Tropical Journal of Pharmaceutical Research May 2020; 19 (5): 919-925
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v19i5.2

Original Research Article

Formulation and *in vitro* evaluation of orodispersible tablets of fexofenadine hydrochloride

Durgaramani Sivadasan*, Muhammad Hadi Sultan, Osama Madkhali, Shamama Javed, Aamena Jabeen
College of Pharmacy, Jazan University, Jazan, Kingdom of Saudi Arabia

For correspondence:* ***Email:* *durgimural@rediffmail.com;* ***Tel:*** *+966-534769912*

Sent for review: 4 May 2019 *Revised accepted: 19 April 2020*

Abstract

Purpose: *To develop orodispersible tablets (ODTs) of fexofenadine hydrochloride using three different superdisintegrants in various ratios and to compare their disintegration properties.*
Methods: *Direct compression technique was used for the preparation of ODTs. Mannitol and Avicel CE-15 (microcrystalline cellulose and guar gum) were used as direct compression diluents. The disintegration time of tablets using each polymer (superdisintegrant) was evaluated as well as other tablet properties including weight fluctuation, hardness, friability, wetting time and water absorption ratio.*
Results: *Satisfactory values were obtained for all the evaluated parameters. As the polymer concentration increased, there was a decrease in disintegration time. A comparison of the three different polymers used revealed that CCM3 formulated with 12 % croscarmellose sodium and 14.66 % lactose had the least disintegration time of 32.33 ± 3.23 s. In vitro release studies showed that the maximum drug release of 94.38 ± 0.12 % in 25 min was obtained for ODT tablets containing croscarmellose sodium (CCM3).*
Conclusion: *The orodispersible tablets had quick disintegrating property which was achieved using superdisintegrants. Thus, superdisintegrants improve the disintegration efficiency of orodispersible fexofenadine tablets at low concentrations, when compared to traditional disintegrants.*

Keywords: *Croscarmellose sodium, Direct compression, Fexofenadine, Orodispersible tablets*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

According to FDA, a fast dissolving tablet (FDT) is “a solid dosage form containing medicinal substances which disintegrates rapidly, usually within seconds, when placed upon the tongue” [1]. This property facilitates ingestion of drugs. Usually, FDTs disintegrate within seconds or slightly higher [2]. Orodispersible tablets (ODTs) may be formulated as liquids to facilitate intake and overcome the problems associated with swallowing the solid tablets. Fast dissolving tablets (FDTs) are much useful for young, elderly and handicapped or bed-confined patients, as well as individuals with unremitting nausea, and those without access to portable to water [3-5].

Advances in tableting technology have led to introduction of superdisintegrants which, at low concentrations, enhance the disintegration

efficiency of tablets, relative to normal disintegrants. Superdisintegrants improve the disintegration and dissolution of ODTs produced through direct compression.

Fexofenadine is an antihistamine with selective H_1 receptor antagonist activity which is employed in the treatment of nasal allergies, especially hay fever and to some extent, vasomotor rhinitis. It mitigates rhinorrhea and sneezing, but it is usually less effective against nasal congestion [6]. Rhinitis and urticarial ailments are common among the pediatric and geriatric populations. These groups exhibit a high degree of non-compliance with usage of conventional tablets, thereby justifying the need for orally dispersible tablets of fexofenadine [7]. The purpose of this study was to prepare orodispersible tablets of fexofenadine by direct compression technique using three different types of superdisintegrants in various ratios, to facilitate the disintegration property of the drug. Moreover, the study used various parameters to identify the disintegrating efficiency of superdisntegrants, when compared with traditional disintegrants.

EXPERIMENTAL

Materials

Ac- Di- Sol® (Croscarmellose sodium) from FMC biopolymer and Avicel® CE 15 (methylcellulose and guar gum) were obtained as gift samples from Signet Co-operation. Fexofenadine hydrochloride was a gift from Unichem Laboratories Ltd. Mannitol was procured from Merck laboratories. Phytagel™ (Gellan gum) and Na starch glycolate were purchased from Sigma Aldrich, Bangalore, and Loba Cheme Pvt. Ltd., respectively. Lactose was obtained from Nice Chemicals, India.

Preparation of tablets

Tablets (300 mg each) were formulated with polymers at levels of 8, 10, and 12 % (Table 1). They were subjected to direct compression in a 10 -station Rotary Press bearing flat face bevel edge punches of 9.5 mm diameter. All the formulations contained 60 mg of fexofenadine hydrochloride, with Avicel® CE-15 as diluent, mannitol as directly compressible vehicle/diluent, lactose as a diluent, magnesium stearate as a lubricant (1.6 %), and talc (1.6 %) as a glidant.

Evaluation of ODTs

Pre-compression evaluation of powder blends

The flow qualities of the powder blends were determined in relation to angle of repose, bulk density, tapped density, Carr's index and Hausner ratio.

Post-compression analysis of orodispersible tablets [8]

The prepared orodispersible blends were tested for hardness, thickness, friability, drug content consistency, weight variation test, disintegration test, modified disintegration test, wetting time, water reabsorption and dissolution time.

Changes in tablet weight

This was determined by weighing twenty tablets singly and together. The mean weight of one tablet was estimated from the group weight.

Thickness

A Vernier caliper was used to measure the thickness of each tablet.

Table 1: Compositions of orodispersible tablet formulations

Formulation	Drug (mg)	SSG (mg)	Ac-Di-Sol® (mg)	Phytagel™ (mg)	Avicel® CE-15 (mg)	Mannitol (mg)	Lactose (mg)	Talc (mg)	Magnesium stearate (mg)
SSG 1	60	24	---	---	50	100	56	5	5
SSG 2	60	30	---	---	50	100	50	5	5
SSG 3	60	36	---	---	50	100	44	5	5
CCM 1	60	---	24	---	50	100	56	5	5
CCM 2	60	---	30	---	50	100	50	5	5
CCM 3	60	---	36	---	50	100	44	5	5
GGM 1	60	---	---	24	50	100	56	5	5
GGM 2	60	---	---	30	50	100	50	5	5
GGM 3	60	---	---	36	50	100	44	5	5

Each tablet weighed 300 mg; SSG = sodium starch glycolate, Ac-Di-Sol = croscarmellose sodium, = phytagel (gellan gum), Avicel CE-15 = microcrystalline cellulose + guar gum

Hardness

A Monsanto hardness tester was used to determine the hardness of each formulated ODT.

Friability

This was determined using Roche Friabilator apparatus. Twenty pre-weighed tablets were subjected to rotation at 25 rpm for 4 min, followed by re-weighing after discarding the fines through 60 mesh screens. Friability (F) was calculated in terms of loss (%) in tablet weight, using Eq 1:

$$\%F = (W1-W2)/W1 \times 100 \quad \ldots\ldots\ldots\ldots (1)$$

where *W1* and *W2* are the initial and final weights of tablets, respectively.

Content uniformity

To 20 powdered tablets were added 10mg equivalent weight of fexofenadine hydrochloride tablet power and 10 ml of phosphate buffer, pH 6.8. The mixture was vortexed for 10 min and made up to a volume of 100 ml. Following filtration and appropriate dilution, the solution was subjected to spectrophotometric analysis at 266 nm.

Disintegration time

Disintegration time is an important test in ODT technology since the tablet has to complete disintegration within 1 min as per USP requirement. Tablet disintegration was measured using USP disintegration apparatus. A tablet was positioned in each tube and the basket rack was placed in a beaker of phosphate buffer at 37 ± 2 ˚C. The basket assembly was moved up and down the beaker and the apparatus was operated until no residue was left. The time taken to achieve zero residue was recorded [9,10].

Modified disintegration test

This is a modification of the standard disintegration test procedure so as to eliminate its disadvantages and make it mimic disintegration in saliva, especially for ODT. For this purpose, 10 mL of phosphate buffer, pH 6.8 was put in a petri dish, and an ODT was kept at the middle of the dish (Figure 1). The time taken for the ODT formulation to disintegrate entirely was noted.

Wetting time and water absorption ratio [12]

A tissue paper was folded twice and kept in a petri dish. The tissue paper was moistened using 6 mL of distilled water and the tablet was kept on the tissue paper after weighing. The time required for complete wetting was recorded.

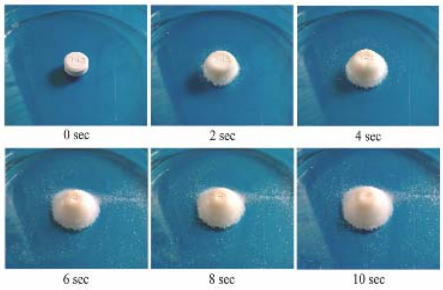

Figure 1: Modified disintegration test

Then, the tablet was re-weighed, and H_2O absorption (R) was calculated using Eq. 2 [13].

$$R = (W2-W1)/W1 \times 100 \ldots\ldots\ldots\ldots (2)$$

where *W1* and *W2* are the initial and final weights of the tablet, respectively.

In vitro drug release studies

Dissolution studies were carried out with USP paddle type apparatus, in phosphate buffer, pH 6.8 (900 mL) maintained at a temperature of 37 ˚C and paddle velocity of 50 rpm. Samples (5 mL each) were taken at 2, 4, 6, 8, 10, 15, 20 and 25 min, and replenished with equivalent volume of phosphate buffer under the same experimental conditions. Following filtration and dilution, the absorbance of each sample was read at 220 nm.

Release kinetic studies

The kinetic model of drug release was elucidated by fitting the dissolutions of all ODTs into standard mathematical models of drug release.

Statistical analysis

Values are presented as mean ± SD, and were statistically analyzed using one-way ANOVA in Microsoft excel. Values of $p < 0.05$ were taken as statistically significant.

RESULTS

Characteristics of powder blends

The values of angle of repose varied between 22.34 and 24.68°. Hausner ratios for all the formulations were between 1.11 and 1.65, while Carr's index values were between 10.29 and 19.44.

General appearance and shape of tablets

The tablet surfaces were smooth, owing to the addition of 1.6 % of magnesium stearate. Capping and lamination were not observed. The surface texture was smooth, and the shape of the tablets was round and uniform.

ODT characteristics

The results obtained for friability, hardness, and content consistency are shown in Table 2. The values obtained for all the parameters were within the limits specified according to USP.

Thickness

Tablet thickness values ranged from 3.42 to 3.52 mm. These values are acceptable for easy disintegration.

Weight variation

Tablet weight variation was within the limit of ± 7 %. It was closely monitored because deviation to the lower limit would cause lower drug content problem and poor drug release, while deviation to upper limit would cause toxicity problems.

Tablet hardness

Tablet hardness was checked at regular intervals during formulation. The hardness was 4 kg / cm^2, which can provide the required integrity during handling and transportation.

Friability

Orodispersible tablets exhibit higher friability values due to their nature. Hence, it is critical to maintain a balance between the disintegration and friability characteristics of the formulation. The friability values of the prepared formulations were within approved limits, and the tablets were highly stable.

Disintegration time (DT)

Disintegration time was determined in the USP disintegration apparatus [14]. The results are shown in Table 3. All formulations completed disintegration at simulated salivary pH of 6.8 within the acceptable limit of 1 min. This is an ideal disintegration time for an ODT according to the USP.

Table 2: Post-compression properties of orodispersible tablets

Formulation	Thickness (mm) [a]	Weight of tablet(mg) [a]	Hardness (kg/cm^2)[a]	Friability (%) [a]	Content uniformity (%)
SSG 1	3.48±0.04	300.1±0.0070	4±0.00	0.04±0.0014	99.58
SSG 2	3.5±0.035	299.9±0.0353	4±0.00	0.019±0.001	99.89
SSG 3	3.49±0.01	300.08±0.055	4±0.00	0.046±0.001	100.04
CCM 1	3.48±0.01	300.12±0.022	4±0.00	0.04±0.0014	99.88
CCM 2	3.42±0.01	299.98±0.044	4±0.00	0.034±0.004	99.75
CCM 3	3.47±0.01	300.12±0.099	4±0.00	0.013±0.004	100.56
GGM 1	3.52±0.02	300.1±0.0282	4±0.00	0.03±0.0014	99.65
GGM 2	3.49±0.02	300.11±0.035	4±0.00	0.04±0.0028	99.54
GGM 3	3.42±0.03	299.89±0.055	4±0.00	0.11±0.0692	99.77

[a] Values are expressed as mean ± SD (n = 3, $p < 0.05$)

Table 3: Disintegration and modified-disintegration times

Formulation	Disintegration time (s)[a]	Modified disintegration time (s)[a]
SSG 1	48.36±3.48	54.26±3.58
SSG 2	47.54±1.34	53.34±1.54
SSG 3	45.54±2.43	49.24±1.53
CCM 1	38.43±1.26	45.33±1.16
CCM 2	36.53±2.24	41.23±2.34
CCM 3	32.33±3.23	38.31±1.23
GGM 1	46.78±2.14	52.28±1.34
GGM 2	44.43±1.23	48.23±1.43

[a] Mean ± SD (n = 3, $p < 0.05$)

Disintegrating property of polymers [15]

The disintegrations of the best formulations in each polymer (SSG 3, CCM3 and GGM 3) were compared. The ODT CCM3 composed with croscarmellose sodium had the lowest DT of 32.33 sec. Gellan gum, the natural superdisintegrant used in the study had a good disintegration property, and its action was comparable with those of other superdisintegrants. The results showed that the DT of gellan gum was lower than that of the synthetic superdisintegrant sodium starch glycolate. The disintegrant qualities decreased in the order: croscarmellose sodium > gellan gum > sodium starch glycolate. Thus, CCM3 containing croscarmellose sodium had the least disintegration time, which may be due to its two-way disintegrant action i.e. water wicking (drawing water into the tablet through capillary action) and swelling. The results of modified disintegration test are shown in Table 3. They correlate with the results of USP disintegration test.

Wetting time and % water absorption

Wetting time is a function of internal structure of a tablet and hydrophilicity of the excipients. The wetting times of all the formulations were within 1 min (Table 4). The wetting times of SSG ranged from 22 to 32 sec, while CCM had wetting times of 18 to 24 sec. For GGM, the wetting times ranged from 23 to 25 sec.

Table 4: Wetting time and water absorption

Formulation	Wetting time (sec)[a]	Water absorption (%)[a]
SSG 1	22.00±1.12	26.89±1.11
SSG 2	32.39±0.58	36.89±1.32
SSG 3	26.01±1.01	34.37±1.96
CCM 1	18.00±0.61	19.24±2.13
CCM 2	17.33±1.55	18.45±2.10
CCM 3	24.87±0.36	31.45±1.63
GGM 1	23.67±0.5	29.69±1.55
GGM 2	22.34±1.58	29.09±1.52
GGM 3	25.33±0.59	35.09±1.92

[a] Values are mean ± SD (n = 3, $p < 0.05$)

***In vitro* dissolution**

The formulations CCM 1, CCM2 and CCM 3 (croscarmellose sodium) showed initial burst release of 62.64, 67.2 and 83.16 %, respectively within 6 min (Figure 2). Then, the release approached peak level at 25 min. Drug dissolution rose with increasing concentration of the polymer. The formulation CCM 3 containing a polymer concentration of 12 % and 14.66 % lactose had the best dissolution profile of 94.38 % at 25 min.

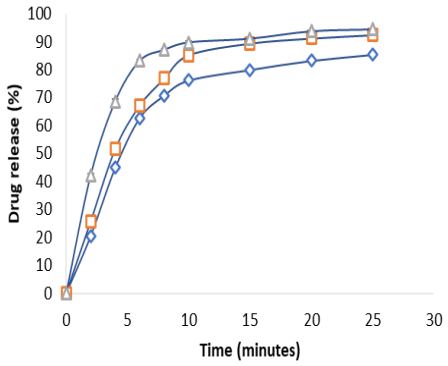

Figure 2: Drug release profile of ODT (croscarmellose sodium). Results are mean ± SD; (n = 3, $p < 0.05$); CCM 1(◊); CCM2 (□); CCM 3 (Δ)

The release profile of the ODT prepared with sodium starch glycolate showed that drug dissolution increased with increasing polymer concentration (Figure 3). The formulation containing 12 % ODT and 14.66 % lactose was found to have the best dissolution profile with 84.48 % drug release at 15 min (SSG 3).

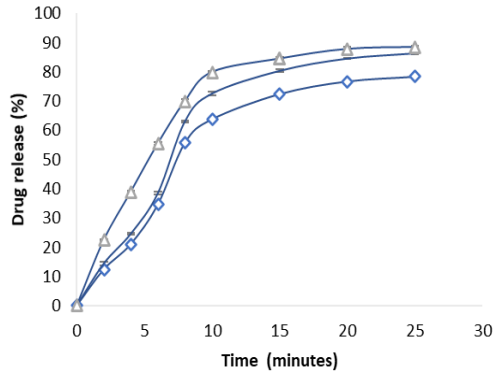

Figure 3: Drug release profile of ODT (sodium starch glycolate). Results are mean ± SD; (n = 3, P < 0.05). SSG 1 (◊); SSG 2 (×); SSG 3 (Δ)

The release profile of the ODT prepared with gellan gum showed a release of 61.56 % (GGM 1), 68.4 % (GGM 2) and 71.28 % (GGM 3) at 8 min (Figure 4). Drug dissolution increased with increasing polymer level. Formulation GGM 3 containing polymer concentration of 12 % and lactose with 14.66 % was found to have the best dissolution profile, with 91.08 % drug release at 25 min.

Release kinetics

Results of *in vitro* dissolution studies were fitted to zero order, first order and Korsmeyer-Peppas

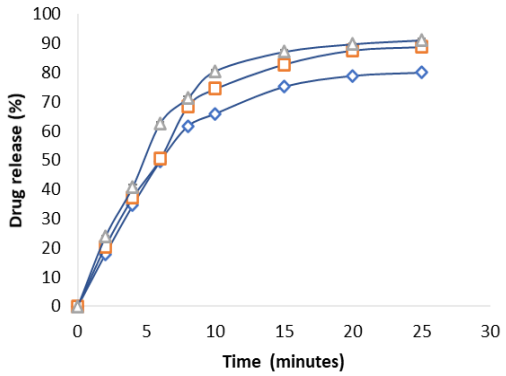

Figure 4: Drug release profile of ODT (gellan gum). Results are mean ± SD; (n = 3, P < 0.05). GGM 1 (◊); GGM 2 (□); GGM 3 (Δ)

equations. The values of R^2 ranged from 0.802 to 0.930 (first order plot) for different formulations (Table 5). The values of slope of Korsmeyer-Peppas plots ranged from 0.47 to 0.774.

Table 5: Release kinetics of ODT

Formulation	Zero order (R^2)	First order (R^2)	Korsemeyer-Peppas (n)
SSG 1	0.827	0.898	0.774
SSG 2	0.812	0.909	0.752
SSG 3	0.74	0.877	0.546
CCM 1	0.681	0.844	0.518
CCM 2	0.671	0.873	0.473
CCM 3	0.522	0.802	0.483
GGM 1	0.772	0.894	0.582
GGM 2	0.782	0.930	0.584
GGM 3	0.729	0.906	0.527

DISCUSSION

Orodispersible tablets of fexofenadine hydrochloride were made using direct compression. The pre-compression parameters showed that the powder blends had sufficient flow properties as per the approved limits. The thickness of the tablets was uniform in each batch. This showed that uniform compression force was applied while punching the tablets.

The uniformity in weight is related to the improvement in powder flow properties through the addition of talc and magnesium stearate, resulting in effective die cavity filling [14]. The ODTs are generally expected to have hardness of 3 to 5 kg/cm^2, since harder tablets are known to have longer disintegration times. The hardness was monitored at regular intervals during punching to keep the hardness value at a uniform level. A deviation from the hardness will result in differences in disintegration time. The tablets were highly stable to any external stress that might be involved during transportation and packaging: the friability values were consistent with the USP limit of < 1 %.

The results of the modified disintegration test, which mimics the disintegration taking place in mouth, correlated with the results of the USP disintegration test.

Formulation CCM 3 had the best dissolution profile of 94.38 % at 25 min. Croscarmellose sodium has water wicking and swelling properties which lead to rapid disintegration of drugs, which in turn, leads to the rapid dissolution of drugs. Gellan gum is a natural gelling agent and its disintegrating property was due to rapid water uptake and swelling which lead to rapid release of drug. The sodium starch glycolate had swelling property which accounted for its disintegration property and made the dissolution faster [15].

The results of the release kinetics study showed that all the formulations obeyed first order drug release profile more closely, i.e., the release rate depended upon the initial concentration of drug. The slope values of the Korsmeyer-Peppas plot showed that the mechanism was non-fickian.

CONCLUSION

The superdisintegrants tested in this study primarily influenced tablet disintegration and dissolution. The results showed that the ODT formulation, CCM3, containing croscarmellose sodium exhibits minimal disintegration time. Thus, croscarmellose Na has potential for use as superdisintegrant in ODT formulations.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

Open Access

This is an Open Access article that uses a funding model which does not charge readers or their

REFERENCES

1. *Bhaskaran S, Narmada GV. Rapid Dissolving tablet Novel dosage form. Ind Pharm 2002; 2: 9-12.*
2. *Seager H. Drug-delivery products and the Zydis fast-dissolving dosage form. J Pharm Pharmacol 1998; 4: 375-382.*
3. *Habib W, Khankari R, Hontz J. Fast-dissolve drug delivery systems, Critical Rev in Ther Drug Carr Sys 2000; 1: 61-72.*
4. *Brown D. Orally disintegrating tablets: Taste over speed. Drug Del Tech 2003; 3: 58-61.*
5. *Mohanachandran P S, Sindhumol P G, Kiran T S. Superdisintegrants: An Overview. Int J Pharm Sci Rev Res 2011; 1: 105-108.*
6. *Piao HM, Balakrishnan P, Cho HJ, Kim H, Kim YS, Chung SJ, Shim CK, Kim DD. Preparation and evaluation of fexofenadine microemulsions for intranasal delivery, Int J Pharm 2010; 1-2: 309-316.*
7. *Nagendrakumar D, Raju SA, Shirsand SB, Para MS, Rampure MV. Fast Dissolving Tablets of Fexofenadine HCl by Effervescent Method. Ind J Pharm Sci 2009; 2: 116-119.*
8. *Bi YX, Sunada H, Yonezawa Y, Danjo K. Evaluation of rapidly disintegrating tablets prepared by a direct compression method. Drug Dev Ind Pharm 1999; 5: 571-581.*
9. *Debjit B, Chiranjib B, Krishnakanth, Pankaj, Chandira RM. Fast Dissolving Tablet: An Overview. J Chem Pharm Res 2009; 1: 163-177.*
10. *Bi Y, Sunada H, Yonezawa Y, Danjo K, Otsuka A, Iida K. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem Pharm Bull (Tokyo) 1996; 11: 2121-2127.*
11. *Gunda RK, Suresh Kumar JN. Formulation development and evaluation of moxifloxacin HCl fast dissolving tablets. Pharm Met 2017; 2: 160-167.*
12. *Chauhan K, Parashar B, Chandel A, Thakur V. Formulation and evaluation of fast dissolving tablets of telmisartan. Int J Pharm Sci Res 2013; 4: 1514-1520.*
13. *Leon Lachman HAL, Joseph L Kanig. The Theory and Practice of Industrial Pharmacy 3rd ed 1986: 293-303.*
14. *Kalia A, Khurana S, Bedi N. Formulation and evaluation of mouth dissolving tablets of oxcarbazepine. Int J Pharm Pharm Sci 2009; 1: 211-214.*
15. *Damodar R, Movva B, Mallikarjun PN, Pasumarthy C, Kona N, Varsha PV. Formulation and evaluation of fast dissolving tablets of Diclofenac sodium by novel hole technology. J Mol Pharm Org Proc Res 2014; 2: 1-6.*