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FORMULATION AND OPTIMIZATION OF ENTERIC COATED TABLET FOR THE TREATMENT OF RHEUMATOID ARTHRITIS USING COMBINATIONAL DRUG THERAPY

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***Abstract*:** Now a days Rheumatic Arthritis increasing in population and for the treatment of Rheumatic Arthritis patient take medicine whole life. For treatment we use various type of NSAID but prolong use of those drug shows many side effects like ulcerative colitis, IBD, CD, Stomach Ulcer, Liver Cirrhosis and many more which occurred with type of drug and duration of treatment. Many Present study describes the Etodolac used in the treatment of Rheumatic Arthritis, but prolong use of Etodolac shows some saviour side effect on human body. Curcumin also used in the treatment of Rheumatic Arthritis. The purpose of study is to develop and formulate such formulation which minimize side effect of Etodolac and treat Rheumatic Arthritis effectively for long duration of treatment. For avoid acid degradation of curcumin we prepare enteric coated tablet which release drug directly into intestine. From the above evaluations of all batches it is concluded that F4 batch was the optimized batch. F4 batch was found stable for 3 months ($40^0C \pm 2^0C$, RH 75%±5%).

Index Terms: Etodolac, Curcumin, Enteric Coated, Eudragit S100, Rheumatic Arthritis.

1.Introduction

The word "enteric" indicates small intestine; thus, enteric coatings avoid dissolution and release of medication before it reaches the small intestine. Most enteric coatings work by presenting a coated surface that's stable at the extremely acidic pH scale found within the abdomen, however breaks down quickly at a less acidic (relatively more basic) pH**. (1-6)**

Rheumatoid arthritis is a chronic inflammatory autoimmune disorder. The cardinal signs of rheumatoid arthritis are stiffness, swelling and pain of one or more joints of the body characteristically most severe in the morning. **(Fig No-1)** Rheumatoid arthritis shows a marked circadian variation in its symptoms. **(8-9).** A group of British volunteers self-assessed the pain and stiffness of affected finger joints every 2 to 3 hours daily for several consecutive days. They also measured the circumference of the arthritic joints to gauge the amount of their swelling, and they performed grip strength tests to determine the effect of the arthritic condition on the hands. The ratings of the severity of joint pain swelling and stiffness were about 3 times higher between in 08:00 and 11:00 than at bedtime. In contrast, hand strength was lower by as much as 30% in the morning than at night. This is typical of rheumatoid arthritis sufferers. **(10-14)**

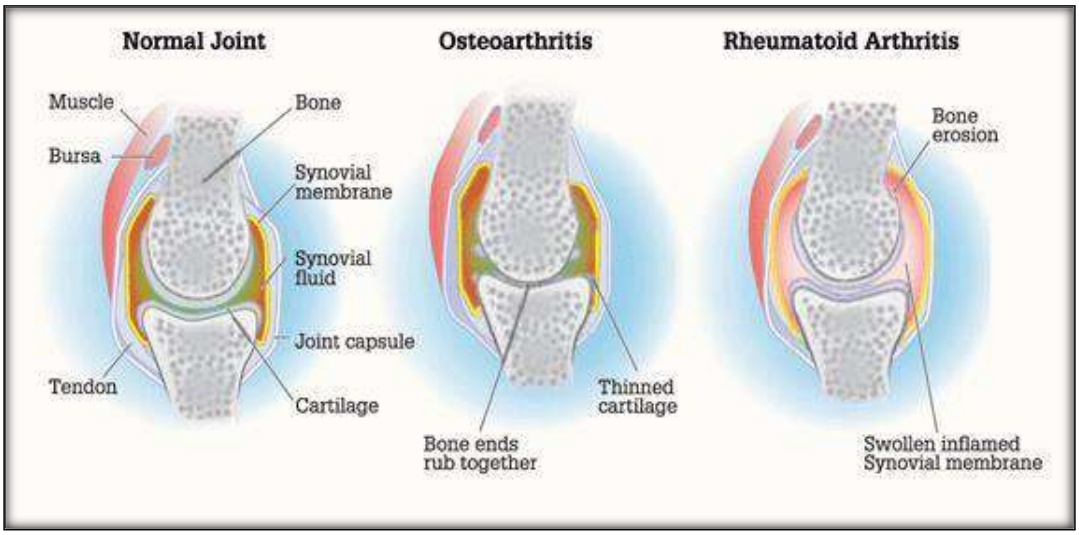


Figure No. 1 Normal and Arthritis join

2.Materials and methods:

2.1 Materials:

Curcumin was obtained as a gift sample from *Oliviya Organics Pvt. Ltd. Chennai, Tamil Nadu,* Etodolac was obtained as a gift sample from *AGM formulation and development Alembic Pharmaceutical LTD , Vadodara, Gujarat.*and all other excipients were obtained from Ana lab Fine Chemicals Mumbai. Double distilled water and analytical grade quality solvents were used throughout the research work.

2.2 Methods:

2.2.1 Preformulation Studies: (1-4, 17-18)

- ❖ The aim of Preformulation studies are follow:
- ✓ To check physiochemical characterization of new drug.
- ✓ To establish the compatibility with different excipients.

2.2.2 Formulation Design

2.2.2.1 Formulation of Core Tablet by Different Concentrations of Binder (Starch Paste 5%-10%)

Procedure for Formulation of Core Tablet: - (19-22)

Prepare core tablet with different concentrations of binder solution. Starch paste in the range of 5%-10%, granules was prepared by wet granulation method. Tablets prepared by direct compression method with 8mm punch. Each tablet resultant weight was 510mg.

Formulation Design of Core Tablet (F1-F3)

Formulation	F1	F2	F3
Etodolac	300mg	300mg	300mg
Curcumin	100mg	100mg	100mg
MCC	80mg	80mg	80mg
Starch Paste	5%	7.5%	10%
Etodolacnesium Stearate	0.5%	0.5%	0.5%
Talc	0.5%	0.5%	0.5%

Table No. 1 - Formulation Table of Core Tablet with Different Conc. Binder Solution

Evaluation of Core Tablet:

1. Thickness and Diameter test.
2. Hardness test.
3. Friability test.
4. Weight variation test.
5. Disintegration Test

Finalization of Core Tablet

Finalization of Core tablet batch depends on evaluation of all three (F1-F3) batches. From evaluation parameters which batch fulfill all parameters, this batch selected for the Coating.

2.2.2.2 Formulation of Finalized Batch of Core Tablet (5% Starch Paste) (22-23)

For core tablet granules prepared by wet granulation method in this 5% Starch Paste in Ethanol use as binder. Tablets prepared by direct compression method with 8mm punch. Each tablet resultant weight was 510mg.

Formulation Table of Core Tablet (F1)

Formulation	F1
Etodolac	300mg
Curcumin	100mg
MCC	80mg
Starch Paste	5%
Magnesium Stearate	0.5%
Talc	0.5%

Table No. 2 - Formulation Table of Selected Core Tablet (5% Binder Solution)

A) Pre-Compression Evaluation Parameters of Selected (5% Starch Paste binder solution) TABLET (26-28)

In Pre-compression evaluation Angle of repose, Bulk density and Tapped density, Carr's index, Hausner's ratio evaluated.

B) Post-Compression Evaluation Parameters of Selected (5% Starch Paste binder solution) TABLET (28-29)

In Post-compression evaluation Thickness and Diameter test, Hardness test, Friability test, Weight variation test, Disintegration test evaluated

2.2.2.3 Coating of Tablet

Preparation of Enteric Coating Solution: - (30)

In enteric coating solution Eudragit S100 is used as enteric coated polymer, PEG 600 use as plasticizer and Ethanol used as solvent. Enteric coating solution was prepared with constant stirring on Magnetic stirrer at 400 RPM.

A) Optimization of Enteric Coating Solution: - (31)

Factor	Eudragit S 100			PEG 600		
Coded level	-1	0	+1	-1	0	+1
Actual level	5%	7.5%	10%	0.5%	1.75%	3%

Table No. 3 - Optimizing Design Values of Eudragit S100 & PEG 600

B) Coating of Tablet in Enteric Coating Solution: - (20-22,32)

For coating of tablet dipping method was used. Coated tables were dried at 35^0C for 12hrs.

Batch	Concentration in Percentage	
	Eudragit S 100	PEG 600
F1	10	0.5
F2	4	1.75
F3	10	3
F4	7.5	1.75
F5	11	1.75
F6	7.5	3.5
F7	7.5	00
F8	5	3
F9	5	0.5

Table No. 4 - Formulation Table of Enteric Coated Solution

Evaluation of Enteric Coated Tablet: (32-35)

1. Thickness and Diameter test.
2. Hardness test.
3. Friability test.
4. Weight variation test.
5. Disintegration Test
6. In vitro drug release studies.
7. Stability Testing

3.Result and discussion:

3.1 Physical properties of drug:

Physiochemical properties	Curcumin		Etodolac	
	Reported	Observed	Reported	Observed
Appearance	Light yellowish orange color powder with characteristic odor.	Bright yellow-orange powder with characteristic odor	White powder with characteristic odor.	White powder with characteristic odor

Table No. 5 - Appearance of Curcumin and Etodolac

3.2 Formulation Compatibility Study by using IR

IR Spectra of Curcumin

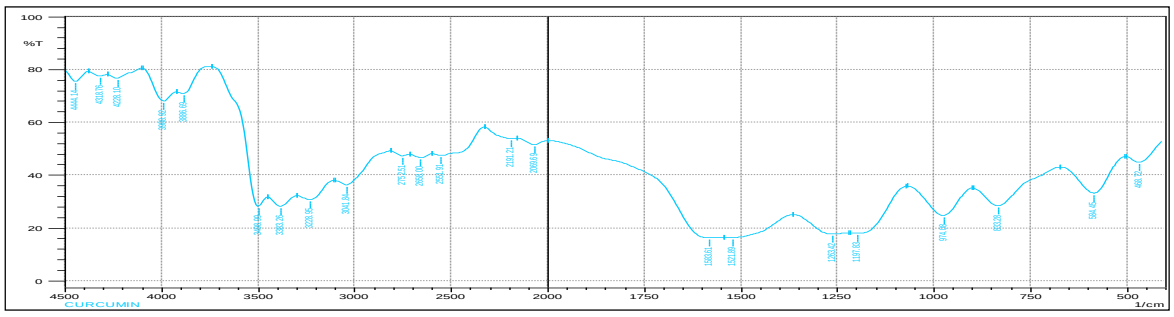


Figure No. 3 – IR spectra of Curcumin

IR Spectra of Etodolac

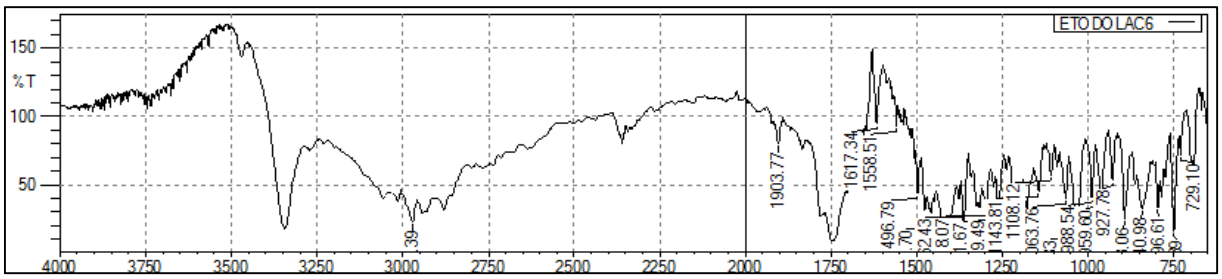


Figure No. 4 – IR spectra of Etodolac

Drug - Drug compatibility study

The FTIR analysis shown no changes in the endothermic peak of the drugs. (**Figure No. 5**) This study indicated there was no drug-drug incompatibility.

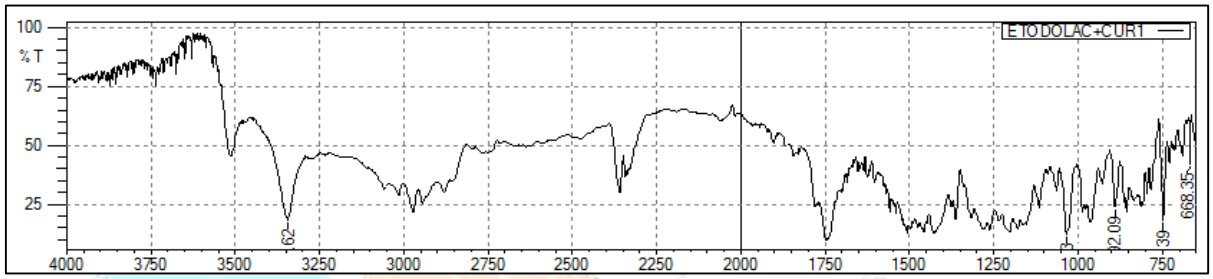


Figure No. 5 – IR spectra of Curcumin & Etodolac Combination

Drug excipients compatibility study

The FTIR analysis shown no changes in endothermic peak of drugs and excipients (**Figure No. 6**) This study indicated there was no drug-excipients incompatibility.

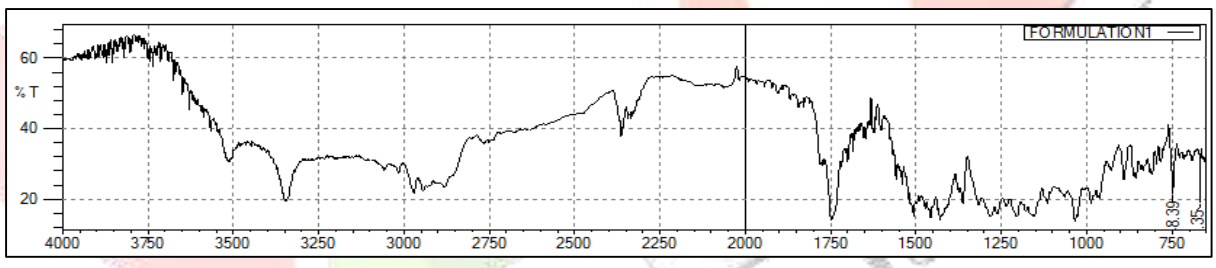


Figure No. 6 – IR spectra of Drug (Curcumin, Etodolac) and Excipient (MCC, Starch Paste)

Drug Excipient Compatibility of Core Tablet

The FTIR analysis shown no changes in endothermic peak of drugs and excipients in core tablet. (**Figure No. 7)** This study indicated there was no drug-excipients incompatibility in core tablet.

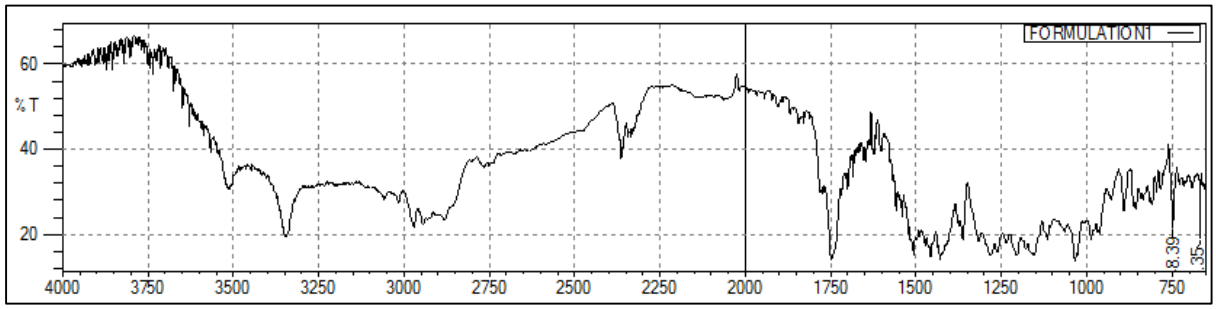


Figure No. 7 – IR spectra of Core Tablet

Drug Excipient of Enteric Coated Tablet

The FTIR analysis shown no changes in endothermic peak of drugs and excipients in coated tablet. (**Figure No. 8)** This study indicated there was no drug-excipients incompatibility in coated tablet.

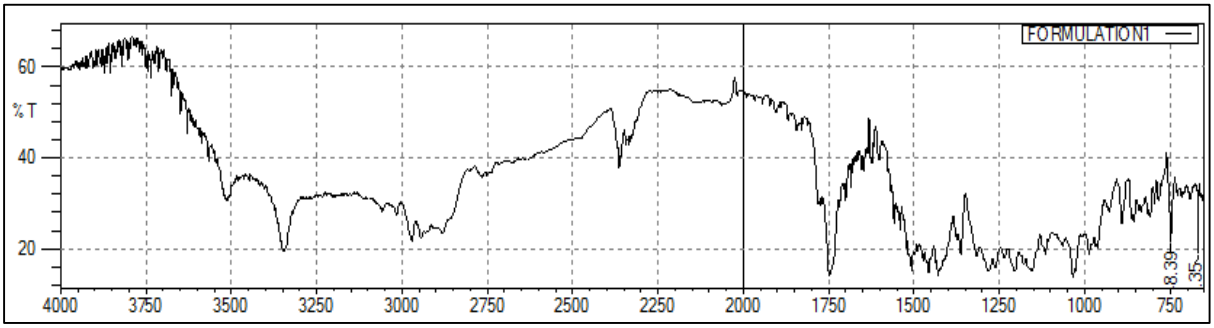


Figure No. 8 – IR spectra of Enteric Coated Tablet

3.3 UV-visible Spectroscopy:

Summary of Validation Parameter

Sr. No.	Parameter	Result of Curcumin	Result of Etodolac
1	Absorption maxima (λmax)	422nm	273nm
2	Linearity Range (µg/ml)	0.5-5	10-60
3	Correlation Coefficient (R^2)	0.9991	0.9996
4	Standard regression equation	y = 0.133x + 0.0119	y = 0.0167x - 0.0085
5	Intercept	0.0119	0.0085
6	Slope	0.133	0.0167

Table No. 6 - Summary of validation parameter of Curcumin and Etodolac in Ethanol

Sr. No.	Parameter	Result of Curcumin	Result of Etodolac
1	Absorption maxima (λmax)	421nm	271nm
2	Linearity Range (µg/ml)	0.5-5	10-60
3	Correlation Coefficient (R^2)	0.998	R^2 = 0.9983
4	Standard regression equation	y = 0.1185x - 0.0005	y = 0.0163x - 0.0041
5	Intercept	0.0005	0.0041
6	Slope	0.1185	0.0163

Table No. 7 - Summary of validation parameter of Curcumin and Etodolac in 0.1N HCl

Sr. No.	Parameter	Result of Curcumin	Result of Etodolac
1	Absorption maxima (λmax)	423nm	270nm
2	Linearity Range (µg/ml)	0.5-5	10-60
3	Correlation Coefficient (R^2)	0.9988	0.9986
4	Standard regression equation	y = 0.1247x + 0.0045	y = 0.0158x - 0.0058
5	Intercept	0.0045	0.0058
6	Slope	0.1247	0.0158

Table No. 8 – Summary of validation parameter of Curcumin and Etodolac in pH 6.8 Phosphate Buffer

3.5 Formulation Evaluation

3.5.1 Evaluation of Core Tablet [Different Concentrations of Binder (Starch Paste 5%-10%]

A) Thickness, Diameter, Hardness

Formulation Number	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)
F1	4.12±0.08	12.02±0.06	4.58±0.25
F2	4.09±0.01	12.09±0.02	6.85±0.25
F3	4.07±0.02	12.08±0.01	9.33±0.38

Table No. 9 - Evaluation Table of Core Tablet Containing Different Conc. of Polymer

B) Friability, Weight Variation, Disintegration

Formulation Number	Friability in Percentage	Avg. Weight Variation (mg)	Disintegration (min)
F1	0.22±0.012	510.18±1.68	4.51±0.09
F2	0.29±0.023	509.61±2.79	9.08±0.07
F3	0.18±0.018	511.60±1.375	13.16±0.14

Table No. 10 - Evaluation Table of Core Tablet Containing Different Conc. of Polymer

Finalization of Core Tablet Batch for Coating

Selection of final batch depends on various evaluation parameters e.g. Thickness, Diameter, Hardness, Friability, Weight Variation and Disintegration Time. After evaluation of above parameters, we selected **"F1"** formulation (which contain **5%Starch Paste**), which shown ideal property for core tablet.

3.5.2 (A) PRE-COMPRESSION EVALUATION PARAMETERS OF SELECTED (5% Starch Paste binder solution) TABLET

Sr. No.	Parameter	Result
1	Bulk Density	0.6988 gm/ml
2	Tap Density	0.7511 gm/ml
3	Carr's Index	6.963 %
4	Hausner Ratio	1.07 gm/ml
5	Angle of Repose	26.28^0

Table No. 11 – Pre-compression Evaluation of Selected Core Tablet

3.5.2 (B) POST-COMPRESSION EVALUATION PARAMETERS OF SELECTED (5% Starch Paste binder solution) TABLET

Sr. No	Parameter	Result
1	Thickness	4.11±0.09 (mm)
2	Diameter	12.01±0.05 (mm)
3	Hardness	4.51±0.25 (kg/cm^2)
4	Friability	0.18±0.012 %
5	Avg. Weight Variation	550.42±1.12 (mg)
6	Disintegration Test	4.45±0.35 (min.)

Table No. 12 - Post-Compression Evaluation of Selected Core Tablet

3.6 EVALUATION OF ENTERIC COATED TABLET:

A) Thickness, Diameter and Hardness

Formulation	Thickness (in mm)	Diameter in (mm)	Hardness (kg/cm^2)
F1	4.198±0.018	12.112±0.0119	4.57±0.32
F2	4.192±0.016	12.119±0.015	4.61±0.36
F3	4.211±0.019	12.124±0.014	4.5±0.25
F4	4.185±0.0194	12.117±0.010	4.62±0.13
F5	4.235±0.0188	12.130±0.016	4.55±0.3
F6	4.165±0.019	12.108±0.029	4.45±0.3
F7	4.226±0.016	12.128±0.015	4.5±0.25
F8	4.174±0.0144	12.112±0.007	4.55±0.3
F9	4.165±0.0198	12.109±0.0084	4.55±0.3

Table No. 13 - Enteric Coated Tablet Evaluation (Thickness, Diameter, Hardness)

B) Friability, Weight Variation

Formulation	Friability in Percentage	Avg. Weight Variation (mg)
F1	0.253±0.023	524.44±1.34
F2	0.211±0.017	527.33±1.43
F3	0.114±0.028	534.65±1.75
F4	0.194±0.025	525.33±1.53
F5	0.115±0.039	530.71±1.94
F6	0.21±0.0024	521.66±1.40
F7	0.265±0.027	523.62±1.38
F8	0.223±0.035	521.32±1.48
F9	0.254±0.029	520.35±1.49

Table No. 14 - Enteric Coated Tablet Evaluation (Friability, Avg. Wt. Variation)

C) Disintegration Time

Formulation Number	Time in Minute (Total -180 minute) 120 minutes in 0.1N HCl + 60 minutes in 6.8 phosphate buffer	
	Initially 0.1N HCl (for 120 minutes)	Phosphate Buffer 6.8 (for 60 minutes)
F1	49 min	-
F2	Not Dissolve	38
F3	Not Dissolve	43
F4	Not Dissolve	27
F5	Not Dissolve	55
F6	89 min	-
F7	Not Dissolve	21
F8	65 min	-
F9	Not Dissolve	16

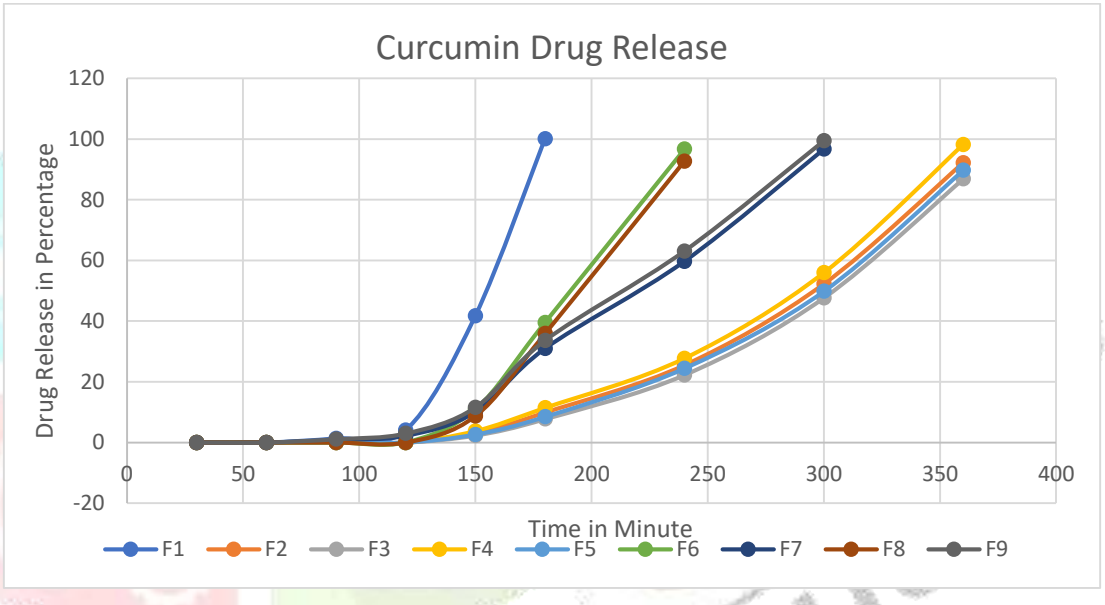
Table No. 15 - Enteric Coated Tablet Evaluation (Disintegration of Enteric coated tablet)

D) *In-vitro* drug release studies of Enteric Coated Tablets

% Drug Release of Curcumin

Time in Minutes	Formulation Number								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
30	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0
90	1.37	0	0	0	0	0	0.79	0	1.08
120	4.11	0	0	0	0	0	2.17	0	2.96
150	41.72	2.96	2.31	3.75	2.60	10.97	10.03	8.73	11.55
180	100.10	9.89	7.72	11.40	8.44	39.55	30.96	35.87	33.63
240		25.48	22.23	27.71	24.39	96.64	59.69	92.67	63.08
300		52.25	47.63	55.93	49.80		96.64		99.38
360		92.17	86.82	98.16	89.71				

Table No. 16 - % Drug Release of Curcumin from Different Formulation Enteric Coated Tablets

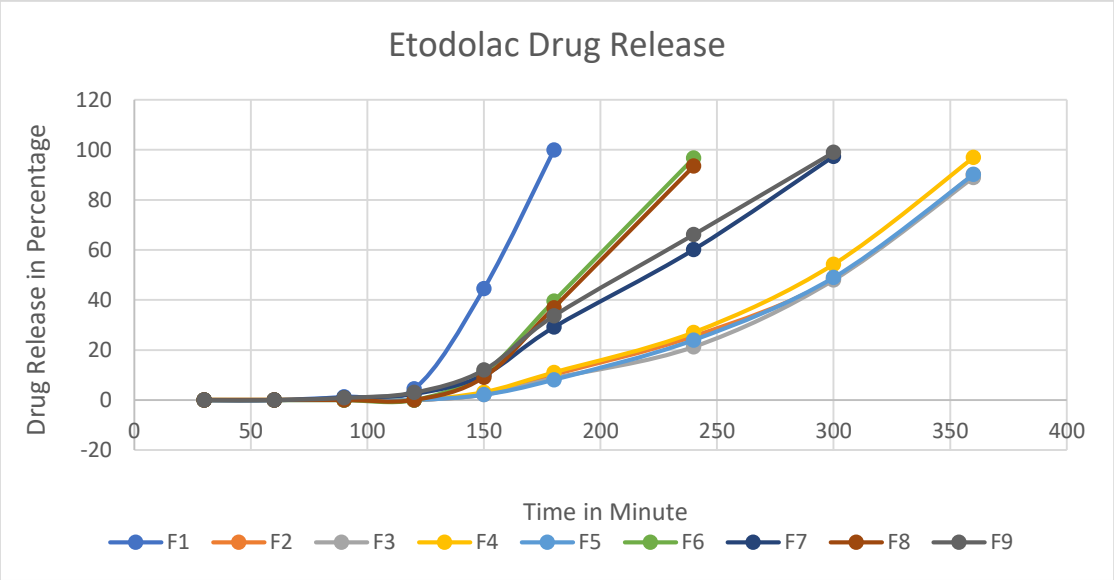


Graph No. 1 - % Drug Release of Curcumin from Different Formulation Enteric Coated Tablets

% Drug Release of Etodolac

Time in Minutes	Formulation Number								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
30	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0
90	1.27	0	0	0	0	0	0.89	0	0.88
120	4.42	0	0	0	0	0	2.47	0	3.01
150	44.52	2.26	2.11	3.12	2.1	10.97	10.01	9.12	12.05
180	99.87	10.12	8.72	10.99	8.11	39.55	29.12	36.88	33.66
240		25.48	21.23	27.01	23.97	96.64	60.1	93.44	66.12
300		48.42	47.93	54.22	48.94		97.34		98.96
360		90.03	88.92	96.90	90.12				

Table No. 17 - % Drug Release of Etodolac from Different Formulation Enteric coated tablets



Graph No. 2 - % Drug Release of Etodolac from Different Formulation Enteric coated tablets

Optimization Data for Drug Dissolution

Response 1: Curcumin Drug Release after 2 hours

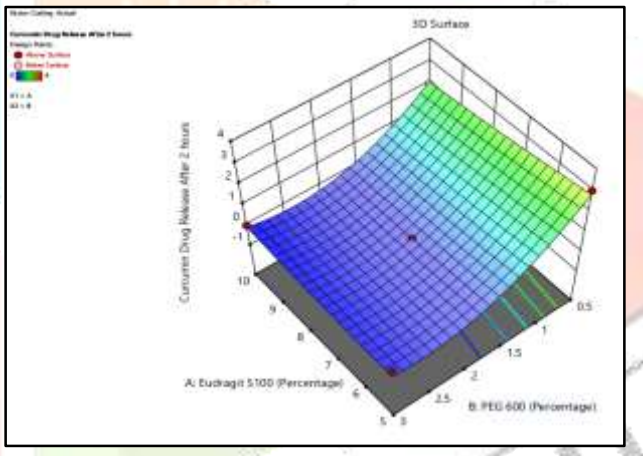


Figure No. 9 – 3D plot for the effect of concentration of Eudragit and Plasticizer on drug release of Curcumin after 2 hours

Response 2: Curcumin Drug Release within 6 hours

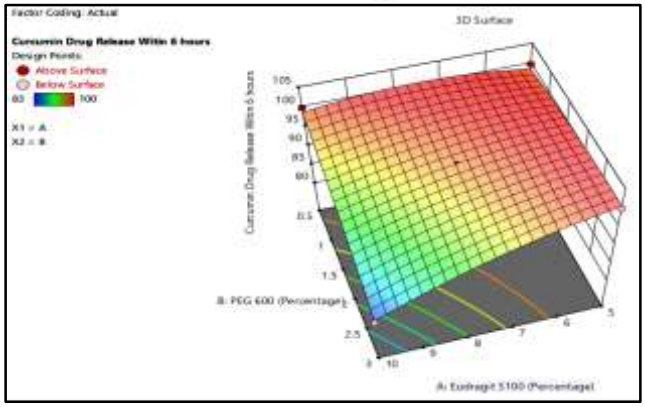


Figure No. 10 – 3D plot for effect of concentration of Eudragit and Plasticizer on drug release of Curcumin within 6 hours

Response 3: Etodolac Drug Release after 2 hours

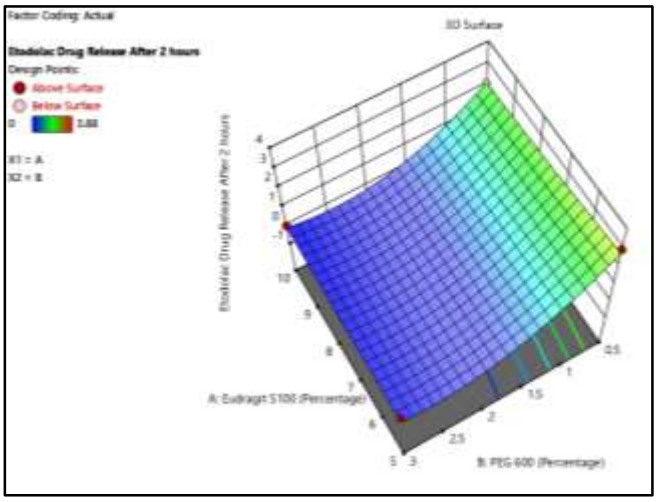


Figure No. 11 – 3D plot for effect of concentration of Eudragit and Plasticizer on drug release of Etodolac after 2 hours

Response 4: Etodolac Drug Release within 6 hours

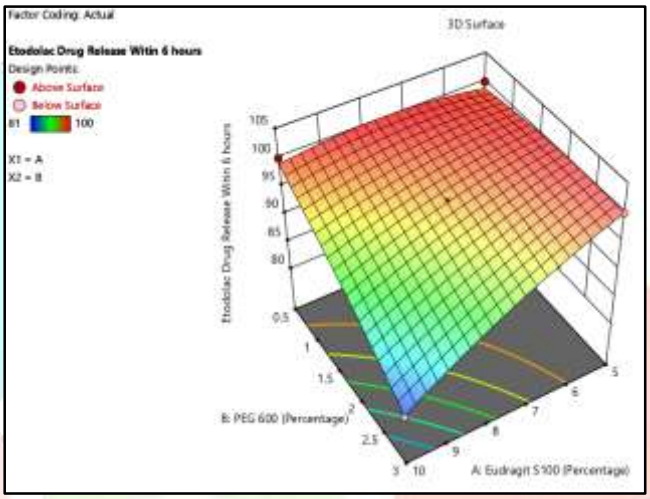


Figure No. 12 – 3D plot for effect of concentration of Eudragit and Plasticizer on drug release of Etodolac within 6 hours

3.6 Stability Testing

From the evaluation of all batches of enteric coated tablets **"F4"** formulation was found better results compared to other formulation. So, for stability study of enteric coated tablet **"F4"** formulation selected and carried out as per ICH guideline for 3 months ($40^0C \pm 2^0C$, RH 75%±5%).

a) Hardness of Tablet:

Time Interval	Hardness in (kg/cm^2)
Initial	4.50±0.35
1 Month	4.5±0.25
2 Month	4.55±0.3
3 Month	4.45±0.25

Table No. 18 - Hardness of Enteric Coated Tablet with a different time interval

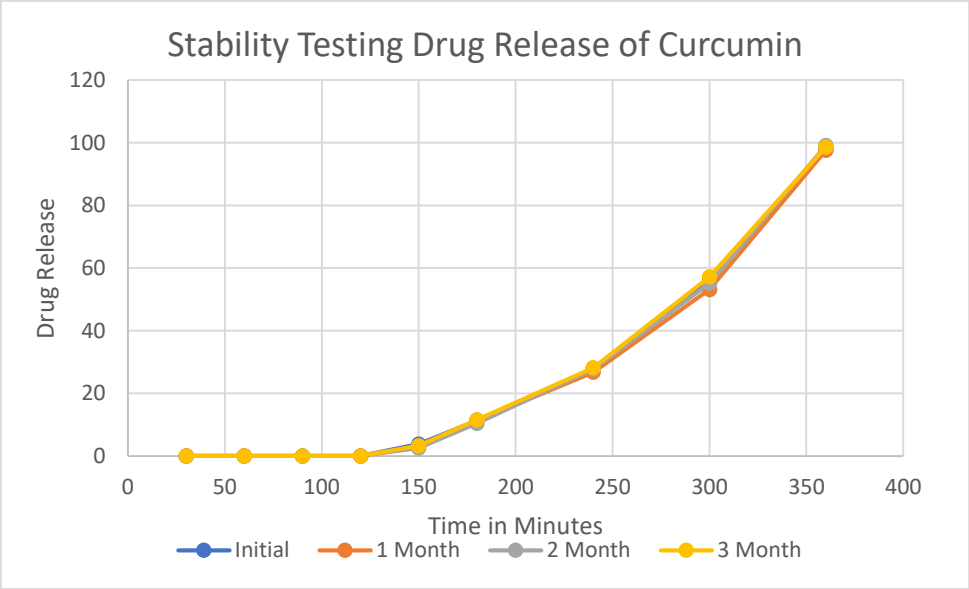
b) Dissolution Study:

Dissolution study was carried out in USP-II Paddle type apparatus in simulated gastric fluid in 900 ml at 50 rpm and the time points of sampling were 30, 60, 90, 120, 150, 180, 240, 300, 360 minutes.

% Drug Release of Curcumin with a different time interval

Time (in Minutes)	% w/w drug dissolved (Curcumin)			
	Initial	1 Month	2 Month	3 Month
30	0	0	0	0
60	0	0	0	0
90	0	0	0	0
120	0	0	0	0
150	3.75	3.11	2.55	3.25
180	11.40	11.22	10.44	11.55
240	27.71	26.704	27.74	28.12
300	55.93	53.12	55.12	57.18
360	98.16	97.55	99.10	98.60

Table No. 19 - % Drug Release of Curcumin from Enteric Coated Tablet with diff. time interval

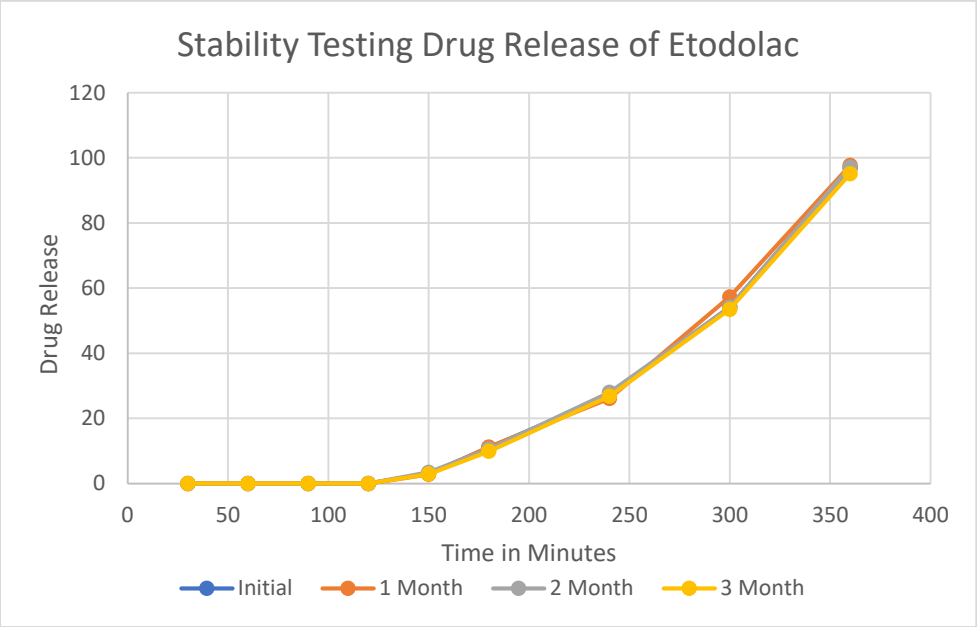


Graph No. 3 - % Drug Release of Curcumin from Enteric Coated Tablet with diff. time interval

% Drug Release of Etodolac with a different time interval

Time (in Minutes)	% w/w drug dissolved (Etodolac)			
	Initial	1 Month	2 Month	3 Month
30	0	0	0	0
60	0	0	0	0
90	0	0	0	0
120	0	0	0	0
150	3.12	2.80	3.42	2.92
180	10.99	11.22	10.55	9.87
240	27.01	26.12	27.99	26.77
300	54.22	57.33	54.11	53.48
360	96.90	97.66	97.12	95.10

Table No. 20 - % Drug Release of Etodolac from Enteric Coated Tablet with a different time interval



Graph No. 4 - % Drug Release of Etodolac from Enteric Coated Tablet with a different time interval

c) Drug Recovery

Time Interval	Curcumin: Etodolac (in ml)	Concentration (in µg/ml)		Recovered conc. (in µg/ml)		% Recovery	
		Curcumin	Etodolac	Curcumin	Etodolac	Curcumin	Etodolac
Initial	0.25:1ml	2.5	10	2.48	9.911	99.20	99.110
	0.5:2ml	5	20	4.91	19.890	98.20	99.450
	0.75:3ml	7.5	30	7.42	29.121	98.93	97.070
1 Month	0.25:1ml	2.5	10	2.41	9.880	96.40	98.800
	0.5:2ml	5	20	5.01	19.920	100.20	99.600
	0.75:3ml	7.5	30	7.39	30.020	98.53	100.067
2 Month	0.25:1ml	2.5	10	2.51	9.88	100.40	98.80
	0.5:2ml	5	20	4.87	20.01	97.40	100.05
	0.75:3ml	7.5	30	7.43	29.87	99.07	96.56
3 Month	0.25:1ml	2.5	10	2.49	9.794	99.60	97.935
	0.5:2ml	5	20	4.97	19.827	99.40	99.136
	0.75:3ml	7.5	30	7.36	29.134	98.13	97.115

Table No. 21 - Drug Ratio Recovery from Enteric Coated Tablet with a different time interval

4. Conclusion:

The present study of Curcumin and Etodolac enteric coated drug delivery system avoids drugs release in a gastric fluid which minimise curcumin degradation and directly release of both drugs in the intestine. The combination of Curcumin and Etodolac used for treatment of Rheumatic Arthritis more effectively because in long term therapy Etodolac gives some saviour side effect such as liver toxicity, intestinal ulcer, Ulcerative Colitis etc. which is minimised by Curcumin which gives more benefits for prolong therapy of Rheumatic Arthritis. Advantages of Curcumin and Etodolac combinational drug therapy can serve as better alternative for prolonged use compared to existing NSAID as comparatively less side effects are associated with Curcumin and Etodolac.

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