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Formulation and Characterization of Acebrophylline and Montelukast sodium Bi-layers tablets Antiasthamatic drug

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Abstract

Oral drug delivery is the most preferred and convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. In present work, Bilayer tablet of Acebrophylline (Sustain Release) & Montelukast Sodium (Immediate Release) were prepared by direct compression method. All trials of Acebrophylline & Montelukast Sodium and were subjected to precompression, post compression & in vitro drug release study. Bilayer tablet were prepared with passed trials of Acebrophylline & Montelukast sodium (i.e. FP-02) compared with ACEBRO-M (Marketed Product) for its pot compression parameters && in vitro drug release study.

Key-words: Bi-layer, Acebrophylline, Montelukast Sodium, Formulation

Introduction

In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bi-layer tablet) has increased in the pharma industry, promoting patient convenience.[5] Bi-layer tablets can be a primary option to avoid chemical incompatibilities between APIS by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). [1]

The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly, and then maintain the desired drug concentration. Combination products-also known as fixed dose combinations are combinations of two or more active drugs produced in a single dosage form. They provide the advantages of combination therapy while reducing the number of prescriptions and the attendant administrative costs and improving patient compliance.

Acebrophylline(ACBR) , 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7H-Purine-7- acetic acid compd. with trans-4-[[(2-amino-3,5-dibromophenyl)methyl]amino] cyclohexanol is the salt obtained by reaction of equimolar amounts of theophylline-7- acetic acid, a xanthine derivative with specific bronchodilator activity and ambroxol, a mucolytic and expectorant. It is a novel drug with bronchodilating, anti-inflammatory and mucuregulating effect due to inhibition of phospholipase A, and phosphatidylcholine [2].

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Montelukast sodium (MTKT), [R-(E)]-1-[[[1-[3-[2-(7-chloro 2quinolinyl) ethenyl] phenyl]-3-[2-(1-hydroxy-1methylethyl) phenyl] propyl] thio] methyl] cyclopropane acetic acid, monosodium salt is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene CysLT1 receptor. Leukotrienes cause narrowing and swelling of airways in lungs and also causeallergy symptoms. By blocking leukotrienes, improves asthma symptoms, help to control asthma and improves seasonal allergy symptoms The combination of these two drugs are used for the treatment of chronic obstructive pulmonary disease (COPD) and bronchial asthma. The review of literature revealed that there are several advantages in treatment with the combination of acebrophylline and montelukast sodium individually. Therefore the present research work aims to develop a combined dosage form of Acebrophylline and Montelukast sodium as Bilayered tablet [3].

Material and Methods

Preformulation study

Preformulation study was carried out as per standard procedure. In this solubility, MP, Standardization of Acebrophylline and Montelukast sodium, Drug - Excipient interaction studies in which DCS, FTIR, Physical compatability studies was carried out.

Formulation of bi-layered tablets

Formulation of immediate release tablet

Various formulation batches of Montelukast sodium were prepared by direct compression method. [4-5]

Procedure

Sieve Montelukast Sodium, Avicel PH 102, Starch DC grade #40& sunset yellow with sieve no. # 100, then sieve crospovidone XL-10, Aerosil & Magnesium stearate with sieve no. # 40 and mixed all ingredients properly.

Note: Total weight of each immediate release tablet= 200mg

Table 1: Working formula for immediate release granules preparation

INGEDIENTS	FM1	FM2	FM3	FM4
Montelukast Sodium (mg)	10.629	10.629	**10.629**	10.629
Avicel PH 102 (mg)	82.371	80.371	**78.371**	76.371
Super Starch 200® (mg)	100	100	**100**	100
Sunset yellow (mg)	1	1	**1**	1
Crospovidone XL-10 (mg)	2	4	**6**	8
Aerosil (mg)	2	2	**2**	2
Magnesium Stearate (mg)	2	2	**2**	2

Formulation of sustained release tablet

Various formulation batches of Acebrophylline were prepared by dry granulation method. Sieve Acebrophylline, Guar gum, HPMC K-100 and Magnesium stearate by sieve no. #40, then slugged and crushed with sieve no. # 20 to make granules. [5-6]

Mixed granules properly with Avicel PH-102, then lubricated with magnesium stearate and talc.

Note: Total weight of each sustained release tablet= 550mg

Table 2: Working formulae for sustained release granules preparation [82]

Concentration of polymers used for sustain release tablet in pecentage	Concentration of Gaur Gum	Concentration of HPMC-K100
	15%	20%
	20%	30%
	25%	40%

INGEDIENTS	FA1	FA2	FA3	FA4	FA5	FA6	FA7	FA8	FA9
Acebrophylline (mg)	202.02	202.02	202.02	202.02	202.02	202.02	202.02	**202.02**	202.02
Guar Gum (mg)	30	30	30	40	40	40	50	**50**	50
HPMC K-100 (mg)	40	60	80	40	60	80	40	**60**	80
Magnesium Stearate (mg)	3	3	3	3	3	3	3	**3**	3
Magnesium Stearate (mg)	6	6	6	6	6	6	6	**6**	6
Talc (mg)	6	6	6	6	6	6	6	**6**	6
Avicel PH-102 (mg)	262.98	242.98	222.98	252.98	232.98	212.98	242.98	**222.98**	202.98

Physical Evaluation of granules

In this section flow property was determined. [6-7]

Compression of bi-layered table[l]:

Bi-layered tablets were prepared using Fluid Pack (27 station) machine. Bi-layered tablets were compressed using

- Tooling – D –Tooling
- Upper Punch – 19.0 mm, elongated, bioconvex,one side breakline punches.
- Lower Punch – 19.0 mm, plain punches.
- Dies - suitable for above punches.

Bi-layered tablet contains two layers i.e., immediate release layer and sustained release layer of Montelukast sodium and Acebrophylline. Bi-layered tablets were prepared by using optimized immediate and sustained release layer. Accurately weighed 200mg of immediate release blend and 550mg of sustained release blend individually. Initially immediate release granules blend was fed manually into the die and then compressed at low compression force to form uniform layer. Subsequently sustained release layer granules blend was added to the die over that layer and completely compressed on tablet punching machine.

Table 3:Trials for Bi-layered tablet compression

Trials	**Formulation FP-01**	**Formulation FP-02**
TRIALS OF ACEBROPHYLLINE SUSTAIN RELEASE TABLET	**FA8 + FM3**	**FA8 + FM3**
+		
TRIALS OF MONTELUKAST SODIUM IMMEDIATE RELEASE TABLET		
RESULT	Sepration of bilayered tablet	**Bilayered Tablet compressed successfully**
STATUS		**TRIAL PASSED**

NOTE: This is bilayer sustain release tablet (Avg. Wt. -750 mg/tab.) contain two layers upper layer is montelukast sodium immediate release have avg wt. 200mg/tab. and another is acebrophylline sustain release tablet have avg wt. 550mg/tab.

Characterization of bi-layered tablets

In this study weigh variation, hardness, friability and thickness was evaluated. [6-9]

***In vitro* Dissolution Studies (by HPLC method)**

The *in vitro* drug release study was performed using HPLC chromatographic method. The developed productwas evaluated for in-vitro drug release of:

- Single Sustain release layer of acebrophylline
- Single Immediate release layer of montelukast sodium
- Developed bilayer tablet.
- Compared with Acebro-M (Marketed Poduct). The samples were analyzed by HPLC method.

Method of analysis for dissolution of Montelukast sodium

Apparatus No.1,

Medium 900ml of 0.5 per cent w/v solution of *sodium dodecyl sulphate* in *water,*

Speed 50 RPM

Time 30 minutes.

Withdraw a suitable volume of the medium and filter. Determine by liquid chromatography

Test solution. Use the filtrate.

Reference solution A 0.020 per cent w/v solution of Montelukast sodium RSin the dissolution medium. Dilute10 ml of this solution to 200 ml with the dissolution medium.\

Chromatographic system

a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Hypersil ODS),

- Column temperature. 40°,

Mobile Phase: A. solution containing 3.85 g of *ammonium acetate* in 1000 ml of *water, and add 1 ml of Triethylamine and* adjusted to pH 5.5 with *acetic acid, and Methanol :; 20:80*

Flow Rate. 1ml per minute, **Spectrophotometer** set at 345 nm **Injection Volume** 10 microlitres

Inject the reference solution and the test solution.

Calculate the content of C35H35CLNO3S in the tablet.

Not less than 70 per cent of the stated amount of C35H35CLNO3S.

Kinetics of *in vitro* drug release[81]

To study the release kinetics *in vitro* drugrelease data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer-peppas. To analyse the mechanism of the drug release rate kinetics o the dosage form, the data obtained were plotted as

- Log cumulative percentage drug remaining Vs time(first order plots)

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- Cumulative percentage drug released Vs square root of time (Higuchi's plots)
- Log percentage drug released Vs log time (Korsmeyer peppas).

Results and Discussion

Acebrophylline raw material obtained from AMI PHARMACEUTICALS, Montelukast sodium raw material obtained from MORPEN LABS has been tested as per lab specifications and the results are listed in table 4. The drug source was identified and found complying with the specifications.

Table 4: Physicochemical Properties of API Profile

S.No.	Parameters	Result	
		Drug A (Acebrophylline)	Drug B (Montalukast sodium)
1	Solubility	ly Souble in water and methanol	reely Soluble in ethanol, methanol and water
2	Melting point	217^{0}C	135.5^{0}C

Short term stability studies

For stability studies reproducible batch of selected optimized formulation was used.
[8-9]

3	Assay	98.4%	99.2%

Table 2: Physicochemical Properties of Polymer Data

Parameters	HPMC K100M	HPMC K15M	GUAR GUM
1.Acidity	5.7 pH	5.5 pH	6.8 pH
2.Density	0.339 g/cm^3 (BD) 0.550 g/cm^3 (TD)	0.334 g/cm^3 (BD) 0.548 g/cm^3 (TD)	0.18 g/cm^3(BD) 0.28 g/cm^3(TD)
3. Viscosity	99.5 mpas	99.2 mpas	4860 mpas
4.Melting point	175^{0}C	170^{0}C	115^{0}C

Table 3: Data of Linearity curve of Montelukast sodium

S.No.	Conc. in mcg/ml	Area
1.	12 mcg	218912
2.	16 mcg	291995
3.	20 mcg	365014
4.	24 mcg	438029
5.	28 mcg	511051

Table 4: Data of Linearity curve of Acebrophylline in 0.1 N Hcl

S.No.	Conc. in mcg/ml	Area
1.	240 mcg	3267212
2.	320 mcg	4359282
3.	400 mcg	5441328
4.	480 mcg	6539428
5.	560 mcg	7629402

Table 5: Data of Linearity curve of Acebrophylline in pH 6.8 Phosphate buffer

S.No.	Conc. in mcg/ml	Area
1.	240 mcg	7125125
2.	320 mcg	9500198
3.	400 mcg	11876102
4.	480 mcg	14251429
5.	560 mcg	16626802

The prepared sustained release granules are physically evaluated for the parameters like angle of repose, bulk density, tapped density, hausner's ratio and carr's index. The obtained results were tabulated below.

Table 6: Physical evaluation results of Acebrophylline granules

Formulation code	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio (H_R)	Carr's index (%)
FA1	24.84 ± 0.29	0.607 ± 0.057	0.667 ± 0.063	1.098 ± 0.11	8.9 ± 0.12
FA2	24.512 ± 0.97	0.567 ± 0.045	0.660 ± 0.057	1.164 ± 0.12	14.1 ± 0.42
FA3	24.625 ± 0.12	0.575 ± 0.058	0.680 ± 0.061	1.182 ± 0.09	15.4 ± 0.11
FA4	27.763 ± 0.25	0.574 ± 0.048	0.652 ± 0.083	1.135 ± 0.07	11.9 ± 0.38
FA5	29.653 ± 0.78	0.605 ± 0.086	0.682 ± 0.049	1.127 ± 0.09	11.2 ± 0.41

FA6	27.210 ± 0.67	0.632 ± 0.024	0.735 ± 0.087	1.162 ± 0.14	14.0 ± 0.32
FA7	24.46 ± 0.92	0.611 ± 0.048	0.679 ± 0.061	1.111 ± 0.11	10 ± 1.10
FA8	**24.32 ± 0.28**	**0.553 ± 0.045**	**0.623 ± 0.054**	**1.12 ± 0.191**	**11.23 ± 0.44**
FA9	25.8 ± 0.31	0.437 ± 0.051	0.478 ± 0.062	1.09 ± 0.071	8.5 ± 0.98

The prepared sustained release granules are physically evaluated for the parameters like angle of repose, bulk density, tapped density, hausner's ratio and carr's index. The obtained results were tabulated below.

Table 7: Physical evaluation results of Montelukast Sodium granules

rmulation code	**Angle of repose** (θ)	**Bulk density (gm/cm^3)**	**Tapped density (gm/cm^3)**	**Hausner's ratio (H_R)**	**Carr's index (%)**
FM1	27.26 ± 0.44	0.607 ± 0.057	0.667 ± 0.063	1.098 ± 0.11	8.9 ± 0.12
FM2	28.556 ± 0.97	0.567 ± 0.045	0.660 ± 0.057	1.164 ± 0.12	14.1 ± 0.42
FM3	**24.122 ± 0.12**	**0.575 ± 0.058**	**0.680 ± 0.061**	**1.182 ± 0.09**	**15.4 ± 0.11**
FM4	26.546 ± 0.25	0.574 ± 0.048	0.652 ± 0.083	1.135 ± 0.07	11.9 ± 0.38

The prepared bilayer tablets are physically evaluated for the parameters like Hardness, Thickness & Friability. The obtained results were tabulated below

Table 8: Post-compression parameters of bilayer tablet

mulation code FP-02	**Hardness (Kg/cm^2)**	**Thickness (mm)**	**Friability (%)**	**Weight (mg)**
Tablet				
1	7.0	4.54	0.23	750

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2	7.2	4.56	0.24	755
3	8.3	4.56	0.23	753
4	8.4	4.57	0.22	748
5	7.5	4.54	0.23	753
6	7.5	4.57	0.25	758
7	7.2	4.53	0.23	759
8	8.0	4.54	0.21	750
9	8.1	4.52	0.23	754
10	8.2	4.54	0.23	755

Table 9: Zero Order Data of Sustain release tablet of Acebrophyline Trials

Time (hrs)	Cumulative Percentage Drug release								
	FA1	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**	**FA9**
1	11.15	12.15	13.15	15.15	13.15	16.15	15.67	**18.51**	17.26
2	16.67	16.89	18.67	17.67	19.67	20.65	19.76	**23.9**	21.99
4	22.76	22.99	27.76	28.72	29.76	26.76	30.88	**34.21**	33.25
8	34.81	35.88	39.78	35.52	40.75	39.12	42.84	**49.28**	47.12
12	50.84	52.81	53.31	50.63	54.24	50.55	57.11	**61.09**	60.17
16	62.11	65.56	66.45	69.26	66.25	65.19	68.9	**72.79**	70.79
20	77.2	78.70	78.40	79.90	80.70	81.90	81.82	**84.51**	83.27
24	80.82	82.71	81.80	85.87	86.81	85.51	87.39	**91.98**	89.0

Table 8.10: First Order Data of Sustain release tablet of Acebrophyline Trials FA1-FA9

Time (hrs)	Log Cumulative Percentage Drug release								
	FA1	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**	**FA9**
1	1.047	1.084	1.118	1.180	1.118	1.208	1.195	**1.267**	1.237
2	1.221	1.227	1.271	1.247	1.293	1.314	1.295	**1.378**	1.342
4	1.357	1.361	1.443	1.458	1.473	1.427	1.489	**1.534**	1.521
8	1.541	1.554	1.599	1.550	1.610	1.592	1.631	**1.692**	1.673
12	1.706	1.722	1.726	1.704	1.734	1.703	1.756	**1.785**	1.779

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16	1.793	1.816	1.822	1.840	1.821	1.814	1.838	**1.862**	1.849
20	1.887	1.895	1.894	1.902	1.906	1.913	1.912	**1.926**	1.920
24	1.907	1.917	1.912	1.933	1.938	1.932	1.941	**1.963**	1.949

Table 8.11: Higuchi Model Data of Sustain release tablet of Acebrophyline Trials FA1-FA9

Sq. root of Time (hrs)	Cumulative Percentage Drug release								
	FA1	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**	**FA9**
1	11.15	12.15	13.15	15.15	13.15	16.15	15.67	**18.51**	17.26
1.414	16.67	16.89	18.67	17.67	19.67	20.65	19.76	**23.9**	21.99
2	22.76	22.99	27.76	28.72	29.76	26.76	30.88	**34.21**	33.25
2.828	34.81	35.88	39.78	35.52	40.75	39.12	42.84	**49.28**	47.12
3.464	50.84	52.81	53.31	50.63	54.24	50.55	57.11	**61.09**	60.17
4	62.11	65.56	66.45	69.26	66.25	65.19	68.9	**72.79**	70.79
4.472	77.2	78.70	78.40	79.90	80.70	81.90	81.82	**84.51**	83.27
4.898	80.82	82.71	81.80	85.87	86.81	85.51	87.39	**91.98**	89.0

Table 8.12: Korsmeyer peppas Data of Sustain release tablet of Acebrophyline Trials FA1-FA9

Log Time (hrs)	Log Cumulative Percentage Drug release								
	FA1	**FA2**	**FA3**	**FA4**	**FA5**	**FA6**	**FA7**	**FA8**	**FA9**
0	1.047	1.084	1.118	1.180	1.118	1.208	1.195	**1.267**	1.237
0.301	1.221	1.227	1.271	1.247	1.293	1.314	1.295	**1.378**	1.342
0.602	1.357	1.361	1.443	1.458	1.473	1.427	1.489	**1.534**	1.521
0.903	1.541	1.554	1.599	1.550	1.610	1.592	1.631	**1.692**	1.673
1.079	1.706	1.722	1.726	1.704	1.734	1.703	1.756	**1.785**	1.779
1.204	1.793	1.816	1.822	1.840	1.821	1.814	1.838	**1.862**	1.849
1.301	1.887	1.895	1.894	1.902	1.906	1.913	1.912	**1.926**	1.920
1.380	1.907	1.917	1.912	1.933	1.938	1.932	1.941	**1.963**	1.949

Table 8.13: % Drug release data of immediate release tablet of Montelukast sodium Trials FM1-FM4

TIME (Min)	% Drug Release			
	FM1	**FM2**	**FM3**	**FM4**
10	83.21	83.95	**88.956**	87.59
20	84.25	86.74	**92.426**	90.98
30	88.26	89.98	**94.683**	93.55

Table 8.14: Comparison of Post Compression Parameters of FP-02 & ACEBRO-M

Reference to Protocol applied: I.P./B.P./U.S.P./ I.H.S.			
Trial	**FP-02**	**Acebro-M**	**Specification**
Description	Bilayer uncoated Tablet having a orange colour layer of montelukast sodium & white colour layer of acebrophylline	Coated Bilayer Tablet having a brown colour layer of montelukast sodium & white colour layer of acebrophylline	IHS
`	Complies	Complies	The retention time of the acebrophylline and montelukast sodium peaks in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard prepration as obtained in the assay
Average Weight (in mg)	750.05	751.03	750 ± 37.5 mg
Variation from Average Wt (%)	+1.12% -1.11%	+2.13% -1.98%	± 5 %
Friability	0.23%	0.29	NMT 1%
Dissolution by HPLC (%w/w) For Acebrophylline:			
1. 1 Hour	18.51	19.811	NMT 25
2. 4 Hour	34.21	32.351	20-40
3. 8 Hour	49.28	46.596	40-60
4. 20 Hour	84.51	83.140	60-85
5. 24 Hour	91.98	88.026	NLT80
Dissolution by HPLC (%w/w) For montelukastSodium	94.683	91.130	NLT 70% as per IP

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Table 8.15: % Drug Release Data of Sustain release tablet of Acebrophyline of FP-02 ACEBRO-M

Time (hrs)	Cumulative Percentage Drug release	
	FP-02	ACEBRO-M
1	18.05	19.811
2	23.15	21.133
4	34.01	32.351
8	49.05	46.596
12	61.00	59.120
16	72.25	70.230
20	84.19	83.140
24	91.33	88.026

Table 8.16: % Drug Release data of Immediate release tablet of Montelukast Sodium of FP-02 & ACEBRO-M

TIME (Min)	% Drug Release	
	FP-02	Innovator
10	88.100	87.260
20	92.020	89.225
30	94.12	91.130

The stability studies of selected batch were carried out in stability chamber (thermo lab) kept at 30ºC & 65% RH and 40ºC & 75% relative humidity conditions for 3 months.

Table 8.17: Stability Studies data of FP-02 after 90 days:

Reference to Protocol applied: I.P./B.P./U.S.P./I.H.S.		
Trial	**FP-02**	**Specification**
Description	Bilayer uncoated Tablet having a orange colour layer of montelukast sodium & white colour layer of acebrophylline	IHS

Identification by HPLC	Complies	The retention time of the acebrophylline and montelukast sodium peaks in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard prepration as obtained in the assay
Average Weight (in mg)	750.02	750 ± 37.5 mg
Variation from Average Wt (%)	+1.11% -1.12%	± 5 %
Friability	0.24%	NMT 1%
Dissolution by HPLC (%w/w) For Acebrophylline:		
1. 1 Hour	18.22	NMT 25
2. 4 Hour	34.05	20-40
3. 8 Hour	49.00	40-60
4. 20 Hour	84.15	60-85
5. 24 Hour	91.56	NLT80
Dissolution by HPLC (%w/w) For montelukastSodium	94.52	NLT 70% as per IP

Conclusion

In present work, Bilayer tablet of Acebrophylline (Sustain Release) & Montelukast Sodium (Immediate Release) were prepared by direct compression method. All trials of Acebrophylline & Montelukast Sodium and were subjected to precompression, post compression & in vitro drug release study. Bilayer tablet were prepared with passed trials of Acebrophylline & Montelukast sodium (i.e. FP-02) compared with ACEBRO-M (Marketed Product) for its pot compession parameters && in vitro drug release study. FP-02 was subjected to stability studies. Based on the above study following conclusion can be drawn:

- In Acebrophylline trials **FA8** was selected from FA1-FA9 because of its best pre and post compression parameters & beter drug release in 24 hours.
- In Montelukast Sodium trials **FA3** was selected from FM1-FM4 because of its best pre and post compression parameters & beter drug release in 30 minutes.
- FP-01 was failed and then **FP-02** was passed for successful compression of bilayer tablet.
- In comparative studies of FP-02 and ACEBRO-M, **FP-02**have better results than ACEBRO-M.
- **FP-02** shown acceptable results in stability studies
- FP-02 has emerged as the best in overall study and comparative study with ACEBRO-M.

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