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FORMULATION AND IN VITRO EVALUATION OF RAPIDLY DISINTEGRATING TABLETS OF LORATADINE

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Loratadine, Superdisintegrants, Rapidly Disintegrating Tablets, Crosscarmellose Sodium, Low Substituted Hydroxyl Propyl Cellulose

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ABSTRACT

The aim of the present research work is to evaluate the impact of superdisintegrants in the formulation and evaluation of rapidly disintegrating tablets. In the present study, Loratadine is the model drug. Rapidly disintegrating tablets of Loratadine was prepared by direct compression method. In this method the different excipients used were Calcium Silicate (FM1000), Pharmattose DCl-21 (anhydrous lactose), Citric acid(anhydrous), Colloidal Silica (Aerosil), Sodium stearyl fumarate, Magnesium Stearate, Crosscarmellose Sodium (AcDiSol), L-HPC(Low substituted hydroxyl propyl cellulose), Microcrystalline Cellulose (Avicel pH-200), Aspartame, Orange flavor and Strawberry flavor. The formulations containing Crosscarmellose sodium and Low substituted hydroxyl-propyl-cellulose as superdisintegrants, disintegrated faster compared to the formulation containing Microcrystalline Cellulose (Avicel pH-200). Pre compression and post compression parameters were evaluated for all eight formulations (F1-F8).Infra-Red study revealed that all polymers and excipients used were compatible with the drug. In vitro drug release showed that almost drug was release in the range of 94-97% range in 10 minutes. Depending upon cumulative drug release, in vitro disintegration time, wetting time results, one formulation F8 was selected for stability studies and subjected to stability studies at 25^0C, 30^0C and 40^0 C for 1 month. Overall, formulation F8 was found to be the best formulation in direct compression method.

INTRODUCTION: Rapidly disintegrating tablets or fast dissolving tablets are gaining prominence as new drug delivery systems. These dosage forms dissolve or disintegrate in the oral cavity within a matter of seconds without the need of water or chewing. These are useful for pediatric, geriatric and dysphasia patients, leading to improved patient compliance. Nonetheless, oral dosing remains the preferred mode of administration for many types of medication due to its simplicity, versatility, convenience, and patient acceptability. In recent years, rapid-disintegrating oral drug formulations have been developed to overcome problems related to swallowing difficulties[1]. When such tablets are placed in the oral cavity, saliva quickly penetrates into the pores to cause rapid tablet disintegration[2-7].

The rapidly disintegrating tablets are synonymous with Fast dissolving tablets; Melt in mouth tablets**,** Rapi-melts, Quick dissolving tablets, Mouth dissolving tablets, Orodispersible tablets. Their characteristic benefits in terms of patient compliance, rapid on-set of action, incresebio-availability and good stability make these tablets popular as a dosage form of choice[8]. Loratadine is long acting anti-histamine with selective peripheral histamine antagonistic activity. Loratadine is a piperidine derivative chemically known as ethyl-4- (8 chloro- 5, 6 dihydro- 11H- benzo [5, 6] cyclohepta [1, 2-b] pyridine- 11- ylid piperidine carboxylate.The bioavailability of Loratadine following oral administration is about 40 to 45 % and significantly affected by the presence of food. The elimination half-life from plasma is reported to be about 3 hrs and is prolonged in renal impairment.

MATERIALS AND METHODS:

Materials: Loratadine was obtained as gift sample from Strides arco laboratories, Bangalore. L- HPC (Low Substituted Hydroxy Propyl Cellulose), Colloidal Silica (Aerosil), Microcrystalline Cellulose (Avicel pH 200), Crosscarmellose Sodium (Ac-Di-Sol), Sodium Stearyl Fumarate were also obtained from Strides arco laboratories.

Methods:

Formulation of Loratadine Rapidly Disintegrating Oral Tablets: Loratadine Rapidly Disintegrating Oral Tablets were prepared by direct compression method according to the formula given in (**table 1**).

TABLE 1: COMPOSITION OF RAPIDLY DISINTEGRATING ORAL TABLETS OF LORATADINE

Ingredients (mg/tab)	Formulation Code							
	F1	F2	F3	F4	F5	F6	F7	F8
Loratadine	10	10	10	10	10	10	10	10
Calcium Silicate	37.5	37.5	37.5	37.5	37.0	37.5	37.5	34.0
Pharmattose (DCL-21)	97.35	97.35	97.35	97.35	97.35	97.35	97.35	97.35
L-HPC	-	-	3.0	-	-	-	3.0	-
Citric Acid (anhydrous)	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Magnesium Stearate	0.5	0.5	0.5	0.5	-	0.5	0.5	-
Sodium Stearyl Fumarate	-	-	-	1.0	1.0	-	-	3.0
Colloidal Silica	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1.5
Aspartame	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
MCC (Avicel pH 200)	-	3.0	-	-	3.0	–	-	3.0
AcDiSol	3.0	–	–	3.0	0.2	0.2	0.2	0.2
Strawberry flavor	-	-	-	0.2	0.2	0.2	0.2	0.2
Orange flavor	0.2	0.2	0.2	-	-	-	-	-

A total number of eight formulations were prepared. All the ingredients were passed through 40-mesh sieve separately and collected, finally compressed into tablets after lubrication with magnesium stearate (1%) or Sodium Stearyl Fumarate (2%) by using 7.6 mm flat bivel edged punch using RIMEK 8 station tablet compression machine. Before tablet preparation, the mixture blend subjected for compatibility studies (IR), and pre-compression parameters like angle of repose, compressibility index, and bulk density. The Rapidly Disintegrating Oral tablets prepared were subjected for post-compression parameters like uniformity of thickness, hardness, friability, weight variation, drug content, wetting time, in vitro disintegrating time, and in vitro dissolution time.

Evaluation of Granules:

Pre Compression parameters:

Angle of Repose: Flow properties of the granules were evaluated by determines the angle of repose and the compressibility index. Static angle of repose was measured according to the fixed funnel and free standing cone method of Banker and Anderson. A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip at a given height (1cm), h, above graph paper placed on a flat horizontal surface. The granules were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. Thus, with R being the radius of the base of the granules conical pile and angle of repose was calculated by using the equation[9].

$$\tan\theta = h/r$$

Where θ is the angle of repose

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A suitable amount of powder from each formulation, previously lightly shaken to break agglomerates formed, was introduced into a 10 ml measuring cylinder. After initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from a height of 2.5cm at 2 seconds intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using following formula[10].

LBD= weight of the powder/ volume of the packing

TBD= weight of the powder/tapped volume of the packing

Compressibility Index: Compressibility index of the powder was determined by Carr's compressibility index[11].

Carr's index (%) = [(TBD-LBD) X 100] / TBD

Evaluation of Tablets :

Wetting Time: A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5 cm) containing 6 ml of simulated saliva pH (phosphate buffer pH 6.8). A tablet was put on the paper, and the time required complete wetting was measured. Six trials for each batch performed; average time for wetting with standard deviation was recorded[12].

Drug Content Estimation: Ten tablets were taken and amount of drug present in each tablet was determined as follows: Tablet was crushed in mortar and transferred to 100 ml flask. The powder was dissolved in pH 4.5.The sample was mixed by using Remi mixer for 5 minutes, after which it was filtered through whatman filter paper. The filtered solutions after appropriate dilution (1 to 10 ml) with 0.1 N HCL were

analyzed by validated UV spectrophotometric method at λmax 280nm.

***In Vitro* Disintegration Time:** *In- Vitro* disintegration time was performed by apparatus specified in USP at 50 rpm. Phosphate buffer 4.5, 900 ml was used as disintegration medium, and the temperature of which maintained at 37±2^{o}C and the time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds[13].

Evaluation of *In Vitro* Dissolution Studies: *In-Vitro* dissolution study was performed by using USP type II Apparatus (Paddle type) [Electro lab (ETC-11L) Tablet Dissolution Tester] at 50 rpm. Phosphate buffer pH 4.5, 900 ml was used as dissolution medium which maintained at 37±0.5^{o}C. Aliquot of dissolution medium (10ml) was withdrawn at specific time intervals (2min) and was filtered. The amount of drug dissolved was determined by UV spectrophotometer (shimadzu, Japan) by measuring the absorbance of the sample at 280nm. Three trials for each batch were performed and average percentage drug release with standard deviation was calculated and recorded[14].

RESULTS AND DISCUSSION: In the present study, Loratadine Rapidly Disintegrating Tablets were prepared by using Crosscarmellose sodium, Low substituted hydroxyl propyl cellulose, and Microcrystalline Cellulose (Avicel pH-200) as superdisintegrants. A total number of eight formulations were prepared by direct compression technique. The value of pre-compression parameters evaluated was within prescribed limits and indicated good flow property. IR spectroscopy was used as means of studying drug-excipient compatibility and confirmed undisturbed structure of loratadine, which indicates no drug-excipient interaction (**Figure 1 and 2**).

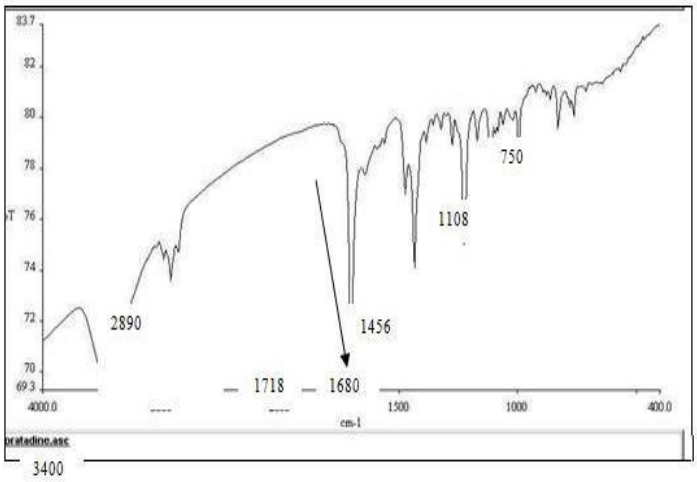

FIG. 3: INFRA RED ABSORPTION SPECTROSCOPY OF LORATADINE

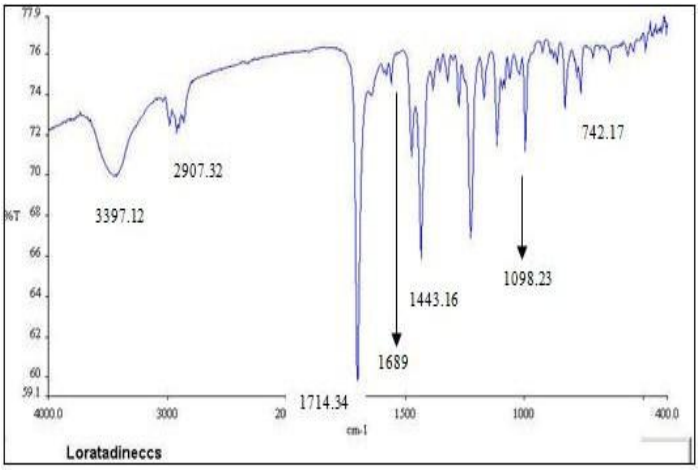

FIG. 4: (INFRA RED ABSORPTION SPECTROSCOPY OF FORMULATION CONTAINING CROSSCARMELLOSE SODIUM)

The data obtained of post compression parameters such as hardness, friability, weight variation, uniformity of content, thickness, wetting time, disintegration time are shown in **table 2**. The hardness was found to be in range of 3 to 4 kg/cm^2 in all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations the friability value is less than 1% and meets the

IP (Indian Pharmacopoeia) limits [15]. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weight of all the tablets was found to be uniform with low standard deviation values indicating efficient mixing of drug, superdisintegrants and excipients. The percentage drug content of all the tablets was found to be between 88.68±0.1069 and 98.32±0.0450 % of loratadine, **Table 3** which was within the acceptable limits.

TABLE 2: PROPERTIES OF GRANULATIONS AND IN-PROCESS PARAMETERS OF TABLETS

Formulation	Angle of repose (θ)	Bulk density	Tapped density	Compressibility Index	Thickness (mm)*	Hardness Kg/cm^2	Friability (%)	Wt. Variation (%)*	Drug content (%)	DT (Sec)	Wetting Time (Sec)
F1	31^0.8′	0.66	0.84	21.37	2.71±0.02	2.5	0.210	2.1±0.12	96.22	10	32
F2	30^0.4′	0.64	0.82	21.9	2.73±0.04	2.4	0.270	1.8±0.31	98.00	43	76
F3	31^0.3′	0.65	0.85	23.53	2.72±0.02	2.4	0.472	1.7±0.24	96.04	23	42
F4	32^0.4′	0.62	0.83	25.3	2.71±0.02	2.4	0.197	2.2±0.19	97.30	26	39
F5	31^0.5′	0.64	0.86	25.58	2.73±0.01	2.5	0.272	1.9±0.15	97.86	28	46
F6	33^0.8′	0.63	0.81	22.22	2.72±0.03	2.5	0.312	2.2±0.20	96.58	24	39
F7	31^0.1′	0.62	0.82	24.39	2.74±0.04	2.2	0.267	1.8±0.14	96.76	25	48
F8	31^0.4′	0.61	0.80	23.75	2.72±0.01	2.5	0.431	2.2±0.23	98.30	16	31

TABLE 3: IN VITRO DRUG RELEASE PROFILE DATA

Time (min)	Percentage amount of Drug released*								
	F1	F2	F3	F4	F5	F6	F7	F8	MT
2	88.04±0.08	87.15±1.10	89.34±1.23	87.78±1.33	87.52±0.09	88.49±1.02	88.04±0.07	86.87±1.02	82.86±0.08
4	90.30±1.05	88.64±1.14	90.77±1.21	89.92±1.89	88.93±1.05	90.02±1.05	90.19±0.98	88.98±1.02	85.37±1.23
6	92.77±1.40	91.43±2.10	92.67±2.19	91.78±1.70	90.79±1.23	90.51±1.98	91.98±1.00	91.09±1.05	85.89±2.10
8	95.36±1.21	91.93±2.47	93.18±1.17	94.20±1.27	92.96±1.15	91.32±1.93	94.52±1.13	94.44±1.05	86.52±1.85
10	95.88±1.24	93.44±2.18	96.31±1.90	95.71±1.01	95.34±2.05	94.62±2.19	96.12±1.85	96.85±2.96	87.87±1.45

All values are expressed as mean ± standard deviation, n=3

The percentage drug release by each tablet in the *In Vitro* drug release studies were base on the mean content of the drug present in respective tablet (**table 4**). The result of *in vitro* disintegration of all the tablets was found to be within prescribed limit to satisfy the criteria of Rapidly Disintegrating Tablet. The values were found to be in the range of 24.62±0.0404 to 29.33±0.0450s (**Figure 3)**. Overall the Rapidly Disintegrating Oral Tablets of Loratadine showed an average of 88 to 98 % drug release range at the end of 12 min which is as per IP specifications of 90-110 % and it was also observed that formulations F9 took shortest time to release the maximum amount of drug whereas the other

formulations took more than 12 min to release the drug.

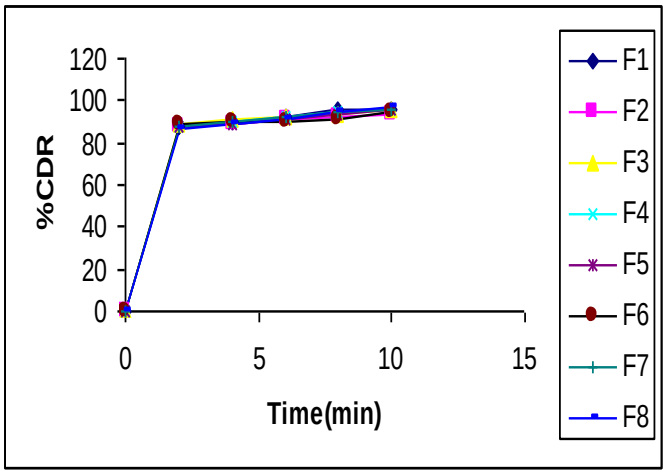

FIG. 3: COMPARATIVE DRUG RELEASE PROFILE OF F1 TO F8

TABLE 4: RESULTS OF STABILITY STUDIES

Parameters	Initial			After 3 months		
	25^0	30^0	40^0	25^0	30^0	40^0
Hardness (Kg/cm^2)	2.8	2.5	2.2	2.6	2.3	2.0
Friability (%)	0.146	0.154	0.172	0.148	0.159	0.176
Wetting time (Sec)	35	31	28	31	28	25
Disintegration time (Sec)	23	19	21	22	19	18
% Drug content	96.84	96.77	96.71	96.81	96.74	96.66
Dissolution studies (%)	97.36	97.28	97.17	97.1	97.21	97.04

Comparison with other formulations, F9 shows a better drug release of 98.32 % at the end of 12 minutes. Further the formulation F9 was compared with marketed formulation (SERORM, sun pharmaceutical industries) and found to be superior in terms of dissolution profile (**Figure 4)**. There was no significant variation in the physicochemical parameters, in vitro disintegration time, and in vitro dissolution profiles after 2 months stability study as per ICH guidelines Q1C.

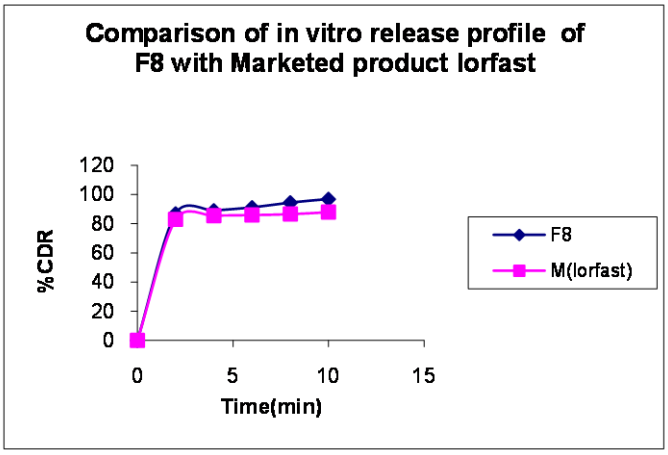

FIG. 4: COMPARISON OF IN VITRO RELEASE PROFILE OF F10 WITH MARKETED PRODUCT

CONCLUSION: Rapidly Disintegrating Oral Tablets of Loratadine is successfully prepared by using different proportions of superdisintegrants, Formulation F8 having Ac-Di-Sol (Crosscarmellose sodium) as the superdisintegrant is the best formulation among of all 8 formulations. Undoubtedly the availability of various technologies and manifold advantages of rapidly disintegrating tablets will surely enhance the patient compliance, low dosing, low side effect, good stability, and its popularity in the near future.

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