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"FORMULATION AND EVALUATION OF CONTROLLED RELEASE TABLET DOSAGE FORM OF NAPROXEN SODIUM USING BILAYER TECHNOLOGY"

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ABSTRACT

The goal of present study is to formulate and evaluate controlled release dosage form of Naproxen sodium using bilayer tablet technology, by wet granulation process. During this wet granulation process various parameters were studied like granulation , dried granules LOD, compression parameters and formula was optimized. In this wet granulation process various controlled release polymers were used like HPMC K4M, HPMC K15, HPMC K 100. Among the used polymers HPMC K4M Showed the high retarding the drug release rate, due to it contain high viscosity in nature. The drug and excipient computability studies and Preformulation studies were performed. In vitro dissolution test was performed by using USP type II (Paddle) apparatus, 1000 ml of phosphate buffer pH7.5 and the paddle was rotated at 50 rpm at temperature (37ºC ± 0.5ºC) similar as that of reference listed drug. The finished tablets were subjected to evaluation parameters and study on pH of different media were studied on controlled release tablets. Three months Stability studies indicate that it was similar as that of innovator product.

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INTRODUCTION

The achievements in the drug development in pharmaceutical products does not maintain similar growth in the drug delivery. Drug delivery meance providing a therapeutic drug concentration to the particular organ or tissue in a specified manner or specified period of time, either locally or systematically. Drug delivery mainly divides in to two types they are spatial placement and temporal drug delivery. Generally drug delivery through the oral and I.V does not maintain drug blood levels with in the therapeutic range for a longer periods of time, if we try to increase the dose it produce toxic levels. An Altenate approach for this is Multiple drug theraphy with dosing interval, But if dosing interval not proper large peacks and valleys may occur, and drug blood levels may not maintain with in the therapeutic range. To overcome above all mentioned problems Controlled drug delivery emerged. Thats why in my attempt i preferd controlled drug delivery systems with bilayer tablet technology.

Advantages

1. Dosage frequency reduced .
2. Patient feels better with this theraphy.
3. Reduction in drug level fluctuation in blood.

MATERIALS AND METHODS

Naproxen sodium, Microcrystalline cellulose pH 101, Cross carmellose sodium, Povidone, Methocel k 4 M Premium CR, Methocel k 15 M Premium CR, Methocel k 100 M Premium LVCR, Eudragit L-100, Magnesium stearate, Talc, Citric acid monohydrate, Iron oxide yellow, Iso propyl alcohol.

Preparation of CR layer And IR layer

Naproxen sodium controlled release bilayer tablets was prepared by wet granulation process .CR and IR layer granules was prepared and compressed into bilayer tablets by usig below formulation design.

CR layer portion

S.NO	Ingredients	Formulation(mg/unit)							
	F1	F2	F3	F4	F5	F6	F7	F8	F9
CR LAYER									
Intra granular material									
API	618.75	618.75	618.75	618.75	618.75	618.75	618.75	618.75	618.75
MCC	12.59	23.22	31.49	80.54	48.82	41.13	28.7	41.32	34.25
Citric acid monohydte	42.53	20.50	23.13	17.50	19.50	22.90	24.10	18.50	21.50
Methocel K4M	101.49	104.99	107.89	110.24	103.94	93.44	134.5	113.99	107
Binder									
IPA	QS	QS	QS	QS	QS	QS	QS	QS	QS
Povidone	33	53.03	33	31	30	29	28	30	32
Extra granular material									
Methocel k 15 M	83.99	70.99	73.49	75.59	54.50	64.50	61.94	72.44	75
Methocel k 100 M	62.99	63.52	64.25	22.47	73.49	62.78	62.00	52.49	64.50
Eudragit L-100	61.99	62.50	65.50	60.50	68.50	85	59.50	62.30	64.50
Magnesium stearate	11	11	11	11	11	11	11	11	11
Talc	21.50	21.50	21.50	21.50	21.50	21.50	21.50	21.50	21.50
Total CR weight	1050	1050	1050	1050	1050	1050	1050	1050	1050

IR layer.

S.n	Ingredient	Formulation(mg/unit)								
		F01	F02	F03	F04	F05	F06	FO7	F08	F09
Intragranular portion										
1	API	206.25	206.25	206.25	206.25	206.25	206.25	206.25	206.25	206.25
2	MCC pH101	84.6	88.3	89.59	83.9	81.6	80.6	85.55	73.84	83.3
Binder										
3	Povidone	17.8	15.5	10.21	15.9	18.2	19.2	14.25	16.50	16.5
4	IPA	QS	QS	QS	QS	QS	QS	QS	QS	QS
5	Iron oxide yellow	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Extra granular portion										
6	CCS	5	5	5	5	5	5	5	14.46	5
7	Magnesium stearate	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
8	Total IR weight	315	315	315	315	315	315	315	315	315
9	Total CR+IR weight	1365	1365	1365	1365	1365	1365	1365	1365	1365

EVALUATION STUDIES:

Evaluation of granules:

Bulk density, Tapped density, Carr's index, Hausner's ratio.

Evaluation of Tablets:

Uniformity of weight, Thickness, Hardness, Friability Dissolution test.

RESULTS AND DISCUSSION

Table no 1. Physical characteristics of API.

S.NO	DESCRIPTION	RESULTS
1	Colour	white
2	Odour	odorless
3	Taste	Bitter
4	Appearance	Crystalline powder
5	LOD	NMT 1.0%

Table no 2. Solubility of API in different media.

Solvent system	Solubility (mg/ml)
Water	245.966
0.1N HCL	0.007
pH4.5Acetate buffer	6.900
pH6.8Phosphate buffer	44.191
pH7.5Phosphate buffer	260.641

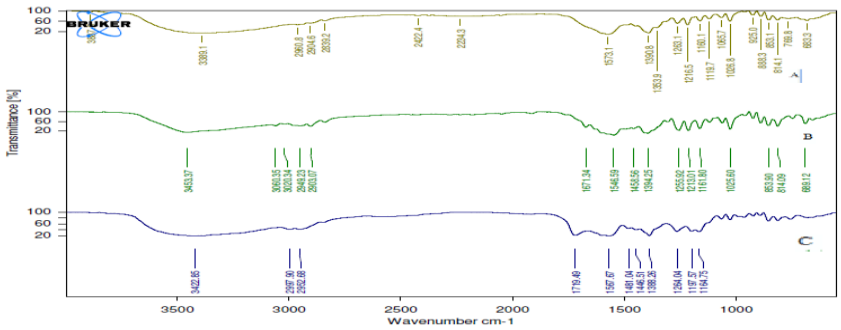

Fig no .1 Drug and excipient compatability studies by FTIR.

A-Naproxen sodium, B-Drug+Mcc, C-Drug+Citric acid monohydrate

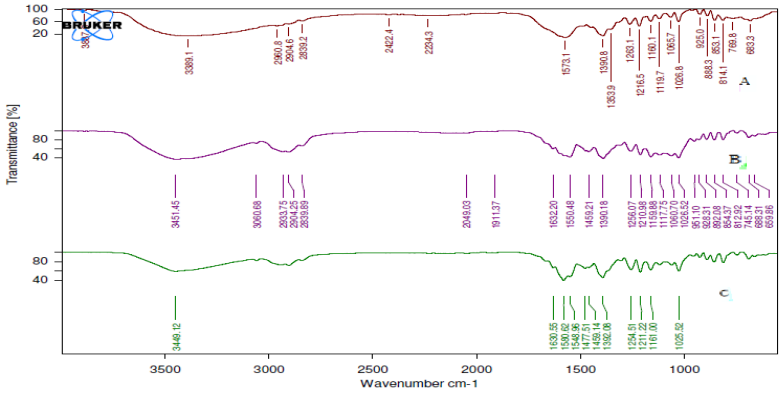

Fig no .2 Drug and excipient compatability studies by FTIR.

A-Naproxen sodium, B-Drug+CCS, C-Drug+Eudragit

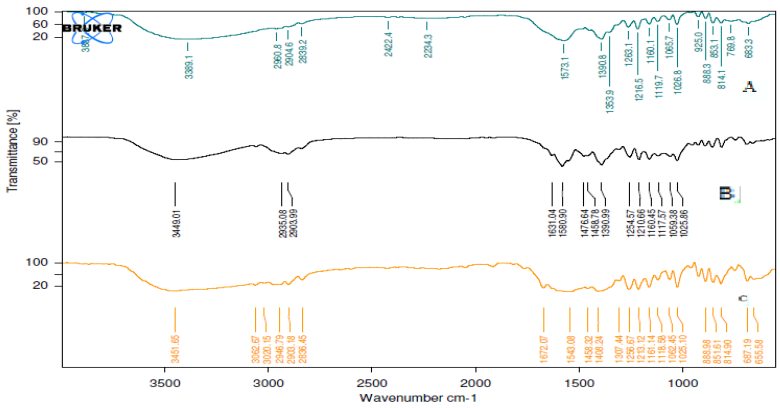

Fig no .3 Drug and excipient compatability studies by FTIR.

A-Naproxen sodium, B-Drug+HPMC K4M, C-Drug+HPMCK15M.

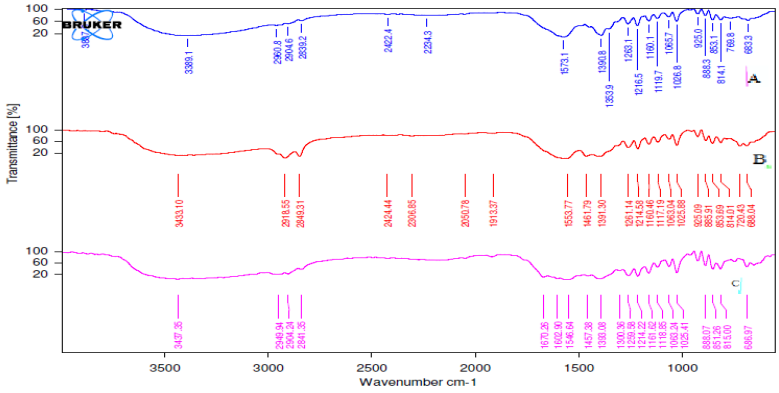

Fig no .4 Drug and excipient compatability studies by FTIR.

A-Naproxen sodium , B-Drug+HPMC K100M, C-Drug+Iron oxide yellow.

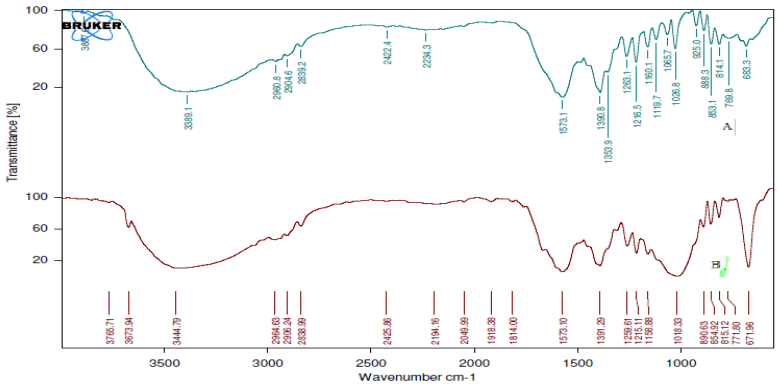

Fig no .5 Drug and excipient compatability studies by FTIR.

A-Naproxen sodium , B-Drug+povidone.

Table no 3. Naproxen sodium CR granules evaluation.

Formulation code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's ratio	Compressibility Index (%)	Angle of Repose (θ)
F1	0.47±0.02	0.62±0.02	1.32±0.01	24.01±0.05	26º58'± 0.04
F2	0.52±0.06	0.63±0.03	1.23±0.02	18.75±0.02	27º10'± 0.01
F3	0.45±0.02	0.54±0.02	1.24±0.03	18.48 ±0.03	31º37'± 0.02
F4	0.45±0.02	0.60±0.03	1.35±0.04	25.81±0.02	25º51'± 0.06
F5	0.51±0.01	0.65±0.03	1.27±0.02	21.31±0.05	25º53'± 0.01
F6	0.42±0.01	0.58±0.03	1.39±0.01	28.00±0.03	26º20'± 0.02
F7	0.43±0.02	0.60±0.01	1.38±0.02	27.78 ±0.03	25º33'± 0.05
F8	0.59±0.02	0.61±0.02	1.22±0.01	18.2 ±0.01	27º32'± 0.01
F9	0.41±0.02	0.58±0.01	1.38±0.03	28.00 ±0.03	27º48'± 0.02

All values Expressed as Mean ± SD (n=3).

Table no 4. Naproxen sodium IR granule evaluation.

Formulation code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's ratio	Compressibility Index (%)	Angle of Repose (θ)
F1	0.47±0.02	0.62±0.02	1.32±0.01	24.01±0.05	26º49'± 0.04
F2	0.52±0.06	0.63±0.03	1.23±0.02	18.75±0.02	27º10'± 0.01
F3	0.45±0.02	0.54±0.02	1.24±0.03	18.48 ±0.03	31º38'± 0.02
F4	0.45±0.02	0.60±0.03	1.35±0.04	25.81±0.02	25º51'± 0.05
F5	0.51±0.01	0.65±0.03	1.27±0.02	21.31±0.05	25º53'± 0.02
F6	0.42±0.01	0.58±0.03	1.39±0.01	28.00±0.03	27º10'± 0.03
F7	0.43±0.02	0.60±0.01	1.38±0.02	27.78 ±0.03	25º33'± 0.03
F8	0.59±0.02	0.61±0.02	1.22±0.01	18.2 ±0.01	27º33'± 0.03
F9	0.41±0.02	0.58±0.01	1.38±0.03	28.00 ±0.03	27º49'± 0.02

All values Expressed as Mean ± SD (n=3).

Table no 5. Naproxen sodium Bilayer tablets evaluation.

Formulation code	Weight variation (mg)	Hardness (Kp)	Thickness (mm)	Friability (%w/w)	Assay (%)
F1	1365.8±4.34	25.02±0.72	7.25±0.03	0.07± 0.05	90.82±0.05
F2	1365.5±2.99	25.77±0.35	7.42±0.01	0.09± 0.03	105.2±0.02
F3	1363.9±1.97	25.77±0.35	7.43±0.01	0.08± 0.02	99.2±0.01
F4	1366.9±2.33	24.14±0.94	7.44±0.04	0.10± 0.05	98.6±0.05
F5	1365±3.89	23.24±0.57	7.34±0.03	0.15± 0.02	99.8±0.01
F6	1362.7±3.65	27.59±1.02	7.48±0.03	0.09± 0.01	88.2±0.09
F7	1361.7±3.77	26.67±0.88	7.43±0.02	0.11± 0.03	89.3±0.02
F8	1366.4±3.78	24.92±2.71	7.40±0.02	0.08± 0.03	96.3±0.01
F9	1364.2±2.30	25.42±0.25	7.43±0.02	0.12± 0.01	98.4±0.02

All values Expressed as Mean ± SD (n=3).

Table no 6. Invitro drug release profiles of API in various formulations.

TIME (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	RLD	Limits
30	31±0.02	31±0.01	35±0.01	33±0.02	33±0.01	33±0.01	30±0.01	34±0.01	26±0.01	27±0.01	NMT 35%
60	37±0.01	36±0.01	40±0.01	37±0.02	37±0.02	35±0.01	38±0.02	38±0.02	40±0.02	49±0.02	
240	57±0.01	56±0.02	59±0.05	55±0.02	57±0.01	51±0.02	64±0.01	64±0.02	62±0.03	65±0.01	35-65%
360	67±0.03	70±0.02	70±0.05	67±0.01	69±0.02	71±0.01	79±0.02	79±0.03	90±0.05	93±0.01	
600	75±0.02	89±0.01	89±0.05	87±0.01	89±0.03	80±0.02	101±0.02	101±0.05	91±0.02	95±0.02	
720	79±0.02	96±0.07	94±0.02	93±0.02	95±0.05	87±0.05	106±0.01	106±0.02	95±0.02	97±0.01	NLT80%

All values Expressed as Mean ± SD (n=3).

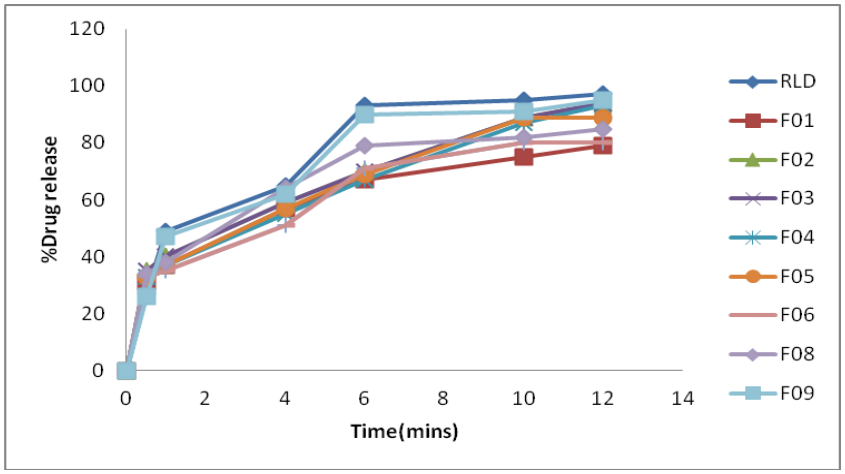

Fig no 1. Invitro drug release profiles of API in RLD & various formula.

Stability studies of the optimized formulation at 40°C and 75%RH for 2 month in a stability chamber.

Table no7 Accelerated stability data.

TIME (Hrs)	Initial	After 1 month	After 2months
0	0	0	0
1	36±0.03	36±0.02	36±0.01
2	43±0.02	43±0.02	42±0.03
4	54±0.01	54±0.01	52±0.03
8	76±0.02	76±0.04	74±0.02
12	92±0.03	92±0.01	90±0.05

All values Expressed as Mean ± SD (n=3).

CONCLUSION

The investigation of project work is to formulate a controlled release Naproxen sodium bilayer tablets of Anti-Inflammatory drug with the help of super disintegrating agent in immediate release layer and rate retarding polymers like HPMC K4M, HPMCK100, HPMC K15M, in controlled release layer of two layered tablet at variable proportions. Drug and excipients compatibility by FT-IR studies revealed there was no interaction between drugs and excipients. The finished bilayer tablets from optimized formula maintains similarity with that of innovator product. Hence it was stable and cost effective product. The in vitro drug release studies are obtained for the innovator drug and various formulations F1, F2, F3, F4, F5, F6, F7, F8, F9 and the optimized formulation trail F9 shows the cumulative % drug release as that of innovator. So it is considered as the optimized formulation in this work.

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