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FORMULATION DEVELOPMENT AND EVALUATION OF MONTELUKAST SODIUM CHEWABLE TABLETS

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ABSTRACT

Chewable Tablets of Montelukast sodium were for the easily swallowable or palatable. Microcrystalline cellulose, Magnesium stearate, Croscarmellose sodium, Aspartame, Mannitol, Hydroxy Propyl Cellulose, Ferric oxide, these are the excipients which are used in the formulation in different ratio. Compatibility studies were carried out by mixing definite proportions of Montelukast sodium and Mannitol, Cellulose microcrystalline, Croscarmellose sodium, Hydroxypropyl cellulose, Magnesium sterate, Aspartame, Ferric oxide and Cherry flavour in the ratios of 1:1,1:2.5,1:3,1:5,1:10 and kept in glass vials, which are stored at 50^0C(3 weeks).The Fourier transform-IR (FTIR) studies indicated the possibility of hydrogen bonding with the drug. HPLC method is carried out for the Montelukast present in the Montelukast sodium chewable tablet formulation. Wet granulation method is employed for manufacturing of Montelukast sodum chewable tablets by optimizing disintegrant (Croscamellose sodium).

KEY WORDS: Montelukast sodium, Microcrystalline cellulose, Magnesium stearate, Croscarmellose sodium, Aspartame, Mannitol, Hydroxy Propyl Cellulose, Ferric oxide, FTIR, HPLC.

1. INTRODUCTION

The oral route of drug administration is the most important method of administering drug for systemic effects. Except in certain case the parental route is not routinely used for self administration, e.g. insulin. The topical route of administration has only recently been employed to deliver drugs to the body for systemic effect. The parental route of administration is important in treating medical emergencies in which the subject is comatose or cannot swallow. Nevertheless it is probable that at least 90% of all drugs used to provide systemic effect are administered by oral route. When a new drug is discovered one of the first question a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect by oral route. Drugs that are administered orally, solid oral dosage forms represent the preferred class of product. Tablet and capsules represent unit dosage forms in which usual dose of drug has been accurately placed.

Tablets and capsules represent unit dosage forms in which one usual dose of drug has been accurately placed. By comparison liquid forms such as syrups, suspensions, emulsions, solutions and elixirs are usually designated to contain one medication in 5 -30ml, such dosage measurements are typically error by a factor ranging from 20-50%, when the drug is self administered by patient.

Chewable tablets are intended to be chewed in the mouth prior to swallowing and are not intended to be swallowed intact. The purpose of the chewable tablet is to provide unit dosage form of medication which can be easily administered to infants and children or to the elderly, who may have difficulty in swallowing a tablet intact. **C**hewable dosage forms, such as soft pills, tablets, gums and most recently chewy squares have long been part of the pharmacist armamentarium.

2. MATERIALS AND METHODS

Apparatus and chemicals: Montelukast sodium by M/s Aptuit Laurus Private Ltd, Hyderabad , Magnesium stearate by Ferro Chemical Corporation, Croscarmellose sodium by Maple Biotech Pvt. Ltd , Aspartame, Mannitol by Ansul Agencies, Mumbai, Hydroxy Propyl Cellulose by Vasco Scientifics Pvt. Ltd.

Method:

Procedure for F1:

1. Montelukast Sodium, Hydroxypropyl cellulose and one fourth of Cellulose, Microcrystalline (PH 102) were sifted through # 40 mesh.
2. Red Ferric oxide was sifted through # 100 mesh and added to materials of step 1.
3. The materials of step 2 were re-sifted through #40 mesh.
4. Remaining Cellulose, Microcrystalline (PH 102) was sifted through #40 mesh and added to materials of step 3.
5. The materials of step 4 were re-sifted through # 40 mesh.
6. Mannitol, Croscarmellose Sodium, Ferric oxide, Aspartame, Artificial cherry flavour was sifted through # 40 mesh.
7. The materials of step 6 were re-sifted through # 40 mesh.
8. Magnesium stearate was sifted through # 60 mesh.
9. The above blend of step 7 was lubricated with Magnesium Stearate.
10. The lubricated blend was compressed into tablets.

Procedure for F2 to F8:

1. Intragranular materials i.e. Montelukast Sodium, 40% of Mannitol were passed through #40mesh.
2. Ferric oxide was passed through #80 mesh and was added to step 1.
3. The materials of step 2 were resifted through # 40 mesh.
4. Equal quantities of step 3 and remaining 60% mannitol were co-sifted through # 40 mesh.
5. Cellulose, Microcrystalline (PH 101) was sifted and resifted through # 40 mesh.
6. The above material was mixed with step 4 in rapid mixing granulator.
7. The binder solution was prepared by dispersing Hydroxypropyl cellulose in sufficient quantity of purified water.
8. The dry mix of step-6 was granulated using binder solution of step-7 to get wet mass of desired consistency.
9. The wet mass was dried in fluid bed dryer at 60º ± 5ºC.
10. Dried granules were milled in Co-mill using 1.13mm screen at medium fast speed.
11. Extragranular excipients i.e. Cellulose, Microcrystalline, Croscarmellose Sodium were sifted through #40mesh.
12. Artificial cherry flavour and Aspartame was passed through # 60 mesh.
13. The above materials of step 11 & step 12 were blended with the dried granules of step 10.
14. Magnesium stearate was passed through #60mesh.
15. The above blend was lubricated with Magnesium stearate of step 14.
16. Then finally the lubricated blend was compressed into Tablets.

Formulation development:

Table.1. Formula for F1

S.No	Ingredients	Quantity(Mg)
1	Montelukast sodium	5.19
2	Mannitol	199.31
3	Cellulose,microcrystalline(PH102)	75.00
4	Croscarmellose sodium	9.00
5	Hydroxypropyl cellulose	6.00
6	Ferric oxide	0.60
7	Aspartame	1.50
8	Artificial cherry flavour	0.40
9	Magnesium sterate	3.00

Table.2. Formula for F2 to F8

S.No	Ingredients	F2(Mg)	F3(Mg)	F4(Mg)	F5(Mg)	F6(Mg)	F7(Mg)	F8(Mg)
Intragranular Excipients								
1	Montelukast sodium	5.19	5.19	5.19	5.19	5.19	5.19	5.19
2	Mannitol	201.61	201.61	200.11	198.61	199.61	199.61	196.61
3	Cellulose Microcrystalline	59.00	57.50	57.50	59.50	57.00	55.50	59.00
4	Croscarmellose sodium	1.50	2.25	3.00	3.75	4.50	5.25	6.00
5	Ferric oxide	0.30	0.30	0.30	0.30	0.30	0.30	0.30
Granulating Fluid								
6	Hydroxypropyl cellulose	6.00	6.00	6.00	6.00	6.00	6.00	6.00
7	Purified water	Q.S	Q.S	.Q.S	Q.S	Q.S	Q.S	Q.S
Extragranulating Excipients								
8	Cellulose,microcrystalline	20.00	20.00	20.00	20.00	20.00	20.00	20.00
9	Croscarmellose sodium	1.50	2.25	3.00	3.75	4.50	5.25	6.00
10	Aspartame	1.50	1.50	1.50	1.50	1.50	1.50	1.50
11	Cherry flavour	0.40	0.40	0.40	0.40	0.40	0.40	0.40
12	Magnesium sterate	3.00	3.00	3.00	3.00	3.00	3.00	3.00
	Total	300	300	300	300	300	300	300

Preformulation studies:

Drug-excipient compatibility studies: The compatibility studies provide the scheme for the drugs combination with excipients in the fabrication of the dosage form. The study was carried out to establish that the

therapeutically active drug has not undergone any changes, after it has been subjected to processing steps during formulation of tablets. Compatibility studies were carried out by mixing definite proportions of Montelukast sodium and Mannitol, Cellulose microcrystalline, Croscarmellose sodium, Hydroxypropyl cellulose, Magnesium sterate, Aspartame, Ferric oxide and Cherry flavour in the ratios of 1:1,1:2.5,1:3,1:5,1:10 and kept in glass vials and stored at 50^0C temperature for 3 weeks. There is no characteristic change is observed.

FTIR Spectroscopy: All the excipients used in the different formulations were mixed with the drug separately in equal ratios and the samples of the final formula of the chewable tablet were analyzed through FTIR studies. FT-IR spectra (400-4400 cm^{-1}) were obtained on a Perkin-Elmer FT-IR spectrophotometer with a resolution of 4 cm^{-1}. KBR pellets were prepared gently by mixing the 1mg sample with 100 mg potassium bromide. The characteristic peaks were recorded.

3. RESULTS AND DISCUSSION

Table.3. Drug–Excipients Compatibility Studies

Ingredients	Ratio	Description	
		Initial	50^0C (3 weeks)
Montelukast Sodium	-	Off white to pale yellow colour powder.	NCC
Montelukast Sodium +Mannitol	1:10	white colour powder	NCC
Montelukast sodium + cellulose microcrystalline (PH 101)	1:10	White to off white colour powder	NCC
Montelukast sodium + cellulose microcrystalline (PH 102)	1:5	White to off white colour powder	NCC
Montelukast sodium+croscarmellulose sodium	1:2.5	White to off white colour powder	NCC
Montelukast sodium+hydroxypropyl cellulose	1:3	Off white to cream colour powder	NCC
Montelukast sodium + aspartame	1:1	White to off white colour powder	NCC
Montelukast sodium + cherry flavour	1:1	Off white to cream colour powder	NCC
Montelukast sodium + ferric oxide	1:1	Light pink color powder	NCC
Montelukast sodium sodium + magnesium sterate	1:1	White powder	NCC

NCC: No characteristic change

Discussion: The drug and excipient compatability studies were performed by means of physical mixture of drug and excipients in different ratios (1:1,1:1,1:2.5,1:3,1:5,1:10) at 50^0C for three weeks and no characteristic change was observed. The compatibility study with FTIR indicate that there is no interaction with excipients. Hence concluded the drug is compatible with the excipients.

Table.4. Pre-compression parameters for formulation

Formula	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner's ratio
F1	42.8±0.03	0.466±0.04	0.626±0.01	25.55±0.51	1.34±0.98
F2	37.23±0.02	0.581±0.06	0.735±0.04	20.95±0.40	1.26±0.22
F3	32.21±0.01	0.588±0.05	0.757±0.02	22.32±0.36	1.28±0.12
F4	29.24±0.01	0.595±0.03	0.769±0.02	22.62±0.22	1.29±0.23
F5	24.70±0.03	0.602±0.04	0.781±0.08	22.91±0.21	1.29±15
F6	20.8±0.08	0.617±0.04	0.806±0.03	23.44±0.19	1.30±0.12
F7	22.71±0.01	0.641±0.04	0.833±0.02	23.04±0.17	1.29±0.29
F8	39.69±0.02	0.649±0.03	0.862±0.03	23.70±0.51	1.32±0.98

Mean±SD, (n=3)

Discussion: The blends were evaluated for the parameters such as angle of repose, bulk density, tapped density, compressibility index & Hausner's ratio. The results of micromeritics properties were found to be within satisfactory limits. F1 formulation done by direct compression was found to be sticking to the punches of the

tablet press, so it was not taken further studies. For F2 to F8 formulations wet granulation method was employed for further studies.

Table.5. Post compression parameters

Formula	Avg. weight(mg)	Thickness(mm)	Hardness(kg/cm^2)	Friability (%)
F2	301±0.12	4.31±0.0005	3.2±0.17	0.99
F3	297.0±0.23	4.29±0.0012	3.0±0.12	0.39
F4	297.4±0.12	4.28±0.0031	3.4±0.14	0.28
F5	298.0±0.01	4.25±0.0034	3.2±0.02	0.20
F6	301.5±0.25	4.26±0.0051	3.2±0.15	0.16
F7	302.2±0.14	4.25±0.0059	3.1±0.10	0.15
F8	301.4±0.28	4.28±0.0032	3.1±0.01	0.19

Mean±SD,(n=3)

Discussion: The average weight of each formulation was not maintained constant, but the weight variation was within limit of ±5%. The hardness of each formulation was evaluated and found to be in acceptable range of 3 to 4.5 kg/cm^2. Tablets thickness was almost uniform in all formulation and was found to be in the range of 4.25mm to 4.60mm. Friability was found to be less than 1% and considered to be satisfactory in the range of 0.15% to 0.99%.

Table.6. Post compression parameters

Formula	Disintegration time (sec)	Water content (w/w)	Assay(%)
F2	65±2	1.92±0.05	101.4±0.03
F3	62±3	1.90±0.09	98.7±0.01
F4	50±2	1.90±0.01	98.0±0.1
F5	42±4	1.84±0.17	100.5±0.18
F6	36±1	1.73±0.05	99.2±0.01
F7	38±3	1.71±0.5	99.3±0.03
F8	38±1	1.75±0.02	99.0±0.5

Mean±SD,(n=3)

Discussion: The prepared Montelukast sodium chewable tablets were evaluated for disintegration time, water content and assay. The results of all the test formulations are within the limit and passed.

- Assay range was found to be 98.0% to 101.4%.
- Disintegration time was within acceptance criteria 1min to1.5 min.
- Water content by Karl fisher method was also within range of 1.70% w/w to 1.95% w/w.

***In - Vitro* Dissolution Study:**

Table.7. *In -Vitro* dissolution data by HPLC analysis for Montelukast sodium

Peak Name	Rt (min)	Area (μV^2 sec)	Theoretical plates	Tailing Factor	Resolution
Montelukast sodium	5.501	581819	2640	1.3	-

Table.8.*In-Vitro* release profiles study of different formulation

Sampling time (minutes)	Drug release profile (% drug release)						
	F2	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
10	80±0.90	82±0.52	82±0.43	85±0.24	88±0.23	86±0.28	86±0.90
15	84±0.82	88±0.85	86±0.56	89±0.51	91±0.29	90±0.35	89±0.82
20	93±0.28	91±0.68	90±0.76	92±0.73	96±0.40	92±0.73	90±0.54
30	95±0.58	93±0.72	95±0.23	94±0.04	98±0.20	96±0.26	93±0.29

Discussion: *In-Vitro* drug release profile for all formulations were carried out by using 0.5% SLS with water as dissolution medium for 30 minutes. From the results obtained it was observed that the formulation F6 with 2.5% concentration of croscarmellose sodium (superdisintegrant) shown better release rate with 98% within 30 minutes than other formulations F2, F3, F4, F5, F7 & F8. Hence it is concluded that F6 is desired formulation. F6 has been taken for further stability studies.

Stability data:

Table.9.Physical and chemical parameters of Montelukast sodium tablets (F6) after 1 month at 40ºC ± 2ºC/75 % RH ± 5 % RH

Parameter	Initial	1 month
Description	Pink colour round shaped tablets	No change
Avg. Weight *(mg)*	301.0	301.2
Hardness *(kg/cm^2)*	3.2	3.0
Thickness *(mm)*	4.26	4.29
Friability *(%)*	0.16	0.14
Water content by KF *(w/w)*	1.73	1.63
Assay by HPLC *(% label claim)*	99.2	101.2

Packing: Blister pack

Table.10.Dissolution profile of Montelukast sodium tablets (F6) after 1 month at 40ºC ± 2ºC/75 %RH ± 5 %RH

Time interval (min)	Drug release percentage (%)	
	Initial	Final
10	88	86±0.25
15	91	89±0.59
20	96	94±0.15
30	98	96±0.85

Packing: HDPE bottle

Table 11. Physical and chemical parameters of Montelukast sodium tablets (F6) after 1 month at 40ºC ± 2ºC/75 %RH ± 5 %RH

Parameter	Initial	1 month
Description	Pink colour round shaped tablets	No change
Avg. Weight *(mg)*	301.0	301.2
Hardness *(kg/cm^2)*	3.2	3.0
Thickness *(mm)*	4.26	4.29
Friability *(%)*	0.16	0.14
Water content by KF *(w/w)*	1.73	1.63
Assay by HPLC *(% label claim)*	99.2	101.2

Table.12. Dissolution profile of Montelukast sodium tablets (F6) after 1 month at 40ºC ± 2ºC/75 %RH ± 5 %RH

Time interval (min)	Drug release percentage	
	Initial	Final
10	88	86±0.84
15	91	88±0.51
20	96	93±0.63
30	98	96±0.19

Packing: HDPE bottle **Mean±SD, (n=3)**

Stability summary report:

- Description remain unchanged
- Assay is unchanged with in the limit 98.0% ± 2.0%.
- Dissolution is more than 95.0% in 30 minutes.
- Hardness, thickness, friability, average weight & water content are within the acceptance criteria.

Discussion: Form one month stability data there was no significant change was observed in stability indicating parameters for the formulation F6.

4. CONCLUSION

Based on the optimization of parameters concluded that chewable tablets of Montelukast sodium can be prepared by wet granulation method using Croscarmellose sodium as superdisintegrant. Chewable tablets of Montelukast sodium with 1.5% of Croscarmellose sodium shown better drug release of 98% with minimum

disintegration & dissolution time with pleasant taste .This will improve patient compliance and increase in bioavailability.

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