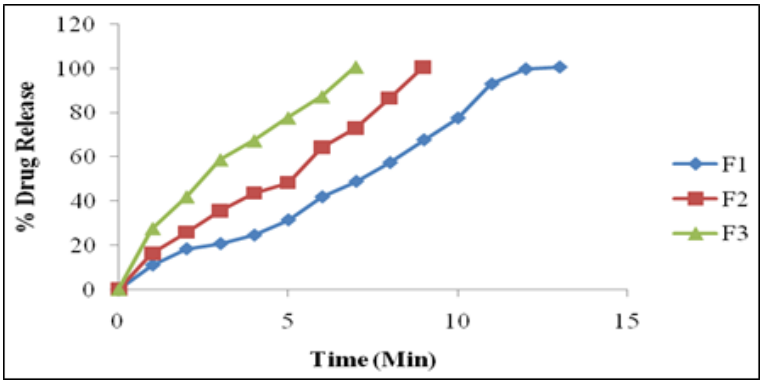

Fig 1: Dissolution profile for formulation F1, F2, F3

As dose is very small, may be dissolving rapidly and also the drug soluble in acidic condition. Due to presence of excess exchangeable ions in the dissolution medium the resinate showed 90% to 100% release of drug in about 6 to 12 minutes. As dose is very small drug released from the resinate may be dissolved rapidly and also the drug soluble in acidic condition.

From the above formulations it was found that the Formulations F3 shows fast disintegration & fast dissolution of tablets than other formulations. So, this formulation was optimized for further studies. These formulations contain 10% Ac- Di-Sol as super disintegrant.

Accelerated Stability Studies of the Optimized ODTs

Accelerated stability studies were carried out according to an International Conference on Harmonization (ICH) guidelines. The optimized formulations were placed in aluminum capped transparent glass vials for three months under storage conditions of 450C±20C and 75%±5%. At the end of each month, these samples were removed and analyzed for post compression tests.

The stability analysis showed that all of the formulations were physically stable when maintained at 450C±20C and 75%±5% RH for three months, with no major differences in the findings. (88).

Table 10: Effect of Stability Studies on ODTs Prepared by Using Vibegron: Tulsion 344 Resinate

Parameters Evaluated	1st month		2nd month		3rd month	
	Storage Condition		Storage Condition		Storage Condition	
	30±20c/ 60±5%RH	40±20c/ 75±5%RH	30±20c/ 60±5%RH	40±20c/ 75±5%RH	30±20c/ 60±5%RH	40±20c/ 75±5%RH
Hardness (kg/cm2)	3.2±0.1	4.1±0.16	3.2±0.44	4.5±0.16	3.9±0.31	4.8±0.16
Friability (%)	0.82	0.75	0.62	0.73	0.82	0.49
In Vitro Dispersion time (sec)	25±0.17	29±0.12	22±0.11	26±0.19	26±0.26	30±0.48
Drug content (%)	100.70±0.10	99.42±0.17	99.72±0.35	98.30±0.67	99.37±0.25	99.36±0.38

Summary and Conclusion

Oral is the most preferred route of drug administration, but is not suitable for the patients with dysphagia. To overcome this problem orodispersible tablets is one of the famous technological innovations in the contract manufacturing and pharmaceutical field. Taste masking and taste assessment are the two main factors taken into consideration while formulating ODTs as they disintegrate and/ or dissolves in

oral cavity. Taste masking in addition is related to patient compliance. Patient compliance is particularly important in pediatrics, geriatric and long drug therapy patients.

In the formulation of orodispersible tablets of taste-masked polymeric complexes, combinations of super disintegrants (separately and in different ratios) were used. The aim was to improve patient compliance and have a fast onset of action. In all formulations, the dispersion produced was soft (without grittiness) with a good mouth feel, and the bitter taste was fully masked.

The disintegration tests performed on all of these formulations revealed that tablets containing resinates disintegrated faster than tablets containing cyclodextrin inclusion complexes, which could be due to the additional use of cation exchange resins as super disintegrants.

In vitro drug release profile of all optimized ODT formulations showed around 90% of drugs release within 10 to 15 minutes in acidic buffer (pH 1.2), implying that the drug will be absorbed fast, increasing the chances of bioavailability.

A three-month stability analysis was carried out. For the optimized formulations, there was no noticeable difference in disintegration time, hardness, friability, or drug content.

Overall, this study concludes that, taste-masked ODTs of the drugs Vibegron not only improve patient compliance but also overcome neglected dysphagia associated with these two drug therapies. A greater understanding of patient compliance in any of the drug treatment will allow proper formulations to be developed which in turn will improve treatment outcomes.

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