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Formulation and Evaluation of Loratadine Orally Disintegrating Tablet by Different Super Disintegrant and Camphor as Subliming Agent.

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Abstract

The objective work to develop loratadine orally disintegrating tablet using different super disintegrant which would disintegrate tablet rapidly in oral cavity. Nine batch of loratadine orally disintegrating tablet was prepared by direct compression method using sodium starch glycolate, cross carmellose sodium, cross povidone as disintegrant in different concentration. Camphor was used as sublimating agent. The compressed tablets are dried for 5 hours to allow sublimation of camphor to increase the porosity of the fast dissolving tablets to improve the dissolution. Approximately 40% of the absorbed loratadine is absorbed via the oral mucosa. The influence of disintegrant concentration on the release of loratadine was studied. Amongst all formulations, formulation F9 prepared by 6% sodium starch glycolate (SSG) showed least disintegrating time of 15 second and faster dissolution. The tablets were evaluated for Carr's index, Angle of repose, hausner ratio, hardness, friability, weight variation, thickness, disintegrating time, drug content and in-vitro drug release.

Key Words

Orally disintegrating Tablet, subliming agent, Loratadine, Direct compression.

Introduction

Orally disintegrating tablets are gaining prominence as new drug delivery system. Pediatric, geriatric, bedridden and mentally ill patient have difficulty in swallowing the conventional dosage form[1]. These dosage form dissolve or disintegrate in the oral cavity within a minute without the need of water or chewing. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa or it can be swallowed as a solution to be absorbed from the gastrointestinal tract. Loratadine is second generation H1 histamine antagonist, Loratadine, ethyl-4-(8-chloro-5, 6 dihydro-11Hbenzo [5, 6] cyclohepta [1, 2b] pyridin-11-ylidene)-1-piperidine carboxylate, is a long acting non-sedating antihistamine with no significant antimuscarinic activity, structurally closed related to dicyclic antidepressant such as imipramine. It is used for the symptomatic relief of allergic conditions such as runny nose, itchy or watery eyes, sneezing, and nasal or throat itching and chronic urticaria. It is also licensed to alleviate itching due to hives. It does not

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readily cross the blood brain barrier. Due to a bypass of first-pass metabolism, approximately 40% of the absorbed loratadine is absorbed via the oral mucosa. Loratadine, a H1 receptor blocker, is absorbed in the proximal part of the gastrointestinal tract; the presence of food enhances its bioavailability. Usually super disintegrant are added to drug formulation to facilitate the break up of tablet content into smaller particle that can dissolve more rapidly than dissolves without presence of super disintegrant. Many substances used us disintegrant like microcrystalline cellulose, sodium starch glycolate, cross povidone, cross carmellose sodium. The independent variables are selected as the quantities of cross carmellose sodium (CCS), sodium starch glycolate and cross povidone[2-5]. The important mechanism of disintegrant action of cross carmellose sodium is water wicking and water swelling. The fibrous nature of CCS provides many sites for fluid uptake and gives it excellent water wicking property. The solubility of cross povidone varies considerably from one solvent to another. Sodium starch glycolate commonly used to improve disintegration and dissolution of solid dosage form. Orally disintegrating tablet is prepared by subliming method. Camphor is added as inert volatile substance. Removal of volatile material by sublimation creates pores in tablet structure, due to which tablet dissolves when comes in contact with saliva[6-8].

Materials and Method

Loratadine is procured from Cadila pharma, Ankleshwar, India. Avicel 102, Cross carmellose sodium, Cross povidone, Sodium starch glycolate, Mannitol and other materials used are of Analytical grade.

Preparation of Mixed Blend of Drug and Excepient

All ingredients were passed through sieve no 60. The super disintegrating agents were taken in varying concentration (02%, 04% and 06%) used to develop tablets. In this study orally disintegrating tablet was prepared by using camphor as subliming agent. All the ingredients were subjected to grinding to obtain degree of fitness. Nine formulations were prepare by using camphor, mannitol as a Diluent and Aspartame as a Sweetning agent. The tablets of weight 150 mg were prepared by direct compression technique using 8 mm punch.

Drug-Excepient Compatibility Study

Differential Scanning Calorimetry (DSC)

The sample was taken in aluminium pan, sealed with aluminium cap and kept under nitrogen purging (atmosphere). The samples were scanned from 0-300°C with the scanning rate of 10°C rise/min using differential scanning calorimeter (Shimadzu, Japan).

Evaluation of Mixed Blend Powder

Determination of densities

A simple test has been developed to evaluate the flowability of a powder by comparing the poured density (ρ_p) and tapped density (ρ_t) of a powder and the rate at which it packed down. Tapped density was determined by taking granules in measuring cylinder and tapping it to a constant volume in a bulk density apparatus. Poured density was determined by three tap method.

% Compressibility or Carr's index

Based on the poured density and tapped density, the % compressibility of the granules was computed using the Carr's compressibility index,

Carr's index (%) = (Tapped density - poured density / Tapped density) x 100

Hausner ratio

Hausner ratio was calculated using the formula:

Hausner ratio = Tapped density / Poured density

Angle of repose

Angle of repose of the granules was determined height cone method.

A funnel was fixed to a desired height and granules were filled in it. They were allowed to flow down on a graph paper fixed on a horizontal surface and angle of repose was calculated using the formula:

$\tan \Theta = 2h / D$, $\Theta = \tan^{-1}(h/r)$

Where h and r is height and radius of the pile respectively.

Evaluation of Orally Disintegrating Tablet

Weight variation[9]

Twenty tablets were individually weighed and average weight was calculated. The individually weight was compared to average weight. The tablets pass the test if not more than two tablets are outside the percentage limit.

Tablet Hardness[10]

The crushing tolerance of tablets was measured using an Pfizer hardness tester. Determinations were made in triplicate.

Tablet Thickness[10]

Tablet thickness can be measured using a simple procedure. 5 tablets were taken and their thickness was measured using Varnier callipers. The thickness was measured by placing tablet between two arms of the Varnier callipers.

Friability[10]

The friability of the tablet determined using friabilaty test apparatus (Veego). It is expressed in percentage. 20 tablets were initially weighed and transferred into friabilator. The friabilator was operated for 100 rotation. After 100 rotation the tablets were weighed again. The % friability was then calculated using the formula,

Friability = [(Initial weight- Final weight) / (Initial weight)] x 100%

Disintegration test

The disintegration test was carried out disintegration test apparatus (Veego). Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed over each tablet. Distilled Water was used as the medium maintained at 37°C ± 0.5 °C and the time for each tablet to disintegrate complete as recorded.

Drug Content

Ten tablets were powered and the blend equivalent to 10 mg of loratadine was weight and dissolved in suitable quantity of Hcl pH 1.2 buffer solutions. Solution was filtered and diluted and drug content analyzed spectrophotometrically at 280 nm using Shimadzu Corporation, UV-1600, Japan.

***In-vitro* dissolution study[17]**

Dissolution study was carried out using USP dissolution test apparatus (Labindia DS8000) type II. The dissolution medium used was 900 ml of HCL acid buffer of pH 1.2 at 37 ± 0.5 °C. The paddle speed was kept at 50 rpm throughout the study. Aliquot of 5 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume. After each sampling suitable diluted with 1.2 pH HCL acid buffer and analyzed spectrophotometrically at 280 nm against suitable blank using UV-visible spectrophotometer (UV-1800, Japan).

Results and Discussion

The powder blend for all formulation containing various concentration of CCS (2,4,6%), SSG (2,4,6%) and Cross povidone (2,4,6%) as superdisintegrant was prepared and then the DSC studies were done that suggests compatible with Superdisintegrant (Fig. 2). The Linearity of loratadine in 1.2 pH Hcl buffer shown in figure 1. The formulated tablets exhibited low weight variation that varies between 2.1 to 3.9 from different batches. Bulk density varies between 0.425 to 0.462 gm/cm^3. The hausner ratio varies between 1.21 to 1.25. Carr's index varies between 17.77 to 19.60. Angle of repose varies between 27.02 to 31.22. The drug content of all the formulations were found to be between 97.02 - 99.89% which was within the acceptable limits as per USP. Addition of a subliming agent had no pronounced effect on hardness and increased friability of the tablets. The porous structure is responsible for faster water uptake; hence it facilitates wicking action of superdisintegrants in bringing about faster disintegration. Tablets with lower friability (0.5%) may not break during handling on machines. The use of a sublimation agent resulted in increased friability probably due to increased porosity by forming pore size into tablet matrix. It was decided to incorporate colloidal silicon dioxide, extragranularly, at a level of 1% (1.5 mg for 150 mg tablet) to decrease the friability of the tablets. Batches F1 to F9 shows good mechanical integrity, but the disintegration time was found to be less than 30 seconds. The results shown in Table 3 reveal that sublimation of camphor from tablets resulted in faster disintegration varies between 12 to 28 seconds. The thickness of tablets varies from 2.11 to 2.27 mm. *In vitro* release studies were carried out using tablet dissolution test apparatus paddle method at 37±0.5 °C, taking 900 ml of pH 1.2 Hcl dissolution medium. Speed of rotation of the paddle was set at 50 rpm. Aliquots of 5 ml were withdrawn after 2, 5, 10, 15, 20 min and analyzed spectrophotometrically at 280 nm. The *in vitro* dissolution study (Table no.4) indicated faster and maximum drug release from formulation F9 (Fig.3). Comparision of F9 with Plain drug and D1 batch without using subliming method (camphor) done as in Fig.4. D1 Batch shows finally drug release 94.11% at 20 minute. Formulation F9 prepared by direct sublimation of camphor

from final tablets (using 6% SSG) showed release 96.66% drug.

Conclusion

The uses of super disintegrant accelerate the disintegration and dissolution of tablet by their ability to absorb large amount of water when it comes in contact to aqueous medium. Camphor is added as inert volatile substance which removes by sublimation, provides larger pore size in tablet matrix which improves disintegration and dissolution. From F1 to F9 batches the F9 batch shows lower the disintegration time 12 second. Prepared fast disintegrating tablets dispersed quickly in mouth indicates effect on dissolution of tablet. Figure 3 shows % cumulative drug release of all nine batchs. F9 batch shows best dissolution profile than all other batches. Table 3 indicates F9 batch shows faster disintegration time 15 second. The study shows that the dissolution rate and disintegration time can be improved by using camphor as the sublimating agent and with the addition of superdisintegrants.

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Figure 1: Linearity of Loratadine in 1.2 pH Hcl buffer.

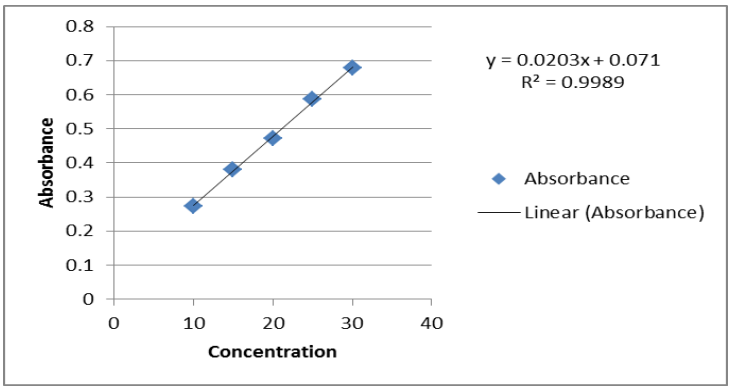

Figure 2: DSC graph of drug Loratadine.

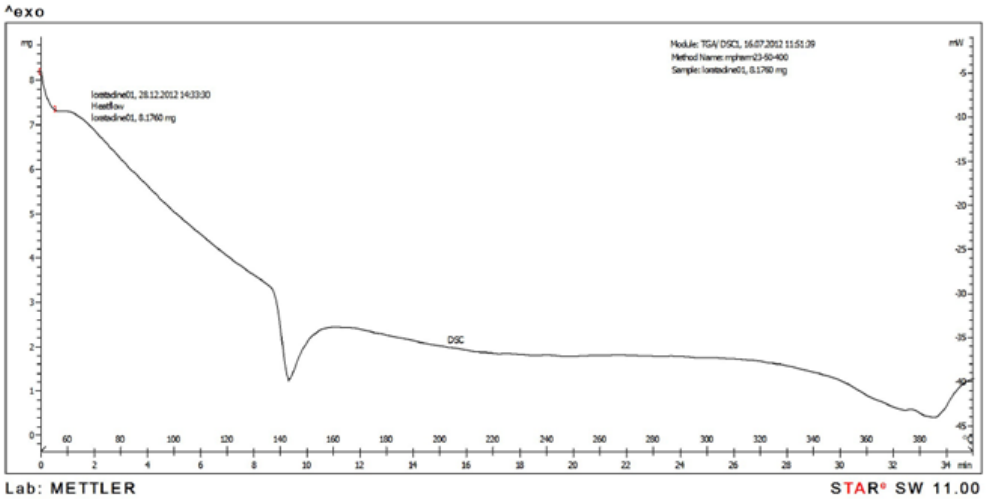

Figure 3: Dissolution study of orally disintegrating tablet .

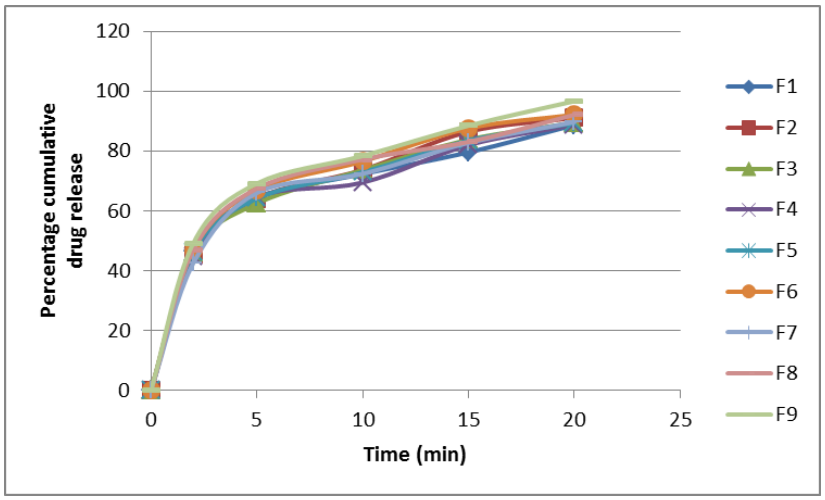

Figure 4: Comparision dissolution study of F9 with plain drug and D1

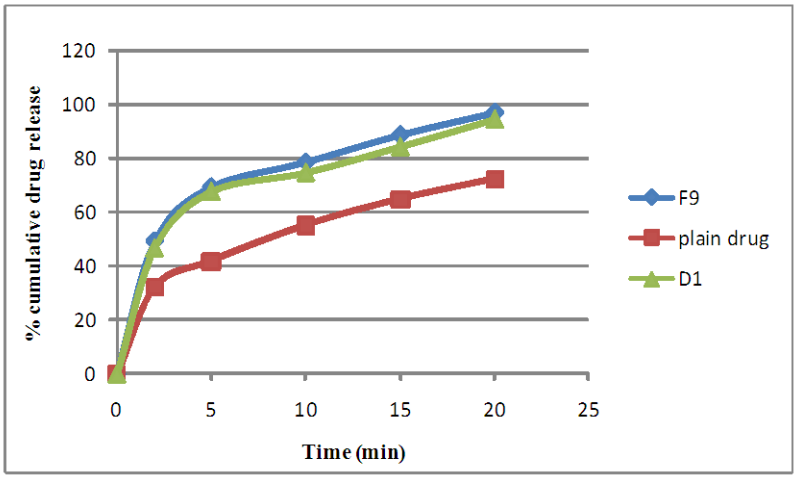

Table 1: Formulation composition for orally disintegrating tablet preparation.

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Loratadine	10	10	10	10	10	10	10	10	10
Avicel PH 102	33.5	33.5	33.5	33.5	33.5	33.5	33.5	33.5	33.5
CCS	6	7.5	9	-	-	-	-	-	-
Cross povidone	-	-	-	6	7.5	9	-	-	-
SSG	-	-	-	-	-	-	6	7.5	9
Aspartame	3	3	3	3	3	3	3	3	3
Citric acid	5	5	5	5	5	5	5	5	5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1	1	1	1	1	1	1	1	1
Silicone dioxide	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Camphor	10	10	10	10	10	10	10	10	10
Mannitol	78.5	77	75.5	78.5	77	75.5	78.5	77	75.5
Total	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Table 2: Evaluation of mixed powder blend.

Batch	Poured density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Carr's index	Angle of repose(Degree)
F1	0.425±0.0070	0.522±0.0028	1.228±0.001	18.58±0.05	28.89±0.02
F2	0.451±0.0014	0.561±0.0021	1.245±0.002	19.60±0.05	29.47±0.78
F3	0.433±0.0042	0.533±0.0049	1.232±0.007	18.76±0.09	30.08±0.21
F4	0.445±0.0078	0.552±0.0028	1.239±0.004	19.38±0.03	31.22±0.04
F5	0.444±0.0056	0.540±0.0007	1.217±0.001	17.77±0.07	30.34±0.09
F6	0.462±0.0035	0.574±0.0063	1.242±0.004	19.51±0.08	29.19±0.01
F7	0.451±0.0020	0.573±0.0049	1.250±0.006	21.29±0.01	28.18±0.19
F8	0.451±0.0014	0.561±0.0021	1.245±0.005	19.60±0.03	28.79±0.12
F9	0.433±0.0042	0.534±0.0063	1.234±0.002	18.91±0.04	27.02±0.29

Table 3: Evaluation of Loratadine orally disintegrating tablet.

Batch	Weight variation(mm)	Thickness (mm)	Hardness (kg/cm^2)	Friability	Drug content(%)	Disintegrating time (sec)
F1	150±0.12	2.11±0.2	3.8±0.02	0.68±0.09	98.43±0.85	28±0.06
F2	150±1.12	2.22±0.3	3.6±0.01	0.54±0.14	97.12±0.54	24±0.08
F3	150±0.58	2.17±0.2	3.9±0.02	0.58±0.08	98.02±1.12	18±0.10
F4	150±0.36	2.19±0.1	3.7±0.01	0.62±0.12	97.02±0.74	25±0.14
F5	150±0.47	2.21±0.4	3.9±0.01	0.48±0.06	99.58±0.35	22±0.06
F6	150±0.25	2.18±0.2	3.7±0.01	0.51±0.16	98.54±0.36	15±0.12
F7	150±0.68	2.17±0.4	3.8±0.02	0.58±0.14	97.44±0.25	20±0.11
F8	150±1.16	2.27±0.1	3.9±0.02	0.71±0.56	98.09±1.11	18±0.06
F9	150±0.96	2.13±0.2	3.7±0.01	0.61±0.79	99.89±0.11	12±0.04

Table 4: % cumulative drug release of orally disintegrating tablet.

Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
00	0	0	0	0	0	0	0	0	0
02	46.56	45.32	46.08	44.68	46.12	46.99	42.54	47.03	49.21
05	64.14	64.12	62.46	64.56	64.15	66.89	65.98	67.45	69.13
10	72.34	73.69	73.62	69.45	72.86	76.56	72.39	77.17	78.34
15	79.56	86.46	83.79	81.98	83.48	87.57	82.74	83.06	88.47
20	88.69	91.05	89.46	88.78	89.31	92.12	89.68	92.12	96.66

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