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Research Article

FORMULATION AND EVALUATION OF MONTELUKAST SODIUM AND LEVOCETIRIZINE DIHYDROCHLORIDE SUBLINGUAL TABLETS

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ABSTRACT

Objective: The objective of the current study was to develop and optimize sublingual tablets of montelukast sodium and levocetirizine dihydrochloride which are effective drugs in the treatment of asthma.

Methods: The sublingual tablets of montelukast sodium and levocetirizine dihydrochloride were prepared by direct compression method using sodium starch glycolate, crospovidone (CP), and croscarmellose sodium (CCS) as superdisintegrants. The tablets were evaluated for physical properties including hardness, weight variation, thickness, friability, drug content, wetting time, water absorption ratio, *in vitro* disintegration time, and *in vitro* dissolution study.

Results: The hardness, weight variation, thickness, friability, and drug content of tablets were within pharmacopoeial limits. An optimized tablet formulation F8 was found to have short wetting time of 18.36 seconds, water absorption ratio of 94.42 and *in-vitro* disintegration time of 45.42 seconds. The results indicated that the amount of super disintegrants such as CP and CCS significantly affected the dependent variables like wetting time, water absorption ratio and *in-vitro* disintegration time. The *in-vitro* drug release was found to be higher for formulation F8 with 94.59% for montelukast sodium and 95.48% for levocetirizine dihydrochloride within 60 minutes. The drug release improved by 1.88 times for montelukast sodium and 1.82 times for levocetirizine dihydrochloride compared to oral marketed immediate release tablet formulation.

Conclusion: From the present study, it can be concluded that sublingual route has potential to improve the bioavailability of the drug by avoiding first pass metabolism, to provide quicker onset of action and to improve patient compliance in the management of asthma.

Keywords: Sublingual tablet, Montelukast Sodium, Levocetirizine Dihydrochloride, *In vitro* dissolution study.

INTRODUCTION

The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes [1-3].

Montelukast sodium is a leukotriene receptor antagonist used in maintenance treatment of asthma and to relieve symptoms of seasonal allergies. It shows high hepatic first pass metabolism and low bioavailability and is effective at low dose. It is usually administered orally [4].

Levocetirizine dihydrochloride is an orally active, third generation, non-sedating selective peripheral H1-receptor antagonist used in seasonal allergic rhinitis, perennial allergic rhinitis, and chronic urticaria. It shows high hepatic first pass metabolism and low bioavailability and is effective at low dose. Allergy is a common problem among all age groups. These diseases require rapid onset of action in order to provide fast relief [5].

In the present study, an attempt has been made to prepare combination tablets of montelukast sodium and levocetirizine dihydrochloride for the treatment of allergic rhinitis using superdisintegrants like crospovidone (CP), croscarmellose sodium (CCS), and sodium starch glycolate (SSG). The superdisintegrants help to increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tablets. These systems may offer superior profile with potential mucosal absorption, thus increasing the drug bioavailability [6].

METHODS

Montelukast sodium was a kind gift sample from Mylan Laboratories, Hyderabad. Levocetirizine dihydrochloride was obtained as gift sample from Symed Laboratories, Hyderabad. CP, CCS, SSG, mannitol, microcrystalline cellulose, talc, and magnesium stearate were obtained from S.D. Fine Chemicals. Pvt. Ltd., India. All chemicals and solvents used were of analytical grade.

Preparation of sublingual tablets

Combination of levocetirizine dihydrochloride and montelukast sodium sublingual tablets was prepared by the direct compression method using different excipients [7]. The excipients used were microcrystalline cellulose (binding agent), mannitol (diluent), saccharine sodium (sweetening agent), and CP, CCS, SSG (super disintegrants). Different concentration of excipients was used to prepare different group of sublingual tablets. Compositions of various formulations are shown in Table 1. All the ingredients were weighed and mixed in a mortar with the help of the pestle. Then the blended material was compressed on the 9 mm flat-biconvex punch using a Rimek MINI PRESS-I MT Rimek Machinery Co. Pvt. Ltd., Gujarat. The total weight of the formulation was maintained at 200 mg.

Evaluation of formulated sublingual tablets of montelukast sodium and levocetirizine dihydrochloride

The evaluation of physicochemical parameters of montelukast sodium and levocetirizine dihydrochloride sublingual tablets was done as per standard procedures. The following parameters were evaluated.

Evaluation of pre-compression parameters of powder

Prior to compression, powder was evaluated for flow and compressibility parameters. Flow properties of powder were determined by angle of repose method. Compressibility index of powder was determined by Carr's index and Hausner ratio. The results are shown in Table 2.

Evaluation of post-compression parameters of tablets

Hardness [8]

The test was done as per the standard methods. The hardness of three randomly selected tablets from each formulation (F1-F9) was

determined by placing each tablet diagonally between the two plungers of tablet hardness tester (with the nozzle) and applying pressure until the tablet broke down into two parts completely and the reading on the scale was noted down in kg/cm^2. The results are presented in Table 3.

Thickness [8]

The thickness of three randomly selected tablets from each formulation was determined in mm using a vernier calliper (Pico India). The average values were calculated. The results are presented in Table 3.

Uniformity of weight [9]

Weight variation test was done as per standard procedure. 20 tablets from each formulation (F1-F9) was weighed using an electronic balance, and the average weight was calculated. The results are shown in Table 3.

Friability[9]

The friability of tablets was measured using six tablets using a Roche friabilator. Tablets were rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets were taken out, dedusted, and reweighed. The percentage friability was calculated from the loss in weight as given in equation below. The weight loss should not more than 1%. The results are shown in Table 3.

Friability (%) = ([Initial weight − Final weight]/initial weight) × 100

Drug content [10]

10 tablets were powdered and the powder equivalent to 15 mg was dispersed in phosphate buffer pH 6.8. Volume of the solution made up to 10 mL by media. The mixture was filtered and 1 ml of the filtrate was diluted to 10 mL using phosphate buffer pH 6.8. The absorbance of the sample preparations was measured at λmax 352.0 nm for montelukast sodium and 231.0 nm for levocetirizine dihydrochloride. The results are presented in Table 4.

Wetting time [11]

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of phosphate buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviation were also determined. The results are presented in Table 4.

Water absorption ratio [11]

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wet tablet was then weighed. Water

Table 1: Composition of montelukast sodium and levocetirizine dihydrochloride sublingual tablets formulations

Ingredients	Quantity for tablet (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Montelukast sodium	10	10	10	10	10	10	10	10	10
Levocetirizine dihydrochloride	5	5	5	5	5	5	5	5	5
CP	5	10	-	-	10	5	10	10	-
SSG	10	5	10	5	-	-	10	-	10
CCS	-	-	5	10	5	10	-	10	5
MCC	25	25	25	25	25	25	25	25	25
Sodium saccharine	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2	2	2	2
Mannitol	137	137	137	137	137	137	132	132	132

CP: Crospovidone, SSG: Sodium starch glycolate, CCS: Croscarmellose sodium, MCC: Microcrystalline cellulose

Table 2: Evaluation of montelukast sodium and levocetirizine dihydrochloride sublingual tablets (pre-compression parameters)

Formulation code	Bulk density* (g/ml)	Tapped density* (g/ml)	Compressibility/ Carr's index* (%)	Hausner's ratio*	Angle of repose*(°)
F1	0.472±0.71	0.549±0.16	14.026±0.23	1.163±0.07	28.56±0.31
F2	0.481±0.33	0.539±0.45	10.761±0.15	1.120±0.06	29.53±0.24
F3	0.441±0.46	0.514±0.06	14.202±0.08	1.165±0.05	27.95±0.19
F4	0.452±0.19	0.526±0.15	14.068±0.14	1.163±0.04	26.57±0.32
F5	0.471±0.55	0.547±0.22	13.894±0.24	1.161±0.06	28.75±0.27
F6	0.462±0.09	0.543±0.43	14.917±0.16	1.175±0.07	29.64±0.17
F7	0.456±0.54	0.537±0.17	15.084±0.22	1.177±0.03	26.37±0.11
F8	0.451±0.05	0.501±0.14	9.980±0.11	1.110±0.05	22.56±0.12
F9	0.445±0.61	0.521±0.18	14.587±0.12	1.170±0.07	28.53±0.22

*Values represented as mean±SD (n=3), SD: Standard deviation

Table 3: Evaluation of montelukast sodium and levocetirizine dihydrochloride sublingual tablets (post-compression parameters)

Formulation code	Thickness* (mm)	Hardness* (kg/cm^2)	Weight variation* (mg)	Friability* (%)
F1	2.3±0.02	3.5±0.31	200.03±0.09	0.394±0.02
F2	2.3±0.01	3.4±0.16	199.94±0.13	0.426±0.05
F3	2.2±0.03	3.3±0.17	199.52±0.06	0.532±0.01
F4	2.3±0.01	3.6±0.23	199.37±0.14	0.511±0.06
F5	2.2±0.01	3.2±0.28	199.46±0.22	0.346±0.03
F6	2.3±0.03	3.7±0.14	199.87±0.24	0.372±0.05
F7	2.2±0.01	3.3±0.23	199.73±0.09	0.416±0.04
F8	2.2±0.03	3.4±0.26	200.10±0.16	0.513±0.06
F9	2.3±0.02	3.7±0.23	199.79±0.23	0.379±0.05

*Values represented as mean±SD (n=3), SD: Standard deviation

Table 4: Evaluation of montelukast sodium and levocetirizine dihydrochloride sublingual tablets

Formulation code	Wetting time* (seconds)	Disintegration time* (seconds)	Water absorption ratio*	Drug content *(%)	
				Montelukast sodium	Levocetirizine dihydrochloride
F1	26.54±0.87	56.52±1.43	78.69±2.11	97.21±1.49	95.31±0.91
F2	34.16±1.84	61.34±1.85	78.61±1.34	99.89±2.16	100.31±0.75
F3	30.83±1.69	74.35±1.64	84.53±1.86	95.47±0.65	96.56±1.29
F4	26.51±2.01	67.51±0.76	75.61±1.77	98.61±1.35	97.81±1.46
F5	25.64±1.74	61.34±1.82	83.65±2.12	97.56±1.75	99.69±0.45
F6	33.56±1.65	55.26±1.47	85.67±1.76	95.70±0.91	101.88±1.64
F7	20.34±2.03	48.33±1.75	91.22±1.65	96.98±1.22	95.94±2.13
F8	18.36±1.55	45.42±1.49	94.42±1.44	101.63±0.79	99.06±1.32
F9	21.03±1.72	49.67±2.05	90.34±1.85	97.32±1.54	98.13±1.47

*Values represented as mean±SD (n=3), SD: Standard deviation

Table 5: Comparative dissolution data of oral marketed immediate release formulation and optimized formulation

Time (minutes)	Cumulative % drug release (optimized formulation)		Cumulative % drug release (oral marketed immediate release formulation)	
	Montelukast sodium	Levocetirizine dihydrochloride	Montelukast sodium	Levocetirizine dihydrochloride
0	0	0	0	0
5	21.94	28.8	15.44	16.93
10	27.12	33.20	19.39	20.99
15	32.34	37.18	23.57	24.08
30	57.70	53.25	32.19	33.56
45	76.03	78.14	41.54	42.69
60	95.48	94.59	50.32	52.35

absorption ratio, R was determined using the following equation. The results are presented in Table 4.

Water absorption ratio (R) = $([W_a - W_b]/W_b]) \times 100$

In-vitro disintegration time [12]

Disintegration time for sublingual tablets was determined using USP tablet disintegration apparatus with phosphate buffer of pH 6.8 as medium. The volume of medium was 900 ml and temperature was 37±0.5°C. The time in seconds taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured. The results are presented in Table 4.

In-vitro dissolution studies [13]

Dissolution study was conducted for all the formulations using USP dissolution test apparatus Type-II (Electrolab, Mumbai, India). 900 ml of phosphate buffer (pH 6.8) was taken as the dissolution medium and rotated at 50 rpm. Temperature was maintained at 37°C±0.5°C for 60 minutes. Five ml of aliquots were periodically withdrawn, and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were filtered, diluted suitably and analyzed at λmax 231.0 nm for levocetirizine dihydrochloride and 352.20 nm for montelukast sodium. The results obtained for all the formulations are represented in Figs. 1 and 2.

Drug-excipient compatibility studies by Fourier transform infrared (FTIR)

The FTIR studies were performed to study drug-excipient interaction in the range 4000-400/cm using an FTIR spectrometer (IR AFFINITY-1 CE, Shimadzu, Japan) equipped with a pyroelectric detector. Data were acquired using IR solution software. The FTIR spectra of montelukast sodium, levocetirizine dihydrochloride, and optimized formulation are shown in Figs. 3-4.

RESULTS AND DISCUSSION

The bulk densities of the blend were found to be in the range of 0.445-0.481 g/ml. The angle of repose varied from 22.56° to 29.64°.

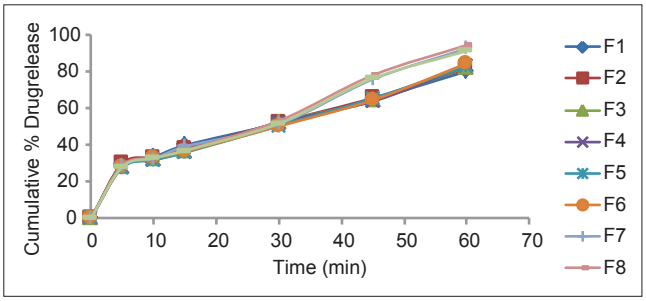

Fig. 1: *In vitro* dissolution profile of all formulations (montelukast sodium)

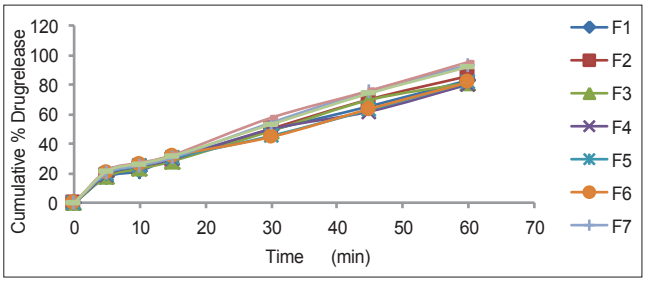

Fig. 2: *In vitro* dissolution profile of all formulations (levocetirizine dihydrochloride)

The low values of angle of repose indicate the free flowing nature of the blend. The tapped densities ranged from 0.501 to 0.549 g/ml, and the Carr's indices were in the range of 9.98-15.084. Hausner ratio was found in the range of 1.11-1.177. The values of compressibility index further confirmed the good compressibility of the prepared blends.

The prepared tablets were evaluated for their hardness, thickness, weight variation, friability, and the results are presented in Table 3. The weight variation was found to be within the prescribed limits, and it

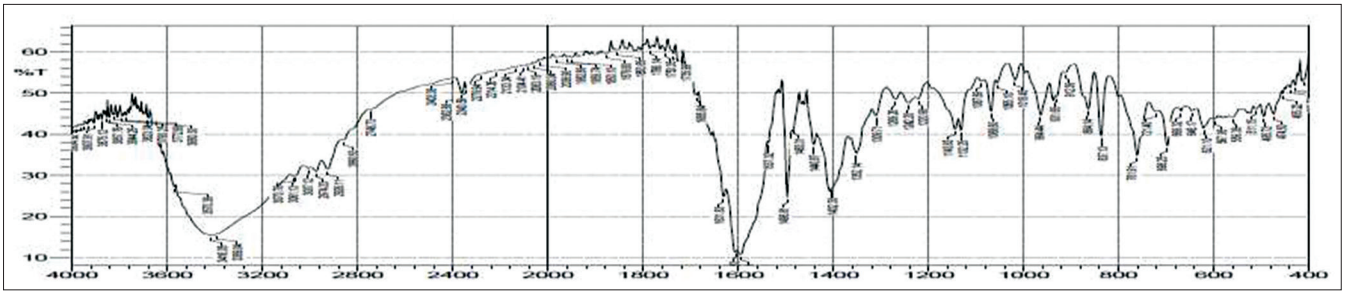

Fig. 3: Fourier transform infrared spectrum of montelukast sodium

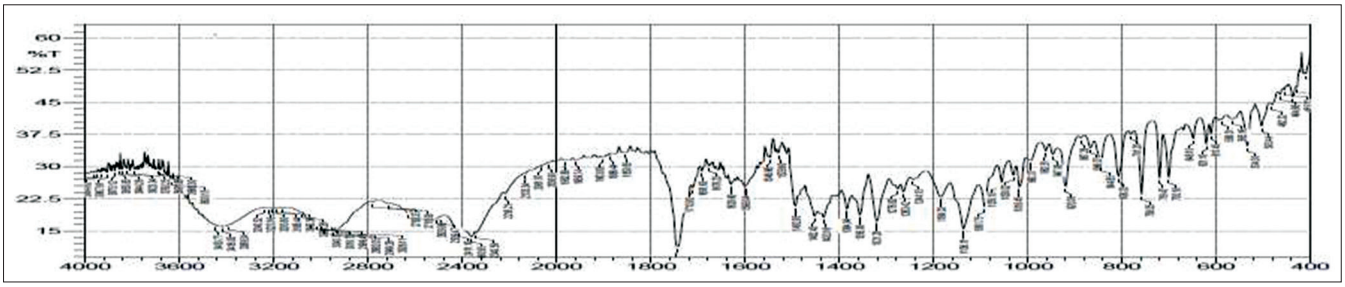

Fig. 4: Fourier transform infrared spectrum of levocetirizine dihydrochloride

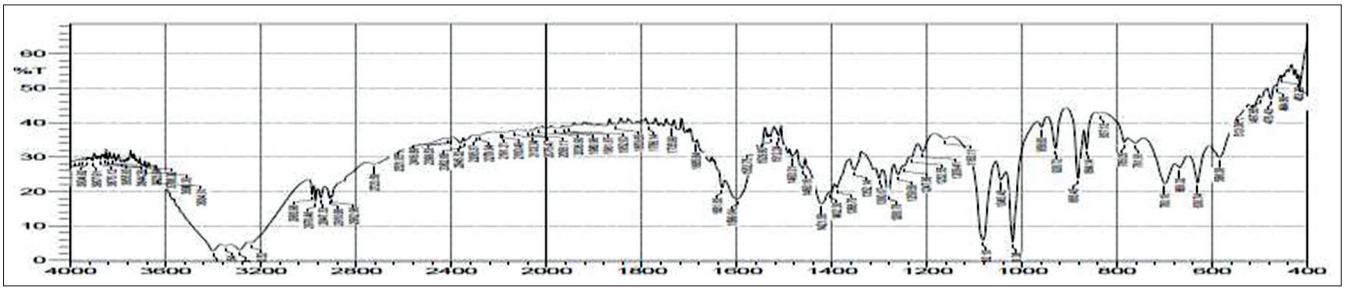

Fig. 5: Fourier transform infrared spectrum of optimized formulation

varies between 199.37 and 200.10. Hardness was found to be in the range of 3.2-3.7 kg/cm^2. Thickness was found to be in the range of 2.2-2.3 mm. Friability was found to be <1% in all the batches, which indicates the tablets' ability to withstand shock during the time of transportation and handling. It is clear from the above said factors that the physical parameters evaluated for the different batches of tablets were within the prescribed limits.

The prepared tablets were evaluated for their disintegration time, wetting time, water absorption ratio, and drug content uniformity and the results are shown in Table 4. The disintegration time varied from 45.42 to 74.35 seconds. The disintegration time was less for formulation F8 which was prepared using CCS and CP. The wetting time varied from 18.36 to 34.16 seconds. Water absorption ratio varied from 75.61 to 94.42. Drug content was uniform within the prepared batches and ranged between 95.47 and 101.63% for montelukast sodium and 95.31-101.88%. It is clear from the above said factors that the physical parameters evaluated for the different batches of tablets were within the prescribed limits.

***In vitro* dissolution studies of sublingual tablets (montelukast sodium and levocetirizine dihydrochloride)**

The drug release pattern of sublingual tablets varied according to the amount of super disintegrant added, and it was found that as the amount of superdisintegrants increases, the drug release increased. The percentage drug release of montelukast sodium and levocetirizine dihydrochloride was found to highest for formulation F8, i.e., 94.59% and 95.48%, respectively, in 60 minutes. The *in vitro* dissolution profiles are depicted in Figs. 1 and 2.

From Table 5, it can be inferred that the drug release of optimized formulation was found to be higher than the oral marketed immediate release formulation. The drug release improved by 1.88 times for montelukast sodium and 1.82 times for levocetirizine dihydrochloride as compared to oral marketed immediate release formulation.

CONCLUSIONS

Sublingual tablets of montelukast sodium and levocetirizine dihydrochloride were successfully prepared by direct compression method using SSG, CP and CCS as superdisintegrants. Sublingual tablets are a promising dosage form to achieve rapid drug release and quicker onset of action which is a prerequisite in the management of asthma.

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REFERENCES

1. Birudaraj R, Berner B, Shen S, Li X. Buccal permeation of buspirone: Mechanistic studies on transport pathways. J Pharm Sci 2005;94(1):70-8.
2. Price TM, Blauer KL, Hansen M, Stanczyk F, Lobo R, Bates GW. Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17 beta-estradiol. Obstet Gynecol 1997;89(3):340-5.
3. Ishikawa T, Koizumi N, Mukai B, Utoguchi N, Fujii M, Matsumoto M,

et al. Pharmacokinetics of acetaminophen from rapidly disintegrating compressed tablet prepared using microcrystalline cellulose (PH-M-06) and spherical sugar granules. Chem Pharm Bull (Tokyo) 2001;49(2):230-2.

4. Priyanka, Pragati Kumar B. Formulation development and evaluation of montelukast sodium chewable tablets. J Chem Pharm Sci 2013;1(6):35-40.
5. Saini S, Nanda A, Hooda M, Komal Dhari J. Formulation and evaluation of mouth dissolving anti-allergic tablets of levocetirizine dihydrochloride. J Chem Pharm Res 2011;3(5):450-5.
6. Sangeetha S, Venkatesh DN, Krishan PN, Saraswathi R. Mucosa as a route for systemic drug delivery. Res J Pharm Biol Chem Sci 2010;1(6):178-87.
7. Rowe RC, Sheskey PJ, Weller PJ. Hand Book of Pharmaceutical Excipients. 4th ed. London, UK: Pharmaceutical Press; 2003. p. 108-581.
8. Basak SC, Selvin CD, Sabapathy R. Formulation and *in-vitro* evaluation of amoxicillin dispersible tablets. Indian Pharm 2006;5(49):71-3.
9. Lachman L, Lieber HA. Pharmaceutical Dosage Forms of Tablets. Vol. II. New York: Marcel Dekker; 1981. p. 241-3.
10. Indian Pharmacopoeia. Vol. II. Delhi: Ministry of Health and Family Welfare, Government of India; 1996. p. 350.
11. Chowdhary KP, Rao NR. Formulation and evaluation of dispersible tablets with pregelatinised starch. Indian Drugs 1998;35(6):368-70.
12. 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;44(11):2121-7.
13. Elder EJ, Evans JC, Scherzer BD, Hitt JE, Kupperblatt GB, Saghir SA, *et al.* Preparation, characterization, and scale-up of ketoconazole with enhanced dissolution and bioavailability. Drug Dev Ind Pharm 2007;33(7):755-65.