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Formulation Development and Evaluation of Desloratadine Tablets

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Abstract: The objective of this research work was to formulate and evaluate the tablets of desloratadine 5mg. The tablets were prepared by direct compression method. The formulation T-I to T-V were optimized by incorporating varying composition of starch 1500 as Disintegrant, microcrystalline cellulose (Avicel PH 102), Di-Tab (Calcium Phosphate Dibasic Dihydrate), Talc, Opadry II white, Aquarius, HPMC 6 cps as a coating agent. The different excipients were tested for their compatibility with desloratadine, and revealed that there was no chemical and physical interaction occurred. The preformulation parameters were analysed for prepared granules before compression. The thickness, hardness, friability, weight variation, disintegration time and drug content uniformity was evaluated for core and coated tablets. The effect of these variables on the drug release profile of desloratadine was also studied. The In-Vitro drug release studied were performed in the USP Apparatus-II (Paddle) using 0.1N HCl as a dissolution media at 50rpm speed and temperature of 37°c ± 2°c. The cumulative amount of drug release was estimated using HPLC method. Based on the evaluatory result T-IV formulation was selected as the best formulation. These results indicated that the selected formulation was stable during the period of stability studies. The In-vitro drug release profile of T-IV formulation was found to be better when compared with marketed product.
Key words: Allergic rhinitis, Desloratadine, Compatibility, Preformulation, HPLC, Stability study.

Introduction

Desloratadine is major metabolite of loratadine. Desloratadine is a white to off-white powder that is slightly soluble in water, but very soluble in ethanol and propylene glycol. Receptor binding data indicate that at a concentration of 2–3 ng/mL (7 nanomolars), desloratadine shows significant interaction with the human histamine H1-receptor[1]. Desloratadine inhibited histamine release from human mast cells in vitro. Results of a radio labeled tissue distribution study in rats and a radio ligand H1-receptor binding study in guinea pigs showed that desloratadine did not readily cross the blood brain barrier[2]. Following oral administration of desloratadine 5 mg once daily for 10 days to normal healthy volunteers, the mean time to maximum plasma concentrations (T_{max}) occurred at approximately 3 hours post dose and mean steady state peak plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) of 4 ng/mL and 56.9 ng·hr/mL were observed, respectively. Neither food nor grapefruit juice had an effect on the bioavailability (C_{max} and AUC) of desloratadine. Desloratadine and 3-hydroxydesloratadine are approximately 82% to 87% and 85% to 89%, bound to plasma proteins, respectively[3]. Protein binding of desloratadine and 3-

hydroxydesloratadine was unaltered in subjects with impaired renal function. Desloratadine is a pregnancy Category C drug without teratogenic effect. Desloratadine passes into breast milk; therefore a decision should be made whether to discontinue nursing or to discontinue desloratadine, taking into account the importance of the drug to the mother. There were no serious adverse events in these trials in patients receiving desloratadine[4].

Desloratadine and its compositions are prone to oxidation and decomposition by acidic excipients to form impurities such as deschlorodesloratadine, dehydrodesloratadine and N-formyldesloratadine[5]. The desloratadine undergoes extensive degradation in the presence of common excipients such as lactose and stearic acid to form N-formyldesloratadine as a major degradation product. The basic salts of calcium, magnesium, or aluminum, plus avoidance of lactose and stearic acid, are used to control the degradation of desloratadine in pharmaceutical compositions. Since desloratadine undergoes extensive degradation in presence of excipients such as lactose to form N-formyldesloratadine as a major degradation product, the use of an effective stabilizer to enhance the stability of the composition would be a significant improvement in the field of solid oral therapeutic compositions[6]. The pharmaceutically acceptable excipients may include but are not limited to diluents such as microcrystalline cellulose, silicified MCC, microfine cellulose, lactose, starch, pregelatinized starch, mannitol, sorbitol, dextrates, dextrin, maltodextrin, dextrose, calcium carbonate, calcium sulfate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide and the like. Disintegrants found useful, but are not limited to carboxymethyl cellulose, sodium crospovidone, polacrilin potassium, starch, pregelatinized starch, sodium starch glycolate etc[7]. Binders found useful include but are not limited to acacia, guar gum, alginic acid, dextrin, maltodextrin, methylcellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, povidone, starch such as corn starch and the like. Therefore the objective of present research work is to develop stable formula for desloratadine tablet.

Experimental:

Matrials:

Desloratadine received as gift sample from Micro labs Pvt Ltd, Bangalore, India. Pregelatinised starch and Opadry II white received as gift sample from Colorcon Asia Pvt Ltd, Goa, India. Di-Tab received as gift sample from Rhodia chemical (India) Pvt Ltd, Mumbai. Microcrystalline cellulose received as gift sample from FMC Biopolymer, Mumbai. All other ingridients, reagents and solvents used are of analytical grade[8].

Methods:

Preparation of desloratadine tablets:

Carry out the dispensing of Active Pharmaceutical Ingredient and Excipients in dispensing both. Sift desloratadine and Di-Tab through #40 mesh. Sift individually Starch 1500, Avicel PH 102 (50%), through #40 mesh. Sift remaining quantity of Avicel PH 102 through #40 mesh. Co-sift sifted material through #40mesh. Sifting of Lubricating Material talc through #40 mesh. Transfer the sifted material into the Bin blender and blend for 25 min at 20 rpm for pre lubrication and then for 5 minutes at slow speed for lubrication with addition of talc. Compress Lubricated material in 8 station compression machine using 6.3 mm normal concave punches, with plain on both sides[9].

Coating of desloratadine tablets:

Add the Coating Material to vehicle under constant stirring with mechanical stirrer for 45 minutes. Add the core tablets into the coating pan and coat the tablets with coating solution. Ideal coater used for the coating of tablets with pan speed 40 rpm, Inlet temperature 65°c and spray rate 0-1. The coating solution contains 10 % solid content and % of build up given as per trials.

Evaluation of lubricated blend

The flow properties of lubricated blend characterized in terms of bulk density, tapped density, compressibility index, Hasuner's Ratio, Loss on drying at 105°C for 5 mins.

Physical Evaluation of coated tablets

The coated tablets were evaluated for weight, hardness, thickness, diameter and disintegration time. For physical evaluation of tablets, 10 tablets were randomly selected from each batch and their average value calculated. Thickness, diameter, Hardness and disintegration time were evaluated by using Vernier Caliper, Monsanto hardness tester, and Disintegration Test Apparatus USP Type II (Paddle) respectively[10].

Drug content estimation

The drug content for each formulation determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of 0.1N Hydrochloric acid, followed by stirring for 20 minutes. The solution was filtered through membrane filter, diluted suitably and absorbance of resultant solution was measured spectromerically at 240 nm using 0.1N hydrochloric acid as blank solution.

In-Vitro drug release profile

In-Vitro drug release studies were performed for all the formulation using 0.1N HCl as dissolution medium. HPLC and UV visible were used for determination of percent of in-vitro drug release

profile with Mobile phase Sodium dihydrogenphosphate dehydrate and filtered and degassed acetonitrile at 240 nm. Tests were carried out in USP Type II apparatus with 500ml volume of dissolution medium at 50 rpm and temperature at 37 ± 0.5^0 c. The sampling is done at regular intervals 5, 10, 15, 20, 30, and 45mins and same volume was replaced by 0.1N hydrochloric acid. The cumulative percent drug release was calculated and plotted against time for all the formulations and Marketed Product to determine the release profile[11].

Stability studies

The promising formulation trials T-III and T-IV tested for stability studies at ($40^0 \pm 2^0$ C; 75% $\pm$ 5 RH) for time period of three months for the drug content and other parameters.

Table 1: Composition of Formulation Trials of Desloratadine

Ingredients	**Rational**	**Quantity per Tablet (mg/tab.) in formulation trials.**				
Pre-Lubrication Materials		**T-I**	**T-II**	**T-III**	**T-IV**	**T-V**
Desloratadine	API	5 (5.034)	5 (5.034)	5 (5.034)	5 (5.034)	5 (5.034)
Di-Tab (Dibasic Calcium Phosphate Dihydrate)	Diluent	20	20	20	20	20
Avicel PH 102 (Microcrystalline Cellulose)	Diluent	60 (59.966)	66 (65.966)	67.5 (67.46)	67.5 (67.46)	69 (68.96)
Starch 1500 (Pregelatinized Starch)	Disintegrant	9	3	1.5	1.5	-
Lubrication Materials						
Talc	Lubricant	6	6	6	6	6
Coating Materials						
Opadry II white	Film former	2	2	-	-	-
HPMC (6 CPS)	Seal Coater	-	-	-	2	2
Aquarius	Film former	-	-	4	2	2
Water	Vehicle	Q.S.	Q.S.	Q.S	Q.S	Q.S
IPA	Vehicle	-	-	-	Q.S	Q.S

Table 2: Result of Lubricated Blend Parameters

Formulation Trials	**Lubricated Blend Parameters**				
	Bulk density (gm/cm^3)	**Tapped density (gm/cm^3)**	**Carr's index (%)**	**Hausner ratio (H_R)**	**Loss on drying at 105^0 C(% L)**
T-I	0.435	0.636	31.64	1.46	6.27
T-II	0.420	0.630	33.33	1.5	5.26
T-III	0.413	0.610	31.86	1.46	5.30
T-IV	0.424	0.614	33.82	1.5	5.32
T-V	0.420	0.592	28.72	1.403	4.49

Table 3: Result of Coated Tablets Parameters

Formulation Trials	Coated Tablets Parameters					
	Weight Variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (Kp)	Disintegration Time (seconds)	Drug Content (%)
T-I	102 ± 1	3.03 ± 0.02	6.36	8.35	32-50	98.6
T-II	102 ± 1	3.10 ± 0.03	6.38	8.56	70-58	99.4
T-III	104 ± 0.5	2.94 ± 0.02	6.34	10.62	175-198	98.8
T-IV	104 ± 2	2.78 ± 0.02	6.39	14.13	175-190	100.6
T-V	104 ± 3	2.77 ± 0.05	6.24	8.69	270-320	98.9

Table 4: Stability Study ($40^0 \pm 2^0$ C; 75% ± 5 RH) of Formulation Trial T-IV

Product: Desloratadine Tablet					
Description		White coloured, round shaped biconvex tablet plain on both side.			
Test parameters		**Initial**	**1 Month**	**2 Month**	**3 Month**
Assay %		100.6	99.1	99.3	99.1
Related substance.					
Loratadine		Not Detected	Not Detected	Not Detected	Not Detected
Highest unknown		0.048	0.06	0.095	0.132
Total unknown impurity		0.143	0.222	0.235	0.383
Water by KF		5.73	5.84	5.97	6.13
Dissolution		**% Drug Release**			
Dissolution Condition: 500ml of 0.1N HCl, USP Type II (Paddle) at 50 RPM	**Time (min)**				
	5	50	37	48	49
	10	77	63	72	76
	15	87	75	79	87
	20	92	85	86	91
	30	97	97	98	99
	40	100	102	101	100

Result and Discussion

Desloratadine provides rapid, first-dose relief from the nasal and non-nasal symptoms of allergic rhinitis, including sneezing, rhinorrhoea, lacrimation and ocular redness. Desloratdine film coated tablets were formulated as per Trial I to Trial V (Table:1) by optimizing concentration of disintegrating agent pregelatinised starch and by using different film and seal coating materials like Opadry II White and Aquarius coating material as film coating materials and HPMC 6 cps as seal coating materials. These formulation developments were done to controle drug release profile as per the reference product. The formulations of all trials were evaluated for lubricated blend parameters before the compression and also evaluated for physical parameters like weight, thickness, diameter, hardness, disintegration time of coated tablets. The main aim of formulation development was to control in-vitro drug release profile as per reference product.

Lubricated blend parameters

The formulation blend of all trials showed good flow properties and compressibility index (Table 2). The bulk density and tapped density ranges from 0.413-0.435 and 0.592-0.636 respectively. Carr's index ranged from 28.72-33.82, hausner ration ranged from 1.403-1.5 and LOD at 105^0 C ranges from 4.49-6.27. The value indicates good flow properties of final blend with less moisture content.

Coated tablets parameters

The shape of all formulations remained White coloured, round shaped biconvex tablet plain on both

side with no visible cracks. The weight of coated tablet ranges from101.6-104.4 mg. Thickness and Diameter were measured by vernier caliper and were ranged between 2.77-3.10 mm and 6.24-6.39 mm respectively. Hardness of tablet was measured by Monsanto hardness tester and was in between 8.35-14.13 Kp. The drug content estimation shows values in the range of 97.8-100.6% which reflect good uniformity in the content among the different formulation. All the coated tablets passed weight variation test as the % of weight variation was within pharmacopoeial limit of ± 10% of the weight. The results are shown in Table 3.

In-Vitro Drug Release Profile

In-vitro drug release profile studies carried out in 0.1 N HCl. The cumulative percent of drug release were calculated according to OGD time points. It was observed that disintegrant and percentage of coating build up on core tablets and type of coating material influences the drug release profile. Drug release profile of formulation T-I and T- II were found to be faster owing to high concentration of disintergrant and 2 % build up of coating as shown in fig 1. Formulation T-III and T- IV shows comparable drug release profile owing to less concentration of disintegrants and 4 % build up of coating as shown in fig 1. Formulation T-V shows slow drug release profile owing to no disintegrant and 4% build up of coating as shown in fig 1.

Comparison of In-Vitro Drug Release Profile with Marketed Product

Promising formulations T-III and T-IV as found by evaluation studies were compared with marketed product. The comparative *in-vitro* dissolution studies presented in Fig 2. The marketed product release drug 99 % in 45 mins, where as formulation T-III and T-IV releases 96 % and 100 % drug in 45 mins respectively.

Stability Studies Report

Formulation T-III and T-IV were selected for stability studies ($40^0 \pm 2^0$ C; 75% $\pm$ 5 RH) for time period of three months. The formulations were evaluated for the drug content, related substances, water content and drug release profile. From three months stability data it was found that formulation T-IV was more stable than trial T-III as the highest unknown and total unknown impurities in formulation T-III were more than T-IV. The stability data of formulation T-IV as shown in table 4.

Conclusion

The desloratidine tablets were formulated by direct compression method and formulation was optimized by adjusting the disintegrant concentration and film coating materials and their percentage build up. The drug release profile of film coated tablets was controlled by reducing the disntegrants concentration from 9 % to 1.5 % and by giving 2 % seal coating of hydroxylpropylmethyl cellulose and 2 % film coating of Aquarius. From the evaluation data, it was concluded that disintegrant concentration of 1.5% of Starch 1500 shows promising drug release profile, further stability data concluded that the formulation trial T-IV was the promising trials as compared with trial T-III and also with marketed product.

Fig 1: In-Vitro Dissolution drug release profile of T-I to T-V formulations

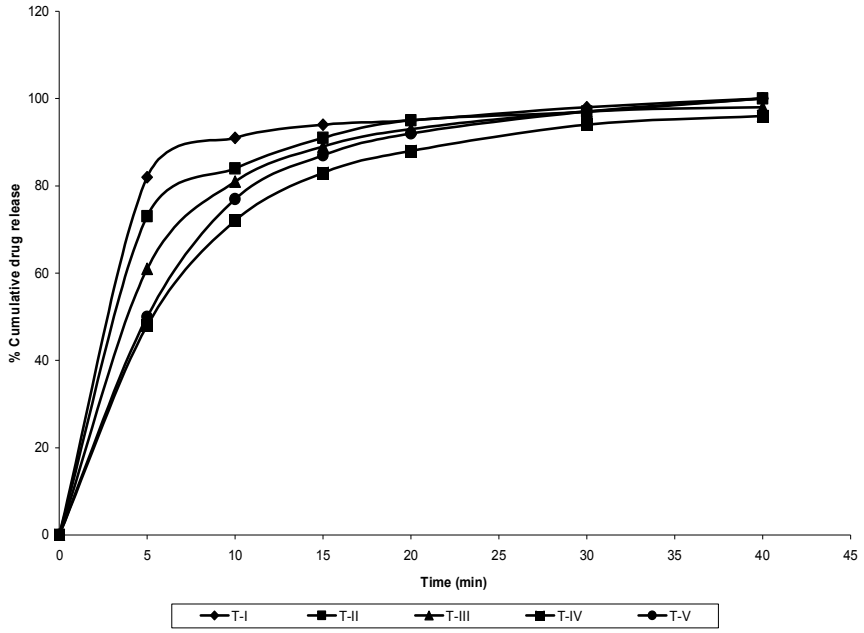
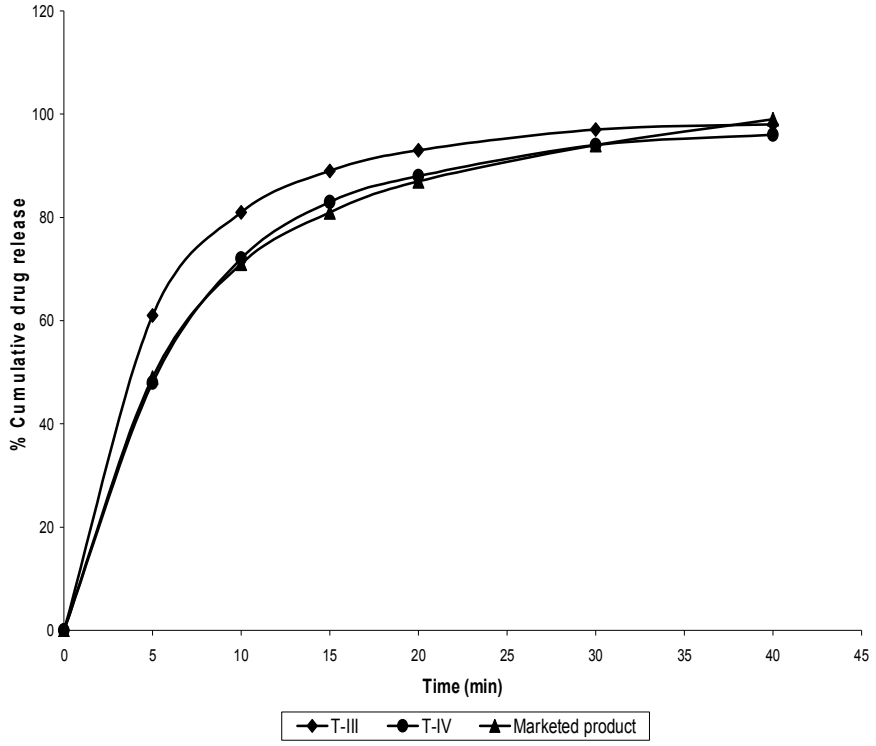


Fig 2: In-Vitro Drug release Profile of T-III, T-IV and Marketed product.



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