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Research Article

DESIGN AND EVALUATION OF BILAYERED TABLETS TO TREAT RESPIRATORY TRACT INFECTIONS

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ABSTRACT

The aim of the present investigation was to develop bilayer tablets for treating respiratory tract infections. In present study Levofloxacin is selected as antibiotic to treat upper and lower respiratory tract infections, but antibiotic taking along with a mucolytic drug shows reduction of acute exacerbation and days of illness. So we selected Ambroxol hydrochloride as mucolytic drug along with antibiotic Levofloxacin. Bi-layered tablets were formulated consisting of Levofloxacin as immediate release layer and Ambroxol HCL as sustain release layer because its half life is only 4 hours so it will not produce pharmacological effect along with Levofloxacin, so Ambroxol layer is sustained by using polymers. Levofloxacin IR layer was prepared, by using starch as disintegrant which shows sufficient hardness and friability and released the drug within one hour. Ambroxol HCL SR layer was prepared, by using HPMC K4M (11%) and HPMC K100M (12.5%) mixture, sustained the drug release upto 12th hour. Bilayer tablets prepared by wet granulation method were evaluated for thickness, hardness, weight variation, friability and drug content. FT-IR studies clearly indicated that there was no drug-polymer interaction. In total 12 formulations F11 batch releases the Ambroxol HCL in sustained manner similar to the release given by marketed sample and same batch releases the Levofloxacin immediately within an hour. The optimized batch was selected for stability studies and confirmed that there was no significant difference over a stability testing period.

Keywords: Ambroxol hydrochloride, HPMC K4M, HPMC K100M, Levofloxacin, Starch.

INTRODUCTION

Respiratory tract infection

The respiratory tract infection is the most common site for infection by pathogens. This site becomes infected frequently because it comes into direct contact with the physical environment and it is exposed to microorganism in the air. The human respiratory tract is exposed to many potential pathogens via the smoke, soot and dust that are inhaled from the air. Two major types of germs, or microorganisms, cause infections in the respiratory tract, those are bacteria and viruses. Bacteria are bigger than viruses and these can be treated by antibiotics. Antibiotics are sometimes called antibacterial for this reason.

There are two common types of respiratory tract infections, Upper and Lower respiratory tract infections. Upper respiratory tract infections include common cold, Otitis media, Sinusitis, Pharyngitis, Influenza, Whooping cough. Lower respiratory tract infections include Bronchitis, Pneumonia, Bronchiolitis.

Dosage form design[1,2]

Multilayer tablets are made by compressing several different granulations fed in to a die in succession, one on top of another, in layer. Each layer comes from a separate feed frame with individual weight control. Incompatible substance can be separated by formulating them in separate layers as a two layer tablet or separating the two layers by a third layer of an inert substance as a barrier between the two.

Sustained drug release[3]

The goal of sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero order release from the dosage form. In zero order release drug release is independent of the concentration of drug in the delivery system (a constant release rate). Sustained release system generally do not attain this type of release and usually try to mimic zero order release by providing drug in a slow first order fashion (concentration dependent). Sustained release dosage form avoids the disadvantages of multiple dosing.

Reason for taking antibiotic along with mucolytic drug in combined dosage form[4]

People taking antibiotic alone experience repeated exacerbations and also it takes time to cure. But the patient taking antibiotic along with a mucolytic drug, there is reduction of acute exacerbation and days of illness. But it is quite difficult to take both drugs at a time in two dosage forms by elderly patients and children. So, both the drugs are taken in unit dosage form. In that, solid dosage form (especially layered tablet) is the better choice for successful delivery of both drugs in combined form.

MATERIALS AND METHODS

Materials

Levoflaxacin and Ambroxol Hcl drugs are gift samples obtained from Richer pharmaceuticals Ltd, Hyderabad. Polymers HPMC K4M & HPMC K100M;Diluents MCC, DCP, lactose; Binders PVP-K30, IPA; Disintegrants starch, SLS; talc, magnesium stearate and aerosol were obtained from Drugs India Ltd, Hyderabad.

Equipment

Double rotary tablet compression machine (karnavati, Rajasthan), Electronic balance (Shimadzu), Vernier caliper (Mitutoyo south Asia pvt ltd.), Hrdness tester (Pfizer), Friabilator (Roche), PH meter (EI), Hot air oven (Minicon Equipments Pvt Ltd.), Dissolution Apparatus (LAB INDIA), UV spectrophotometer (Shimadzu 1800), FT-IR spectrophotometer (Shimadzu).

Methodology[5]

Bilayered tablets were prepared by wet granulation method. Various steps (Sieving, Dry mixing, Preparation of binder solution, Granulation, wet mass sieving, Drying, sieving of dried granules and finally compression after addition of lubricants) involved in wet granulation method.

Preformulation Studies

Loss on drying studies

$$LOD\ (\%) = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

The experimental value of Loss on drying for Ambroxol is 0.25%. It complies with in the limit of 0.5%

The experimental value of Loss on drying for Levofloxacin is 2.23%. It complies with in the limit of 2 – 3%

Micromeritic properties evaluation

Angle of repose of Ambroxol and Levofloxacin were assessed by fixed funnel method. Carr's index values were obtained by using Loose Bulk density and Taped Bulk Density values which were determined using a bulk density test apparatus.

Plain Ambroxol and Levofloxacin exhibited extremely poor flow properties. Hence necessary to use suitable fillers like Lactose, DCP (di calcium phosphate), MCC (micro crystalline cellulose). Incorporation of these fillers into plain drugs improved flow properties, in these MCC showed possible flow properties.

Formulation Development

In present work Levofloxacin immediate release layer was optimized first by preparing total 7 trial batches. Ambroxol sustained release layer was optimized by combining, total 12 trials of Ambroxol layer formulations with optimized Levofloxacin layer.

Levofloxacin immediate release layer was prepared with various disintegrants such as Starch, Lactose, Dicalcium phosphate and SLS. Selected disintegrant also checked for various concentrations.

Ambroxol sustained release layer was prepared with polymers such as HPMC K4M and HPMC K100M separately and mixing at various concentrations also. Total 12 batches of Ambroxol layer were prepared and combined with optimized Levofloxacin immediate release layer to form Bilayered tablets.

Table 1: Results of micromeretic property evaluation

S. No.	Powders/Drugs	Angle of Repose (^{0}) $\theta = \tan^{-1}$ (h/r)	Loose bulk Density (LBD) (g/ml)	Tapped bulk Density (TBD) (g/ml)	Carr's index %
1.	Ambroxol(AMB)	47^{0}15'	0.348	0.543	35.88
2.	Levofloxacin(LEVO)	46^{0}91'	0.321	0.512	37.12
3.	AMB+Lactose	42^{0}01'	0.265	0.364	27.23
4.	LEVO+Lactose	42^{0}53'	0.271	0.375	27.84
5.	AMB+DCP	43^{0}75'	0.197	0.276	28.46
6.	LEVO+DCP	43^{0}18'	0.193	0.274	29.63
7.	AMB+MCC	30^{0}38'	0.221	0.282	21.43
8.	LEVO+MCC	31^{0}64'	0.206	0.263	21.62

Table 2: Trials for Levofloxacin layer

S. No.	Ingredients	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
1.	Levofloxacin	500	500	500	500	500	500	500
2.	MCC	89	83.5	76	79	83.5	83.5	83.5
3.	Starch	19.5	25	32.5	29.5	-	-	-
4.	Lactose	-	-	-	-	25	-	-
5.	Dicalcium Phosphate	-	-	-	-	-	25	-
6.	SLS	-	-	-	-	-	-	25
7.	PVP K30	22	22	22	22	22	22	22
8.	IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s
9.	Purified Talc	6.5	6.5	6.5	6.5	6.5	6.5	6.5
10.	Aerosil	6.5	6.5	6.5	6.5	6.5	6.5	6.5
11.	Magnesium Stearate	6.5	6.5	6.5	6.5	6.5	6.5	6.5

Table 3: Formulation Development of Ambroxol layer

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ambroxol Hcl	75	75	75	75	75	75	75	75	75	75	75	75
HPMC K4M	22.5	30	37.5	45	---	---	---	---	30	30	32.5	36
HPMC K100M	---	---	---	---	30	37.5	45	52.5	30	30	37.5	45
MCC	175.5	168	160.5	153	168	160.5	153	145.5	138	136	128	117
PVP K30	9	9	9	9	9	9	9	9	9	11	9	9
IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Purified Talc	6	6	6	6	6	6	6	6	6	6	6	6
Aerosil	6	6	6	6	6	6	6	6	6	6	6	6
Magnesium Stearate	6	6	6	6	6	6	6	6	6	6	6	6

Table 4: Evaluation of Levofloxacin granules

Trials	Angle of Repose (^{0}) $\theta = \tan^{-1}$ (h/r)	Loose bulk Density (LBD) (g/ml)	Tapped bulk Density (TBD) (g/ml)	Carr's index (%)	Drug content (%)
1	21^{0}52	0.272	0.316	13.89	98.46
2	21^{0}08	0.289	0.334	13.21	99.79
3	21^{0}43	0.324	0.376	13.65	98.96
4	23^{0}56	0.294	0.344	14.27	99.13
5	23^{0}54	0.281	0.327	14.18	98.55
6	24^{0}78	0.301	0.356	15.45	99.66
7	23^{0}63	0.286	0.337	14.91	98.32

Table 5: Evaluation of Ambroxol granules

Formulation	Angle of Repose (^{0}) $\theta = \tan^{-1}$ (h/r)	Loose bulk Density (LBD) (g/ml)	Tapped bulk Density (TBD) (g/ml)	Carr's index (%)	Drug content (%)
F1	$21^0$04	0.304	0.351	13.41	98.75
F2	$21^0$09	0.317	0.367	13.63	99.32
F3	$21^0$46	0.310	0.360	13.89	98.55
F4	$24^0$88	0.318	0.378	15.87	99.87
F5	$24^0$23	0.294	0.346	15.02	98.36
F6	$24^0$09	0.307	0.360	14.72	98.69
F7	$24^0$78	0.311	0.368	15.21	99.12
F8	$25^0$56	0.265	0.312	15.06	98.74
F9	$23^0$98	0.332	0.391	14.91	99.15
F10	$21^0$14	0.299	0.346	13.54	98.53
F11	$22^0$53	0.270	0.317	14.63	99.82
F12	$24^0$96	0.282	0.336	15.82	99.15

RESULTS AND DISCUSSIONS

Evaluation of granules

Flow properties of granules were studied by calculating Angle of repose and Carr's index values for both Ambroxol granules and Levofloxacin granules.

It was confirmed that both the drugs were exhibited excellent flow properties, when the drugs were granulated with excipients.

Evaluation of Bilayered tablets

Average weight: Twenty tablets from each batch were weighed and the average weights were calculated.

Thickness: Three tablets from each batch were used and average thickness values were calculated by using Vernier caliper.

Hardness: Measured by using Pfizer hardness tester.

Drug content: Drug content determination is done by UV method.

Friability test: Friability is the loss of weight of tablet in the container/package

$$\text{Friability} = \frac{(W_1 - W_2) \times 100}{W_1}$$

W1-weight of the tablet before test

W2-weight of the tablet after test

Table 6: Results of Bilayered tablet evaluation

Formulation	Uniformity of Weight mg ± SD (n=20)	Hardness Kg/cm^2± SD (n=10)	Thickness mm ± SD (n=5)	Friability (%)	Drug content (%)
F1	951±1.25	6.4±0.32	5.5±0.055	0.435	98.70
F2	951±1.21	6.4±0.29	5.7±0.010	0.492	99.25
F3	952±0.15	6.9±0.24	5.1±0.017	0.501	99.42
F4	950±3.28	6.3±0.41	5.3±0.012	0.563	97.52
F5	951±0.98	6.1±0.32	5.5±0.072	0.478	98.24
F6	949±2.32	6.8±0.32	5.9±0.021	0.242	98.63
F7	950±2.67	5.8±0.39	5.7±0.054	0.414	98.15
F8	953±0.96	6.4±0.42	6.0±0.034	0.417	99.42
F9	951±1.56	6.5±0.29	5.4±0.022	0.318	99.14
F10	950±2.23	7.5±0.12	5.3±0.071	0.021	99.25
F11	950±0.56	6.4±0.14	5.4±0.042	0.113	99.30
F12	950±1.12	6.9±0.51	5.7±0.088	0.124	99.17

All batches showed that their weights were within 949 to 952 mg/tablet, hardness and friability values were within limits.

Disintegration test

The disintegration for Levofloxacin immediate release layer was determined using the disintegration apparatus. One tablet was placed in each of six tubes placed in a beaker containing 1000 ml of purified water maintained at 37 ± 2^0C.

Table 7: Disintegration data for Levofloxacin layer

Trials	Time in minutes
Trial 1	9 min
Trial 2	11 min
Trial 3	25 min
Trial 4	7 min
Trial 5	20 min
Trial 6	27 min
Trial 7	24 min

It was confirmed that Trial 1 and trial 4 had their disintegration time very less but they failed in hardness test, Trial 3,5,6,7 were not suitable for immediate release due to their long disintegration time, Trial 2 showed sufficient hardness and their disintegration time was also suitable for immediate release.

Invitro dissolution studies

In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 12 hr, at 100 rpm, 0.1 N HCl (pH 1.2) was used as a dissolution medium for first 2hr followed by pH 6.8 phosphate buffer for further 10 hr. Drug content in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer applying simultaneous estimation method for Ambroxol and Levofloxacin.

(Table 8) In these Trial 1 and Trial 4 shows good dissolution data within one hour but those trials were failed in hardness and friability test. Trial 2 was considered as optimized formulation due to their small disintegration time and good dissolution over other trials. Optimized levofloxacin layer, Trial 2 was selected for compression with various Ambroxol hcl formulations to formulate Bilayer tablets.

Table 8: Cumulative % Drug release of Levofloxacin layer

Time in hours	Cumulative % Drug Release						
	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
pH 1.2 buffer							
0	0	0	0	0	0	0	0
1	92.1	75.9	61.2	96.5	61.4	62.3	60.5

Table 9: Cumulative % Drug release of Ambroxol hcl layer

Time in hours	Cumulative % Drug Release											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
pH 1.2 buffer												
0	0	0	0	0	0	0	0	0	0	0	0	0
1	30.7	28.9	26.4	21.7	33.5	30.2	27.2	23.3	28.9	27.7	26.1	14.3
2	43.1	39.7	35.3	29.6	47.3	41.5	36.1	31.5	35.4	33.2	32.8	21.7
pH 6.8 buffer												
4	49.3	46.5	43.1	38.4	54.8	50.6	46.3	40.8	42.4	41.3	39.7	33.3
6	79.4	74.8	63.6	48.8	82.5	79.3	64.7	49.1	50.3	48.7	47.2	41.2
8	95.2	93.4	82.3	63.3	98.1	92.5	80.3	63.9	73.7	69.9	68.3	50.9
10	-	-	94.7	74.5	-	-	97.8	79.5	89.2	86.4	80.7	61.1
12	-	-	-	84.5	-	-	-	91.3	-	-	96.1	75.3

In total formulations F4, F8, F11 and F12 batches of Ambroxol hcl layers were sustained the drug release up to 12 hours. In these F11 showed the drug release pattern very similar to the marketed sample that is almost 96% drug release within 12 hours.

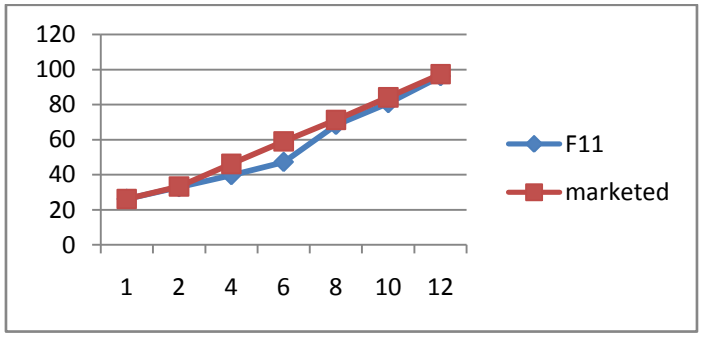

Fig. 1: Cumulative % drug release of F11 batch Ambroxol layer compared with Marketed Sample

Drug release kinetics for F11 Ambroxol hcl sustained release layer

As shown in table no.10 various kinetic models were giving linear relationship. The best linearity was found in Zero order model (high r^2 value), in which the drug release rate is independent of concentration of the drug. In peppas model, we obtained n value as 0.5121 which is greater than 0.45 and less than 0.89 indiacates Non-fickian diffusion.

Stability studies

Stability studies for the present work were carried out at 25 ± 2^{0}C / 60% ± 5% RH, 40 ± 2^{0}C /75% ± 5 RH. Samples were withdrawn after 3month and evaluated for their physical parameters and *in-vitro* dissolution behavior.

Table 10: Drug release kinetics for Ambroxol hcl layer of F11 batch

	Zero	Higuchi	Peppas	First order	Hixson Crowell
	Q Vs T	Q Vs T	LogC Vs LogT	Log %RemainVs T	(Q1/3-Qt1/3) Vs T
Slope	7.0156	27.7343	0.5121	-0.0161	0.2173
Intercept	11.1537	-8.8117	1.3630	2.4119	-0.0301
Correlation	0.9791	0.9592	0.9589	-0.8963	0.9438
R^2	0.9587	0.9202	0.9195	0.8033	0.8907

Table 11: Stability Data of optimized F11 batch bilayered tablets of Ambroxol hcl SR and Levofloxacin IR

	Tests	Initial 0 month	After 3 month
1.	Description	Complies	Complies
2.	Average Weight	951.2mg	951.2 mg
3.	Average thickness	5.6mm	5.6mm
4.	Average Hardness	6.4 kg/cm^2	6.4kg/cm^2
5.	Friability	0.17%	0.19%
6.	Dissolution Profile	**AMB LEV**	**AMB LEV**
	(Cumulative % drug release)	1hr- 26.3 75.2	1hr-26.4 75.9
		2hr-32.9	2hr-33.2
		4hr-39.2	4hr-41.1
		6hr-48.1	6hr-49.8
		8hr-65.3	8hr-65.7
		10hr-81.8	10hr-83.5
		12hr-96.1	12hr-96.7
7.	Assay	99.4%	98.8%

*storage conditions: 25^{0}C±2^{0}C at 60%±5%RH

Table 12: Stability Data of Optimized F11 batch bilayered tablets of Ambroxol hcl SR and Levofloxacin IR

	Tests	Initial 0 month	After 3 month
1.	Description	Complies	Complies
2.	Average Weight	951.2mg	951.2 mg
3.	Average thickness	5.6mm	5.6mm
4.	Average Hardness	6.4 kg/cm^2	6.4kg/cm^2
5.	Friability	0.17%	0.28%
6.	Dissolution Profile	**AMB LEV**	**AMB LEV**
7.	(Cumulative % drug release)	1hr- 26.3 75.4	1hr-27.5 76.8
	Assay	2hr-32.9	2hr-35.2
		4hr-39.2	4hr-44.1
		6hr-48.1	6hr-56.8
		8hr-65.3	8hr-69.7
		10hr-81.8	10hr-86.5
		12hr-96.1	12hr-97.7
		99.4%	98.8%

*storage conditions: 40^{0}C±2^{0}C at 75%±5%RH

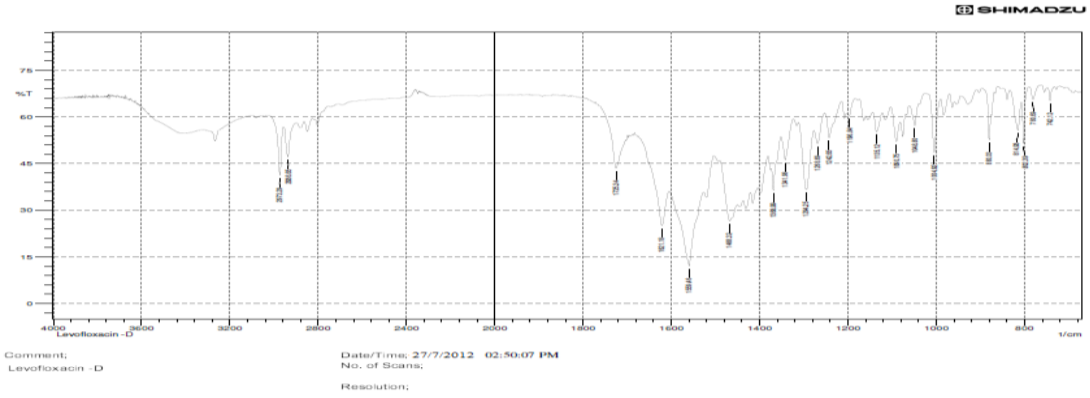

Fig. 2: FT-IR spectrum of Levofloxacin pure drug

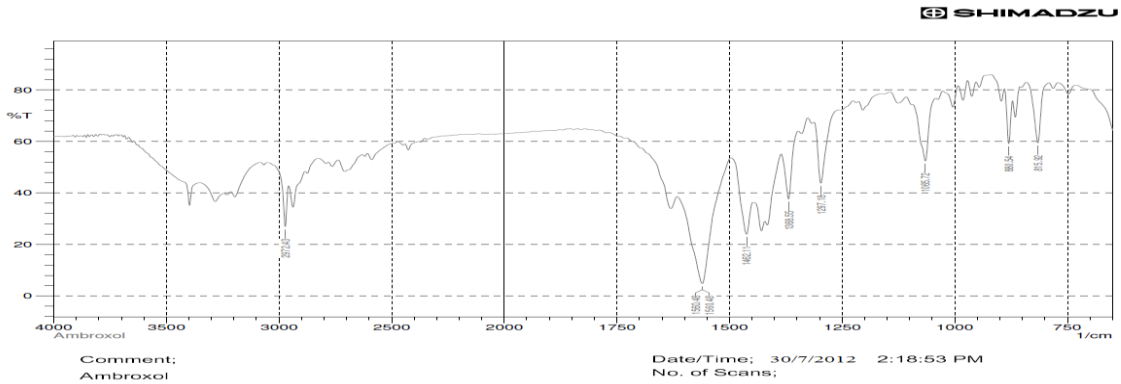

Fig. 3: FT-IR spectrum of Ambroxol hcl pure drug

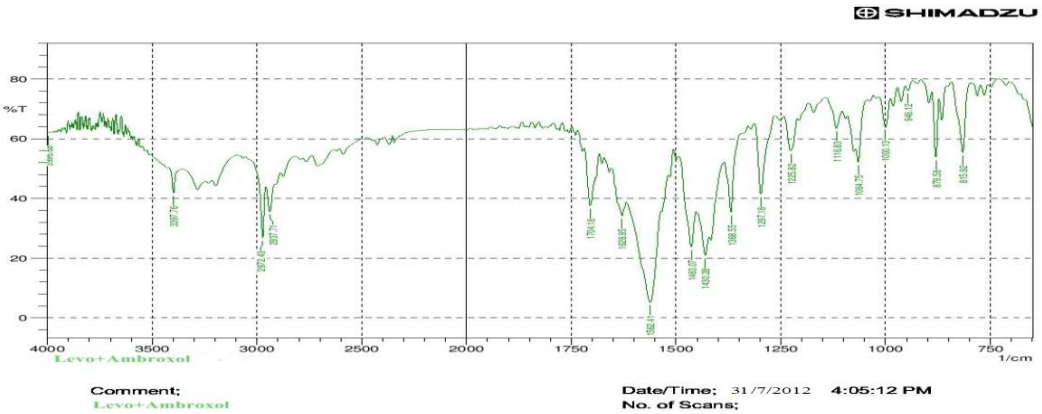

Fig. 4: FT-IR spectrum of final optimized F11 batch

Compatibility studies

FT-IR spectroscopy was employed to ascertain the compatibility of drugs with excipients.Ambroxol and Levofoxacin with excipients showed no significant variation in height, intensity and position of peaks, suggesting that drug and excipients were compatible.

CONCLUSION

The Bilayered tablets containing Ambroxol hydrochloride SR and Levofloxacin IR were successfully prepared by wet granulation method. The physiochemical evaluation results for the granules of all trials pass the official limits in angle of repose, compressibility index and drug content.

Initially Levofloxacin layer was optimized based on Hardness, Friability, Disintegration time and Dissolution studies of 7 trials. Optimized Trial 2 Levofloxacin layer was selected for compression with 12 formulations of Ambroxol hcl layer and Bilayered tablets were evaluated for weight variation, thickness, hardness, friability and in-vitro dissolution.

In total 12 bilayered formulations, the optimized formulation was F11th batch which releases the Ambroxol hcl in sustained manner similar to the release given by the marketed sample.

F11 batch was selected for stability studies and confirmed that there was no significant difference over a stability period.

Optimized F11 Ambroxol hcl sustained release layer was studied for drug release kinetics and the best linearity was achieved with Zero order drug release model and n value of peppas model indicates Non- fickian diffusion.

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