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A Study on the Effect of Superdisintegrants and Processing Methods on the Physicochemical and In-Vitro Release Characteristics of Immediate Release Tablets of Olopatadine Hydrochloride

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ABSTRACT

The present investigation attempted to study the effect of superdisintegrants and processing methods on the physicochemical and in-vitro release characteristics of immediate release tablets of olopatadine hydrochloride. To achieve this goal various formulations of olopatadine were prepared by direct compression, wet granulation and fluidized bed granulation methods to achieve maximum drug content with reference to innovator. Varying proportion of superdisintegrants such as crosspovidone XL, sodium starch glycolate, croscarmellose sodium used to compare drug release profile with innovator. Different formulations were prepared and evaluated with respect to various precompression and postcompression parameters. The results indicate that the superdisintegrants used have influenced on the disintegration time. The final selection of the formulation F10 (f_2 = 91.9) containing crosspovidone XL was based on highest f2 value among all formulations with reference to marketed product.

Key words: olopatadine, direct compression, wet granulation, fluid bed granulation, superdisintegrants, drug release

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INTRODUCTION

Immediate release oral dosage forms, i.e., tablets and capsules, are most widely used drug delivery systems available [1]. The tablets is the most widely used because of its convenience in term of self-administration, compactness, and ease in manufacturing [2]. Various techniques can be used to formulate immediate release tablets like direct compression, wet granulation and dry granulation. Direct compression, is one of the techniques that requires the incorporation of a superdisintegrant into the formulation. Direct compression does not require the use of water or heat during the formulation procedure and the compression forces, when used to achieve tablets of suitable hardness without compromising the rapid disintegration characteristics [3]. However the most common is wet granulation technique. The wet granulation process offers several advantages. For example, high dose drugs that experience poor flow and/or poor compactibility can be granulated to obtain suitable flow and cohesion for compaction [2]. There is another approach of granulation of fine powders, that can be performed in a fluid bed processor by spraying solvent or a solvent/binder solution onto a fluidized powder bed. [4]. The mixing, spraying and drying phases are the consequent process stages needed to convert powders to free-flowing granules [5].

Despite increasing interest in controlled-release drug delivery systems, the most common tablets that are intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastro-intestinal tract still remains the dosage form of choice. An important variable in any tablet system is the rate at which the drug substance dissolves and for many solid dosage forms, disintegration precedes drug dissolution. Hence, the proper choice of disintegrants and its consistency of performance are of critical importance to the formulation development of such tablets. Superdisintegrants such as croscarmellose sodium, sodium starch glycolate and crospovidone are now frequently used in tablet formulations to improve the rate and extent of tablet disintegration thereby increasing the rate of drug dissolution [6].

Olopatadine hydrochloride is an antiallergic agent with histamine H1 receptor antagonistic action that is indicated for the signs and symptoms of allergic rhinitis, chronic urticaria, eczema dermatitis, prurigo, pruritis cutaneous, psoriasis vulgaris, and erythema exsudativum multiform. Olopatadine exhibits potent antihistamine activity in vivo following its systemic administration [7]. Olopatadine significantly suppresses histamine-induced wheal, flare, and itch, starting 30 minutes after oral administration. Olopatadine is more effective than fexofenadine and bepotastine. These results suggest that olopatadine can suppress skin symptoms caused by histamine soon after administration [8]. Topical therapy has been the preferred treatment for ocular allergic disease. Eye drops can be applied easily and seldom lead to systemic side-effects. Moreover, the physical presence of the drops themselves will have a washout effect, helping to remove the inflammatory mediators and, thereby, lessening some of the symptoms. So study suggests that the orally administered olopatadine is expected to improve allergic conjunctivitis [7].

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As discussed earlier, the methods of granulation have influence on the outcome of the tablets with the desired quality. Taking this into account, the present study was aimed to develop Olopatadine immediate release tablets by different granulation techniques like direct compression, wet granulation and fluidized bed granulation and to evaluate physicochemical and release characteristics and compare with the commercial tablets. This study will help with advantage of the right processes for manufacturing of tablets that meet with the desired standards.

MATERIALS AND METHODS

Olpatadine HCl was obtained as gift sample from Cadila healthcare Ltd. Ahmedabad, India. Sodium starch glycolate, crosscarmellose sodium and crosspovidone were obtained as gift sample from Signet Chemicals Mumbai, India. Other ingredients used were of analytical grade.

Experimental work:

Immediate release tablets were prepared by direct compression, wet granulation, fluidized bed granulation methods. The formulations were developed by using different techniques in various ratios of excipients.

The formula of tablets prepared using three different methods is given in Table 1.

Formulations F1 and F2 were prepared by direct compression. Olopatadine and excipients sifted through sieve no 40 # and thoroughly mixed in a blender approximately for 5 min. This mixer was lubricated for 2 min. with Magnesium Stearate which was already passed through sieve 60. The lubricated granules were then compressed in to tablets on a 16 station rotary machine punch size 6.5 mm. Formulations F3 to F5 were prepared by wet granulation method. Olopatadine and excipients sifted through sieve # 40 and thoroughly mixed in a Rapid Mixer Granulator (RMG) approximately for 10 min. hydroxyl propyl cellulose (HPC) was dissolved in sufficient quantity of water, and used as a binder solution for F4 formulation, HPC directly mixed with excipients for formulation F3, olopatadine dissolved in sufficient quantity of water and used as binder in formulation F5. Formulation F6 to F10 were prepared by fluidized bed granulation method. Wet granules were dried at 60-65^{0}C till a loss on drying (LOD) of dried granules obtained is not more than 1.5% w/w. Dried granules were passed through sieve # 30. The dried granules were mixed with extragranular in a blender for 5 min. which was already passed through sieve # 40. The mixture was lubricated for 3 min. with magnesium stearate which was already passed through sieve # 60. The lubricated granules were then compressed in to tablets on a 16 station rotary machine punch size of 6.5 mm.

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TABLE 1: FORMULATION OF OLOPATADINE HCl IMMEDIATE RELEASE TABLETS

Trials	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Type of granulation	DC	DC	WG	WG	WG	FBG	FBG	FBG	FBG	FBG
	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab	mg/tab
Ingredients			Intra granular							
Olopatadine HCl	5	5	5	5	5	5	5	5	5	5
Lactose DCL	105.6	52.8	-	-	-	-	-	-	-	-
Lactose monohydrate	-	-	105.6	104.1	106.1	107.2	64.5	64.8	64.8	64.8
microcrystalline cellulose	-	-	-	-	-	-	42.52	39.9	39.9	39.9
Hydroxy propyl cellulose	4	4	4	4.5	3.5	2.4	2.4	3.5	3.5	3.5
Sodium starch glycolate	5	5	3	3	3	3	3	3	-	-
Crosspovidone XL	-	-	-	-	-	-	-	-	-	3
crosscarmellose sodium	-	-	-	-	-	-	-	-	3	-
Purified water	-	-	qs	qs	qs	qs	qs	qs	qs	qs
			Extragranular							
Lactose DCL	-	52.8	-	-	-	-	-	-	-	-
Sodium starch glycolate	-	-	2	3	2	2	2	3	-	-
Crosspovidone XL	-	-	-	-	-	-	-	-	-	3
crosscarmellose sodium	-	-	-	-	-	-	-	-	3	-
Magnesium Stearate	0.4	0.4	0.4	0.4	0.4	0.4	0.6	0.8	0.8	0.8
Tablet Weight	120	120	120	120	120	120	120	120	120	120

Evaluation:

All formulations F1 - F10 were analysed for precompression (angle of repose, carr's index, hausner's index) and postcompression (hardness, thickness, weight variation, disintegration time, content uniformity, in-vitro dissolution studies) parameters.

In-vitro dissolution study:

The dissolution studies of the prepared tablets were carried out using USP XXIII apparatus II. Dissolution was performed in 900 ml of pH 1.2 buffer medium at 37±0.5°C and at 50 rpm. Aliquots samples were withdrawn at 5, 10, 15, 30, 45 and 60 minutes and analysed by UV spectrophotometer at 220nm. Sink condition was maintained throughout experiment by replacing with pH 1.2 buffer medium.

RESULTS

All formulations F1 – F10 showed Precompression parameters and postcompression parameters like hardness, thickness, friability and weight variation were within acceptable limits in reference to innovator (Table 2 and Table 3). However variation in drug content was observed in formulations. Formulations F1 to F5 showed less than 95% drug content and formulations F6 to F10 showed more than 95% drug content which was comparable to innovator.

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TABLE 2: PRECOMPRESSION PARAMETERS

code	Angle of repose (°) Mean±S.D	Bulk density (gm/cc) Mean ±S.D	Tapped density (gm/cc) Mean ±S.D	Compressibility index Mean ±S.D	Hausner's ratio Mean ±S.D
F1	29.25 ± 0.21	0.352 ± 0.001	0.411 ± 0.002	14.43 ± 0.49	1.169 ± 0.007
F2	28.08 ± 0.45	0.352 ± 0.001	0.413 ± 0.002	14.77 ± 0.17	1.173 ± 0.002
F3	27.77 ± 0.54	0.357 ± 0.002	0.417 ± 0.002	14.4 ± 0.90	1.168 ± 0.01
F4	27.72 ± 0.23	0.35 ± 0.005	0.406 ± 0.01	13.86 ± 0.52	1.161 ± 0.01
F5	27.6 ± 0.16	0.357 ± 0.001	0.418 ± 0.002	14.51 ± 0.71	1.17 ± 0.009
F6	25.36 ± 0.23	0.265 ± 0.002	0.299 ± 0.001	11.16 ± 0.68	1.126 ± 0.008
F7	24.18 ± 0.47	0.274 ± 0.003	0.308 ± 0.002	11.15 ± 1.05	1.126 ± 0.13
F8	24.67 ± 0.24	0.284 ± 0.001	0.317 ± 0.001	10.31 ± 0.45	1.115 ± 0.01
F9	24.02 ± 0.40	0.285 ± 0.001	0.3172 ± 0.002	10.08 ± 0.50	1.112 ± 0.01
F10	24.26 ± 0.003	0.283 ± 0.002	0.308 ± 0.01	10.15 ± 0.06	1.113 ± 0.001

TABLE 3: POSTCOMPRESSION PARAMETERS

code	Thickness (mm) Mean±S.D	Hardness (Kg/cm^2) Mean±S.D	Friability (%) Mean±S.D	weight variation(mg) Mean±S.D	DT (sec) Mean±S.D	Drugcontent uniformity Mean±S.D (%)
F1	2.9±0.01	7.9±0.100	0.28±0.06	119.76±0.61	28.33±0.57	89.13±0.40
F2	2.87±0.001	7.93±0.25	0.27±0.04	120.86±0.63	29.33±1.15	90.62±0.35
F3	2.87±0.01	8.4±0.20	0.18±0.008	119.46±0.47	47.66±0.57	91.44±0.40
F4	2.9±0.01	8.1±0.20	0.18±0.005	119.93±0.12	48.66±0.57	91.49±0.24
F5	2.9±0.005	8.27±0.25	0.21±0.01	119.86±0.26	51.33±0.57	93.24±0.23
F6	2.91±0.01	8.07±0.15	0.15±0.008	119.56±0.54	52.33±1.15	98.33±0.28
F7	2.89±0.005	8.07±0.20	0.15±0.004	119.93±0.12	49±1.00	98.73±0.64
F8	2.91±0.005	8.33±0.37	0.15±0.008	119.66±0.77	65.33±1.52	98.62±0.54
F9	2.9±0.01	8.4±0.30	0.16±0.004	120.0±0.40	57.66±1.52	99.31±0.34
F10	2.9±0.01	8.23±0.30	0.15±0.004	120.03±0.12	54.66±1.52	99.1±0.14

The disintegration time (DT) of the different formulations (F1 to F10) is shown in Table 3. The effect of superdisintegrants and mode of incorporation of superdisintegrants were examined. It was shown that DT time ranged between 28.3 sec. to 65.3 sec., the least DT was taken by the formulation F1 (28.3 sec.) and maximum DT by F8 (65.3 sec.). There was no significant difference in DT observed between F1 and F2 ($P>0.05$) as they contain equal proportion of sodium starch glycolate (SSG), in both cases the SSG was incorporated intragranular. Comparison of the effect of intragranular and extragranular incorporation of SSG in formulation F3 to F6 indicated that, there was no significant influence brought out by the mode of incorporation of superdisintegrants, though all these formulations contain equal proportion of superdisintegrants. However comparison of F1 and F2 with F3 to F6 in respect of DT indicated that, the process of incorporation of SSG appeared to increase the DT. DT of F8 (65.3 sec.) was higher than that of F7 (49 sec.) [$P<0.001$], though the process of incorporation of Superdisintegrant was same in these two formulations. On increasing the concentration of SSG in extragranular addition has increased the DT of the formulations. This finding suggests

that the concentration of the SSG is influencing factor on DT rather than the process of incorporation of superdisintegrants. Overall crospovidone XL showed comparatively faster disintegration times than croscarmellose sodium and sodium starch glycolate. Crospovidone are densely cross-linked homopolymers of N-vinyl 2-pyrrolidones. Their porous particle morphology enables them to rapidly absorb liquids into the tablet by capillary action and to generate rapid volume expansion and hydrostatic pressures that result in tablet disintegration [9].

In-vitro dissolution studies:

The release profile for formulations F6 to F10 was carried out at pH 1.2 buffer medium. Each experiment was done three times (Table 4 and Figure 1). The release study was limited to the above formulations based on the acceptable limit for drug content 95 to 102% with reference to innovator. Formulations F6 to F10 showed 90% drug release in 60 min and the maximum percentage release (99.35%) was observed in the formulation F10 in 45 min as compared to other formulations. Although crosspovidone XL, crosscarmellose sodium (CCS) and sodium starch glycolate (SSG) are used to provide the same function within formulation, they differ in their chemical structure, particle morphology and powder properties. The results showed that crosspovidone XL achieve much faster dissolution of olopatadine in 45 min when compared to SSG and CCS. It is also understood that the concentration of diluents (lactose monohydrate, MCC) or the mode of addition of superdisintegrants (intragranular or Extragranular) did not seem to have influence on the dissolution of olopatadine as all formulations have shown dissolution of about 90% in 60 min. Comparison of dissolution between the formulations showed that the formulation F10 containing crosspovidone XL showed faster dissolution of olopatadine in a shorter time (45min) however not significantly as compared to other formulation (F6 to F9, $P>0.05$). This finding clearly demonstrates that all three superdisintegrants (SSG, CCS, crosspovidone XL) appear to influence the drug dissolution rate at the same level. On comparison between innovator and prepared formulations no significant difference in dissolution rate was noted ($P>0.05$).

The similarity factor f2 was applied to compare dissolution profile of formulations F6 to F10 with marketed product (innovator) in pH 1.2 buffer medium. It was observed that the dissolution profile of the above formulations were similar to that of innovator (f2 = 50-100), however the highest f2 value was obtained with formulation F10 (91.9). based on f2 value it can be suggested that crosspovidone seems to be an ideal superdisintegrant for achieving faster dissolution of olopatadine.

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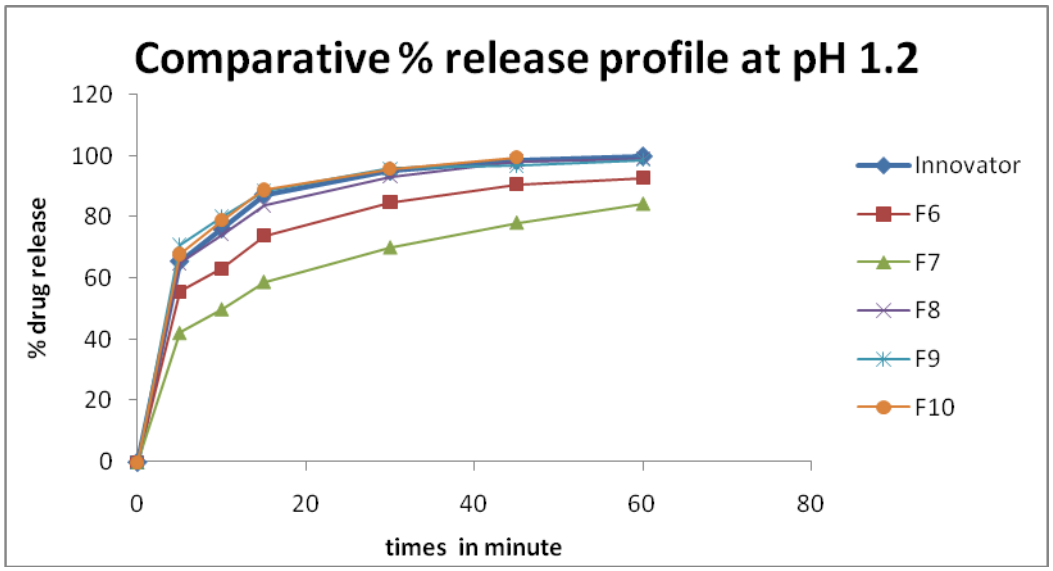
TABLE 4: COMPARATIVE % RELEASE PROFILE OF F6 TO F10 AT PH 1.2

time in minute	Innovator	F6	F7	F8	F9	F10
0	0	0	0	0	0	0
5	65.7	55.71	57.24	64.99	70.74	67.86
10	76.4	63.21	67.08	74.37	80.01	78.95
15	87.5	73.99	76.33	83.76	88.45	88.69
30	95.2	84.89	87.29	93.19	95.74	95.59
45	98.6	90.75	92.70	97.91	96.61	99.35
60	100	92.78	95.22	98.92	98.47	-
f2	-	56.03	61.5	87.98	82.9	91.9

FIGURE 1: COMPARATIVE % RELEASE PROFILE OF FORMULATION F6 TO F10 WITH INNOVATOR



DISCUSSION

Dissolution is essential for a drug to be absorbed through biological membrane into systemic circulation for therapeutic efficacy. Conventional tablet formulations generally required rapid disintegration to aid dissolution. Super disintegrations are added to oral dosage formulations to facilitate disintegration. Commonly used superdisintegrants such as crosspovidone XL, crosscarmellose sodium, and sodium starch glycolate are highly efficient at low concentration levels (2–5 w/w %) in the tablet formulation for facilitating the rate and extent of tablet disintegration.

Several approaches have been followed for the preparation of immediate release tablet formulations. They are dry, wet granulation and fluidized bed granulation methods. Commercial literature suggests that more often dry or wet granulation method have been employed for the manufacturing of immediate release tablet formulation of olopatadine. Fluidized bed granulation is another approach which yields products of high quality like uniformity of drug

contents, high percentage yield, and least batch to batch variation. However it is considered that fluidized bed granulation approach may not be cost effective as compared to dry or wet granulation methods.

In this study immediate release tablet formulation of olopatadine was developed by direct compression, wet granulation and fluidized bed granulation methods using varying proportion of super disintegrants such as crosspovidone XL, CCS and SSG. The effect of processing method and super disintegrants on physico-chemical and in-vitro release characteristic of olopatadine was also examined. It was observed that the physico-chemical characteristics like flow properties, solid state characteristic by DSC analysis were not significantly influenced by either super disintegrants or other excipients such as HPC. The release profile of all formulations (F6 to F10) prepared by fluidized bed granulator indicate that the drug dissolution rate was not significantly influenced by type of super disintegrants and mode of incorporation (extragranular or intragranular). However, analyzing similarity factor f_2 to compare dissolution profile of these formulations showed that the highest f_2 value was found in F10 formulation that indicates corspovidone XL as the best superdisintegrant for achieving faster dissolution of Olopatadine.

Immediate release tablet formulation of olopatadine can be developed by proper selection of super disintegrations in order to achieve faster dissolution of characteristics of the drug. More importantly fluidized bed granulation method appears promising for development of immediate release tablet formulation of olopatadine with higher drug content suitable for reaching therapeutic efficacy of drug as compared to wet granulation or direct compression. The mode of addition of super disintegrants or other excipients did not seem to affect the physico-chemical and in-vitro release characteristic of olopatadine.

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