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FORMULATION DESIGN OF FAST DISSOLVING TABLETS OF FEXOFENADINE HYDROCHLORIDE BY SUBLIMATION METHOD

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ABSTRACT

In the present work, fast dissolving tablets of fexofenadine hydrochloride were designed with a view to enhance patient compliance by sublimation method. In this method, camphor was used as the subliming agent (upto 30% w/w), crospovidone and croscarmellose sodium (2-8% w/w) were used as super-disintegrants. Estimation of fexofenadine hydrochloride in the prepared tablet formulations was carried out by extracting the drug with methanol and measuring the absorbance at 259 nm. The prepared formulations were further evaluated for hardness, friability, drug content uniformity, *in vitro* dispersion time, wetting time and water absorption ratio,. Based on *in vitro* dispersion time (approximately 5-14 sec), two promising formulations (one from each super-disintegrant) were tested for *in vitro* drug release pattern in pH 6.8 phosphate buffer and short-term stability (at 40ºC/ 75% RH for 3 months) and drug-excipient interaction (IR spectroscopy) were studied. Among the two promising formulations, the formulation (SCP_3) containing 8% w/w of crospovidone and 30% w/w camphor as the subliming agent emerged as the overall best formulation ($t_{50\%}$4.3 min) based on drug release characteristics in pH 6.8 phosphate buffer compared to commercial conventional tablet formulation ($t_{50\%}$15 min). Short-term stability studies on the promising formulations indicated that there are no significant changes in drug content and *in vitro* dispersion time ($p<0.05$).

KEYWORDS: Fexofenadine hydrochloride, fast dissolving tablets, Cros-carmellose sodium, Crospovidone

INTRODUCTION

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus does not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. It is estimated that 50% of the population is affected by this problem. Recent advances in Novel Drug Delivery Systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is "Fast Dissolving Tablets (FDT)[1-4]". Fexofenadine HCl (FXD), is a non-sedating anti-

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histamine used in the symptomatic relief of allergic conditions including seasonal allergic rhinitis and urticaria[5]. The concept of formulating fast dissolving tablets containing taste masked fexofenadine HCl offers a suitable and practical approach in serving desired objective of faster disintegration, dissolution characteristics, non-bitter with good mouth feel and increased bioavailability.

MATERIALS

Fexofenadine HCl (FXD) was a gift sample from Aurobindo Pharmaceuticals, Hyderabad. Cros-carmellose sodium (CCS) and Crospovidone (CP) were gift samples from Wockhardt Research Centre, Aurangabad. All the other ingredients were of analytical grade.

EXPERIMENTAL

Preparation of Fast Dissolving Tablets by Sublimation Method[6]

The ingredients after sifting through sieve No. 44 were thoroughly mixed in a tumbling cylindrical mixer for 10 m at 15 rpm. Then aerosil was sifted through sieve No. 100 and added to blend to impart the hardness to the tablet and thoroughly mixed. The tablets were compressed on 7 mm flat round punch. The compressed tablets were then subjected to sublimation at 60ºC for 6 hours in a hot air oven. The tablets were evaluated for *in vitro* dispersion time in pH 6.8 phosphate buffer and mean tablet weight before and after sublimation. The formulae used for the preparation of tablets were shown in table-1.

TABLE 1

Composition of Different Batches of Fast Dissolving Tablets of Fexofenadine Hydrochloride

Ingredients* (mg)	Formulation Code						
	SC_0	SCP_1	SCP_2	SCP_3	$SCCS_1$	$SCCS_2$	$SCCS_3$
Fexofenadine HCl	30.00	30.00	30.00	30.00	30.00	30.00	30.00
Camphor	30.00	15.00	30.00	45.00	15.00	30.00	45.00
Crospovidone	--	3.00	7.50	12.00	--	--	--
Croscarmellose sodium	--	--	--	--	3.00	7.50	12.00
Aerosil (2%)	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Aspartame	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Pineapple flavor	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Talc	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Sodium stearyl fumarate	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Mannitol	72.00	84.00	64.50	45.00	84.00	64.50	45.00

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Total	150.00	150.00	150.00	150.00	150.00	150.00	150.00

** All the quantities expressed are in mg/ tablet*

Formulations SCP_3 and $SCCS_3$ were selected as the promising and used for further studies.

Evaluation of tablets

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation[7]. Hardness and friability of the tablets were determined by using Monsanto Hardness Tester and Roche friabilator respectively. For content uniformity test, ten tablets were weighed and powdered. The powder equivalent to 30 mg of FXD was extracted into methanol and liquid was filtered (Whatmann No. 1 filter paper). The FXD content in the filtrate was determined by measuring the absorbance at 259 nm after appropriate dilution with methanol. The drug content was determined using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations[8]. For determination of wetting time and water absorption ratio[9], a piece of tissue paper folded twice was placed in a small petridish (internal diameter of 5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio 'R' was calculated using the equation: $R=100(W_a–W_b)/W_a$; where W_a is weight of tablet after water absorption and W_b is weight of tablet before water absorption. For determination of *in vitro* dispersion time, one tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5º and the time required for complete dispersion was determined[10]. IR spectra of FXD and its formulations were obtained by KBr pellet method using Perkin-Elmer FTIR series (Model 1615) spectrophotometer in order to rule out drug-carrier interactions.

Dissolution study[11]

In vitro dissolution of FXD fast dissolving tablets was studied in USP XXIII type-II dissolution apparatus (Electrolab, Model-TDT 06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5º as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium (5 ml) were withdrawn at specified intervals of time and analyzed for drug content by measuring the absorbance at 259 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of FXD released was calculated and plotted against time.

Stability Testing

Short-term stability studies on the promising formulations (SCP_3 and $SCCS_3$) were carried out by storing the tablets at 40º/ 75% RH over a 3 month period. At an intervals of one month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time.

RESULTS AND DISCUSSION

Fast dissolving tablets of fexofenadine HCl were prepared by sublimation method employing crospovidone and croscarmellose sodium as super-disintegrants in different ratios along with up to 30% w/w of camphor as a subliming agent. Directly compressible mannitol (Pearlitol SD 200) was used as a diluent to enhance mouth feel. A total of six formulations and a control formulation SC_0 (without super-disintegrant) were designed. As the blends were free flowing (angle of repose <30º, and Carr's

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index <15%) tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specification i.e., below 7.5%. Drug content was found to be in the range of 95 to 99%, which is within acceptable limits. Hardness of the tablets was found to be within 2.6 Kg/cm². Friability below 1% was an indication of good mechanical resistance of the tablets. Water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 54-80% and 7-66 s respectively. Among all the designed formulations, two formulations, viz., SCP_3 and $SCCS_3$ were found to be promising and displayed an *in vitro* dispersion time ranging from 6 to 14 s, which facilitates their faster dispersion in the mouth.

Overall, the formulation SCP_3 containing 8% w/w of crosspovidone along with 30% w/w of camphor as a subliming agent was found to be promising and has shown an *in vitro* dispersion time of 6 s, wetting time of 7 s and water absorption ratio of 80.0% when compared to control formulation (SC_0) which shows 238 s, 246 s and 51% values respectively for the above parameters (Table 2).

In vitro dissolution studies on the promising formulations (SCP_3 and $SCCS_3$), the control (SC_0) and commercial conventional formulations (CCF) were carried out in pH 6.8 phosphate buffer, and the various dissolution parameter values viz., percent drug dissolved in 5 m, 10 m and 15 m (D_5, D_{10} and D_{15}), dissolution efficiency at 10 m (DE_{10} m)[12], $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ are shown in table 3 and the dissolution profiles depicted in Fig. 1. This data reveals that overall, the formulation SCP_3 has shown nearly three and half-fold faster drug release ($t_{50\%}$ 4.3 m) when compared to the commercial conventional tablet formulations of fexofenadine HCl ($t_{50\%}$ 15 m) and released 5-times more drug than the control formulation in 10 m.

TABLE 2

Evaluation of Fast Dissolving Tablets of Fexofenadine Hydrochloride

Parameters	Formulation code						
	SC_0	SCP_1	SCP_2	SCP_3	$SCCS_1$	$SCCS_2$	$SCCS_3$
Hardness*±SD (kg/cm²)	2.53±0.152	2.56±0.152	2.6±0.20	2.5±0.152	2.59±0.02	2.55±0.05	2.60±0.01
Thickness	2.19	2.24	2.29	2.26	2.21	2.26	2.3
Friability (%)	0.82	0.75	0.84	0.74	0.8	0.78	0.82
Percent drug content*±SD	97.74±0.62	97.76±0.72	95.68±0.592	99.03±0.78	97.77±0.62	99.03±0.78	95.68±0.59
In vitro dispersion	237.77±3.31	49.05±1.67	19.06±1.54	5.67±0.73	62.23±1.98	25.57±0.70	14.41±0.69

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time*±SD (Sec)							
Wetting time*±SD (sec)	245.63±2.63	54.02±1.18	21.89±1.92	7.26±0.92	65.94±1.72	29.59±1.32	17.61±1.30
Water absorption ratio*±SD (%)	50.57±2.05	59.54±1.38	76.81±2.46	80.22±0.91	54.27±1.12	70.17±0.98	76.24±0.98
Weight Variation	(148 – 154 mg) within the IP limits of ±7.5%						

**Average of three determinations*

TABLE 3

***In Vitro* Dissolution Parameters in pH 6.8 Phosphate Buffer**

Formulation code	D_5 (%)	D_{10} (%)	D_{15} (%)	DE_{10} m (%)	$t_{50\%}$ (m)	$t_{70\%}$ (m)	$t_{90\%}$ (m)
SC_0	6.00	17.00	22.00	18.41	>30	>30	>30
SCP_3	52.00	85.00	100.00	49.12	4.3	8.3	11.0
$SCCP_3$	45.00	77.00	100.00	49.12	6.1	9.2	12.4
CCF	26.00	41.00	49.00	31.34	15.00	>30	>30

SC_0=Control formulation (without superdisintegrant), CCF=conventional commercial formulation, D_5=percent drug released in 5 m, D_{10}=percent drug released in 10 m, D_{15}=percent drug released in 15 m, DE_{10} m=dissolution efficiency in 10 m, $t_{50\%}$=time for 50% drug dissolution, $t_{70\%}$=time for 70% drug dissolution.

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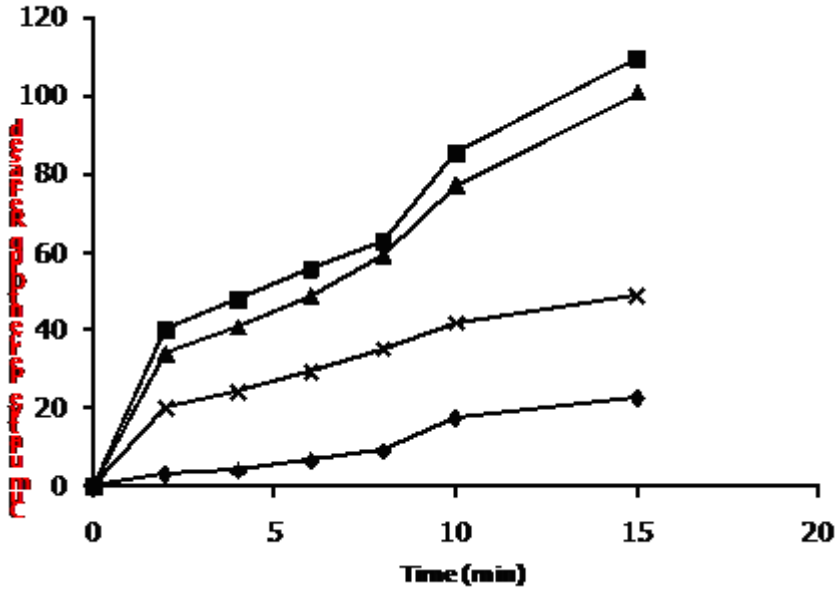
Fig. 1

Percent cumulative release of FXD from FDTs in pH 6.8 phosphate buffer



Plot showing cumulative percent drug release of fexofenadine HCl from FDTs of control formulation (FXD) and superdisintegrant used formulations at pH 6.8. (–♦–) Control formulation, (–■–) Crospovidone used tablet, (–▲–) Croscarmellose sodium used tablet, (–x–) Commercial conventional tablet.

IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of SCP_3, $SCCS_3$ showed all the characteristic peaks of fexofenadine HCl pure drug, thus confirming that no interaction of drug occurred with the components of the formulation. Short-term stability studies of the above formulations indicated that there are no significant changes in drug content and *in vitro* dispersion time at the end of 3 months period ($p<0.05$).

CONCLUSION

The present study conclusively indicates that formulation SCP_3 is very much promising as mouth dissolving (fast disintegrating) tablets of fexofenadine HCl with an *in vitro* dispersion of less than 6 sec.

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