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Research Article

ROLE OF SUPERDISINTEGRANTS FOR *IN VITRO* CHARACTERISATION OF LORATADINE ORO-DISPERSIBLE TABLETS

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ABSTRACT

The purpose of present study was to develop an optimized Oro-dispersible tablet (ODT) containing Loratadine as model drug. In this investigation ODT of Loratadine was prepared using different superdisintegrants by direct compression method. Three superdisintegrants Sodium starch glycolate, Croscarbamelose sodium, Crospovidone XL 10 were selected and optimized concentration of best superdisintegrant was selected on the basis of physiochemical properties and in-vitro dissolution of ODT. Individual superdisintegrants as well as combination of superdisintegrants at different concentrations were trailed and optimized. Effect of disintegrant on disintegration and dispersion of tablets was evaluated. Wetening time of formulation containing Crospovidone XL 10 was least and tablets showed fastest disintegration. The drug release from ODT increased with increase in concentration of superdisintegrants and was found to be highest with formulation containing Crospovidone XL 10.

Keywords: Oro dispersible tablets, Superdisintegrants, Crospovidone XL 10

INTRODUCTION

Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. Many patient groups such as elderly, children, and patients like mentally retarded, uncooperative and nauseated on reduced liquid intake diets have difficulty in swallowing these dosage forms. Swallowing problem is common in children because of their underdeveloped muscular and nervous systems. To fulfill these medical needs, a novel type of dosage form has developed for oral administration known as orally disintegrating tablets (ODT). This is an innovative technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient. The orally disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation. Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially superdisintegrants and sugar based excipients. Loratadine is an anti-histaminic drug used for treatment of allergic reactions like Hey fever, allergic rhinitis. The main aim of this study is to formulate an ODT for Loratadine using suitable superdisintegrants by direct compression with a keen consideration to optimize the disintegration and in-vitro release along with other tablet characteristics. For the purpose of study three superdisintegrants selected are Croscarmelose sodium, Crospovidone XL 10 and Sodium starch glycolate. (1-2)

MATERIALS AND METHODS

Materials

Loratadine pure was a gift sample from Dr Reddy's Laboratories, Hyderabad.Mannitol SD 200, Pre gelatinized starch, Micro crystalline cellulose, Sodium starch glycolate, Croscarbamelose sodium, Crospovidone XL 10 and Colloidal silicon dioxide were purchased from Sigma-Aldrich, Germany. Sodium stearyl fumarate was purchased from Merck Specialties Private Limited, Mumbai. All the other ingredients were purchased from the local market.

Method

Micromeritic Properties

The loose bulk density and tapped density of the pure drug and tablet blend were determined using density apparatus (Mac Bulk Density Apparatus, IP). The angle of repose was determined using the fixed funnel method. Carr's Index (CI) and Housner's ratio (HR) were calculated.

Table 1: Micromeritic Characteristics of formulations

Parameters	Formulations												
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	Pure drug
CI	17.7	18.2	18.5	15.9	17.2	20.6	24.7	19.3	22.6	18.7	22.0	19.9	30.6
HR	1.21	1.20	1.22	1.18	1.2	1.26	1.34	1.24	1.29	1.23	1.28	1.25	1.44
Angle of Repose	28.4	25.6	24.09	26.78	23.9	27.2	25.5	26.08	22.96	24.05	23.45	24.3	36.02

Formulation of tablet

The orodispersible tablet of Loratadine was prepared by direct compression method using Sodium starch glycolate, Croscarmelose sodium and Crospovidone XL 10 as superdisintegrants (Table 2).

The drug and ingredients were co-sifted through 40# and blended for 10 minutes. . Sodium stearyl fumarate and Colloidal silicon dioxide were sifted through 60# and added to above mixture and blended for 5 minutes. Then the lubricated blend was compressed in 8 mm round flat punches. (Single station tablet compression machine, Cadmach, India) (3)

Physicochemical characterization of tablets

Diameter and Thickness of the tablets (n=3) were measured using "Vernier-caliper" (Mitutoyo Dogmatic, CD-8" CSX), and average was calculated. The hardness of the tablets (n=10) was determined (Dr. Schleuniger Hardness Tester, 8M). The % friability of tablets (n=10) was determined using Roche Friabilator (Electrolab, EF-1W). Weight variation test of the tablets (n=20) was carried out as per the official method. Disintegration time was determined by using USP device (Electrolab, Double unit, ED-2). To perform disintegration test, one tablet was placed in each tube and the basket arch was positioned in a 900 ml beaker of water at $37^0C \pm 2^0C$.

Table 2: Formulation design of ODTs

Sl. No.	Ingredients	Formulations											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Loratadine	10	10	10	10	10	10	10	10	10	10	10	10
2	Mannitol SD 200	55	55	55	55	55	55	55	55	55	55	55	55
3	Pre-gelatinized starch	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5
4	MCC	72	68	64	72	68	64	72	68	64	68	68	68
5	Sodium Starch Glycolate	8	12	16	-	-	-	-	-	-	6	6	-
6	Croscarmelose sodium	-	-	-	8	12	16	-	-	-	6	-	6
7	Crospovidone XL 10	-	-	-	-	-	-	8	12	16	-	6	6
8	Colloidal Silicon Dioxide	2	2	2	2	2	2	2	2	2	2	2	2
11	Sodium Stearyl Fumarate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total weight (mg)		160	160	160	160	160	160	160	160	160	160	160	160

*MCC: Micro Crystalline Cellulose

In vitro Dispersion time

Many reports suggest that conventional DT apparatus may not give correct values of DT for ODTs. The amount of saliva available in the oral cavity is very limited (usually less than 6 ml) whereas the conventional DT apparatus uses a large amount of water with very rapid up and down movements. ODT is required to disintegrate in such small amount of saliva within a minute without chewing the tablet. In a simplest method to overcome this problem, 6 ml of simulated saliva fluid of pH 6.2 was taken in a 10 ml measuring cylinder. Temperature was maintained at 37±2°C. An ODT was put into it and time required for complete disintegration of the tablet was noted. (4)

Wetting time and water absorption ratio

A piece of paper folded twice was kept in a Petri dish (internal diameter 5.5 cm) containing 6 ml of purified water. A tablet having a small amount of Rosaline dye powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time. The same procedure without Rosaline dye powder was followed for determining the water absorption ratio, and determined according to the following equation $R = [(W_a - W_b)/W_b]\ 100$ where, W_b and W_a were the weights of the tablet before and after used. (5-7)

Assay

Assay of Loratadine orally disintegrating tablets were carried out by using HPLC (WATERS-2650) at ambient condition using column packed SA100*3.00 mm, 3 µm. Sample was analyzed using UV Visible detector at 220 nm. Flow rate was kept 0.5 ml/min with injection volume 20 micro liters. Run time was 28 min, showing retention time of 5.4 min. Methanol, Acetonitril and Buffer (PH 4.4) in ratio 30:15:55v/v was used as mobile phase. (8-9)

Table 3: Evaluation parameters of formulation

Formulations Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Weight variation test (mg)	160.2±0.24	158.8±0.61	159.4±0..87	160.2±0.52	160.7±0.26	161±0.9	159±0.45	159.9±0.62	160.5±0.85	160.4±0.6
Thickness (mm)	2.72±0.02	2.81±0.03	2.75±0.02	2.71±0.06	2.76±0.03	2.85±0.04	2.71±0.02	2.8±0.03	2.76±0.02	2.78±0.04
Hardness (N)	55-62	50-62	52-60	54-65	52-60	50-63	55-63	49-55	52-64	52-60
% Friability	0.27±0.04	0.34±0.05	0.29±0.02	0.27±0.03	0.3±0.04	0.35±0.02	0.25±0.06	0.38±0.03	0.29±0.04	0.3±0.03
Disintegration time (Sec)	29±1.22	21±0.97	10±0.76	16±0.99	8±0.81	8±0.7	14±0.45	8±0.98	8±0.55	10±0.89
Dispersion time (Sec)	35±1.2	25±1.08	14±0.76	17±0.88	12±1.32	10±0.77	19±0.9	10±0.44	9±0.45	11±0.87
Wetting time (Sec)	24±0.08	20±0.04	11±0.12	10±0.05	8±0.1	8±0.12	8±0.04	7±0.07	7±0.07	8±0.08
%Water absorption ratio	105±2.34	133±1.45	147±1.34	126±1.56	148±0.98	137±2.12	130±1.2	154±1.64	160±1.15	142±1.02
Assay	99.2±.98	99.6±1.2	99.4±1.31	99±0.8	100.1±0.9	100±0.87	98.8±1.11	99.9±0.56	99.5±0.76	100.7±0.5

***In Vitro* Dissolution Test**

Dissolution study of tablets was performed in USP I (Basket) dissolution test apparatus (Electrolab, TDT O8L) using 900ml of simulated gastric fluid without enzyme as dissolution media. The tablets were loaded into each basket of dissolution apparatus; the temperature of dissolution media was maintained at 37°C±0.5°C with stirring speed of 50 rpm throughout the study. The samples were withdrawn at suitable interval of time and analyzed by HPLC (Waters- 2650) with UV-Visible detector along with derivatization technique at 220 nm. Methanol, Acetonitril and Buffer (PH 4.4) in ratio 30:15:55v/v was used as mobile phase. (8-10)

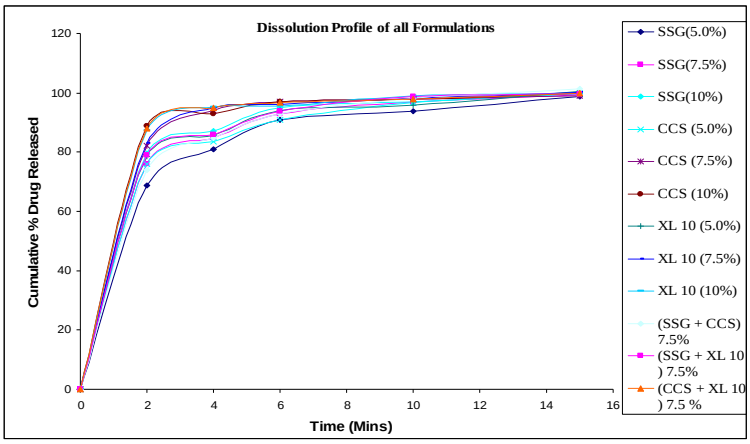

Fig. 1: % Cumulative Drug release of Loratadine of all formulations

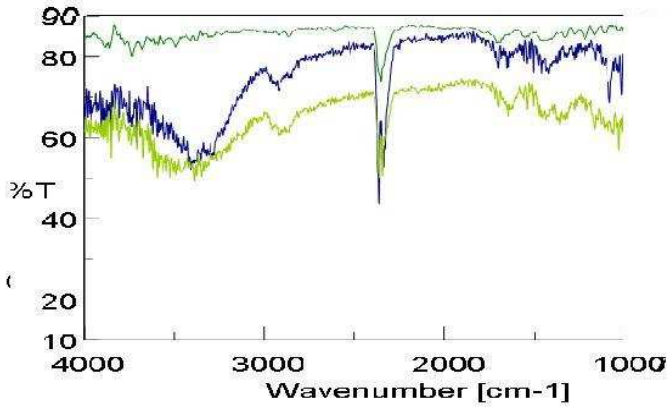

Fig. 2: Comparative FTIR peaks

1. Loratadine
2. Final formulation, F8 (Initial condition)
3. Final formulation (3M, 50 C / 75 %RH)

FTIR study

The identification of pure drug and drug excipient compatibility study was done in the range of 4000-300 cm^{-1} by KBr disc technique using Jasco FTIR-4100. The spectra of optimized formulation were correlated with the characteristic peaks of loratadine.

DSC Study

The experiment was performed in (Mettler Toledo DSC 823e) with a non-hermetically sealed aluminum pan. The sample of 4 gm was heated under an argon atmosphere up to 50^{0}C and allowed to stabilize at this temperature for 1minute; the temperature was then raised to 150^{0}C at a rate of 20 ^{0}C /min

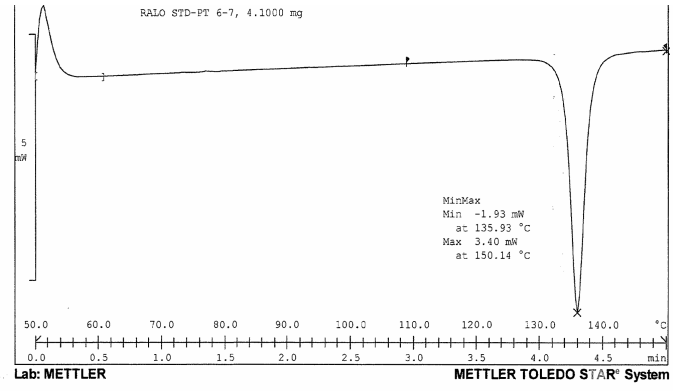

Fig. 3: DSC Thermogram of Loratadine

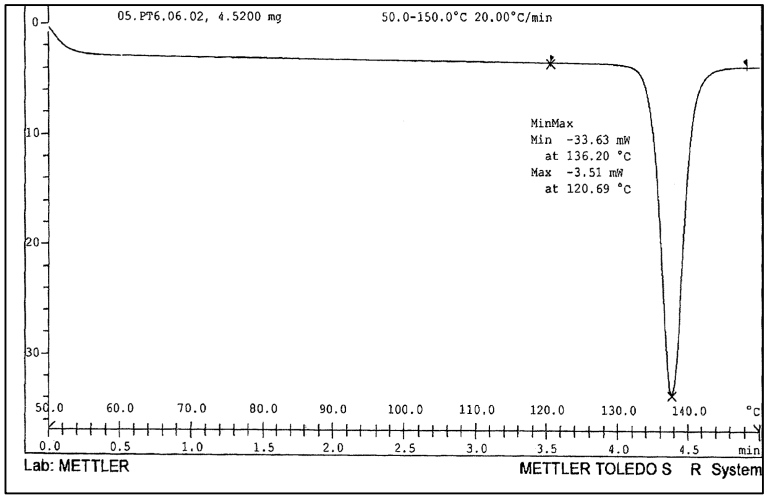

Fig. 4: DSC Thermogram of F8

Stability Studies

Stability study was carried out by exposing the formulation to different conditions including stress conditions of temperature and pressure for three months. Generally stability study is done at initial 30ºC/65% RH (for 1, 2, 3, 6, 9, 12, 24 months) and 40ºC/75%RH (for 1, 2, 3, 6 months). After the study the samples were checked for any change in release pattern. (11-12)

RESULT AND DISCUSSION

The flow properties of the pure drug studied were bulk density, tapped density, Carr's compressibility index and hausner's ratio. The mean compressibility index was found to be 30.6% and mean hausner's ratio was 1.44 (Table 1). These values indicated that the drug possessed slightly poor flow which was improved using glidant and suitable directly compressible diluent to follow direct compression as the tableting method (Table 2). Different tablet formulations of Loratidine were prepared by direct compression technique with an average weight ranging from 158.8 -161.1 mg. The tablets of different batches showed uniform thickness (2.7 to 2.88 mm). Tablets were studied for hardness, disintegration, friability. The hardness was found to be within the range of 49 to 64 N. The percentage friability ranged from 0.22 to 0.38 which was within the official limit (< 1 %). Disintegration time was found to be in 4-29 sec, which was maximum for F1 and varying the proportion of superdisintegrant the disintegration time decreased for F8 and F9. Among three superdisintegrants, Sodium starch Glycolate, Croscarmelose Sodium and Crospovidone XL 10, Crospovidone XL 10 was found to have good disintegrant property. Dispersion time, disintegration time and Wettening time of formulation containing Crospovidone XL 10 were better. F10 was showing maximum drug content of 100.7% which was within the range of 90 to 100%. Wetting time for the tablet formulations was found to vary in the range 6-24 sec. It was observed that the disintegration process started by wetting of the tablets. F9 was found to show good water absorption ratio. All the data for evaluation of physical parameters were shown in Table 3. Dissolution profiles of all formulations were compared and dissolution of F8 and F9 show better results. The drug release from formulation increases with increase in concentration of superdisintegrants (Fig 1).There is no significant difference in drug release at 7.5% and 10% concentration hence tablets of formulation F8 were put on short term stability by keeping it in humidity chamber at different conditions of temperature and humidity for the period of three months. From stability studies for three months showed no incompatibility between drug excipients parameters of formulation including physical parameters, assay and dissolution profile were within specification limit, thus indicating the optimized formulation to be stable.

The IR absorption spectra of the pure drug and its mixture with each of the excipients used individually was taken in the range of 4000-1000 cm^{-1} using KBr disc method. The major peaks were reported for evaluation of purity as shown in Fig 2. The major peaks found were C=O stretch at 1703 cm^{-1} , C=C, C=N stretch (Aomatic) at 1599 cm^{-1} , C–N, C –O Stretch Carbamates at 1225 cm^{-1} and C=C aromatic out of deformation at 830 , 780, 763 cm^{-1} . DSC studies revealed that Loratadine showed the sharp peak (Melting Point) at 136.20^{0}C. The melting range was (minima and maxima of peak) 120.69^{0}C to 136.20^{0}C. Thus from the DSC study as shown in Fig 3 and 4 was confirmed that there was no change in the endothermic peak of the drug and hence the drug and the excipients were well compatible with each other.

CONCLUSION

The intention of developing oro-dispersible tablet of Loratadine was to provide rapid peak plasma concentration to achieve desired pharmacological response.

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