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PREPARATION AND EVALUATION OF MATRIX TABLET FOR TARGETED DELIVERY OF ANTI-INFLAMMATORY AGENT TO THE COLON

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INTRODUCTION

The targeted delivery of pharmaceutical agents has gained significant attention in recent years, aiming to enhance the therapeutic efficacy and minimize side effects. In this context, the development of matrix tablets for colon-specific drug delivery holds great promise. This study focuses on the preparation and evaluation of a matrix tablet containing an anti-inflammatory agent intended for targeting the colon. The use of such a formulation could offer numerous advantages, including improved drug absorption, reduced systemic exposure, and increased patient compliance. By employing specific coating techniques and incorporating colon-targeting polymers, this research aims to optimize the formulation parameters to achieve efficient drug delivery to the colon, ultimately providing a potential solution for the treatment of inflammatory bowel diseases and related conditions.

KEYWORDS: Evaluation, Matrix tablet, Anti-inflammatory agent, Colon target.

METHODOLOGY

Chemicals: Indomethacin, Eudragit S100, Ethyl cellulose, Lactose (DCL 21), Talc, Magnesium stearate, Eudragit FS 30D, Tri Ethyl Citrate, Purified talc.

Equipments: Weighing balance, Bulk density apparatus, Compression machine (8 station), Coating pan, Hardness tester, Thickness tester, Disintegration apparatus, Dissolution apparatus, FTIR Spectrophotometer 8300, U.V spectrophotometer

Preformulation Studies
Evaluation of indomethacin (API) physical characteristics of API

S. No	Tests	Specification	Results
1	Colour	White or off white powder	White or off white powder
2	Solubility	Practically insoluble in water, freely solublein acetone, methanol and in methlyene chloride. It dissolves in dilute solution of alkali hydroxide and carbonates	Complies
3	Melting point	75.0° -78.0°C	76.4°C
4	Moisturecontent	NMT 0.5 w/w%	0.3% w/w

The color, solubility, melting point and moisture content of the API were evaluated. Itwas found to be within the range of the monograph.

1.2 Angle of repose of indomethacin

S. No	Raw material (API)	Angle of repose (Degree)	Average
1	Indomethacin	$38^0.14'$	$38^0.56' \pm 0.69$
2	Indomethacin	$39^0.36'$	
3	Indomethacin	$38^0.12'$	

The angle of repose of API was found to be $38^0.56' \pm$ 0.69. Hence the drug belongs to fair flow and requires glidants to improve the flow property.

1.3 Bulk density and tapped density of indomethacin

S. No	Raw material (API)	Bulk density(g/ml)	Average bulk density (g/ml)	Tapped density(g/ml)	Average tapped density (g/ml)
1	Indomethacin	0.459	0.453 ± 0.01	0.612	0.614± 0.003
2	Indomethacin	0.452		0.614	
3	Indomethacin	0.448		0.618	

The average bulk density and tapped density was found to be 0.453 ± 0.01 and0.614± 0.003 g/ml respectively.

1.4 Powder compressibility and Hausner's ratio

Raw material (API)	Compressibility index (%)	Hausner's ratio
Indomethacin	26.22	1.35

Based on Compressibility index and Hausner's ratio, it indicates the Indomethacin (API) belongs to poor flow property.

1.5 Particle size distribution

Sieveno	Empty weight of sieve	Quantity retained (gm)	Mass retained (gm)	Cumulative mass retained(gm)	Cumulative % retained	Percentage passing %
#20	367.8	368.55	0.75	0.75	4.34	95.66
#30	417.65	417.85	0.2	0.95	5.5	94.5
#40	358.05	365.65	7.6	8.55	49.56	50.44
#60	343.45	343.65	0.2	8.75	50.72	49.28
#80	340.75	340.9	0.15	8.9	51.59	48.41
#100	332.5	332.85	0.35	9.25	53.62	46.38
Base	540.45	548.45	8	17.25	100	0

From the particle size analysis it was concluded that the particles size of the API was found to be moderately coarse powder.

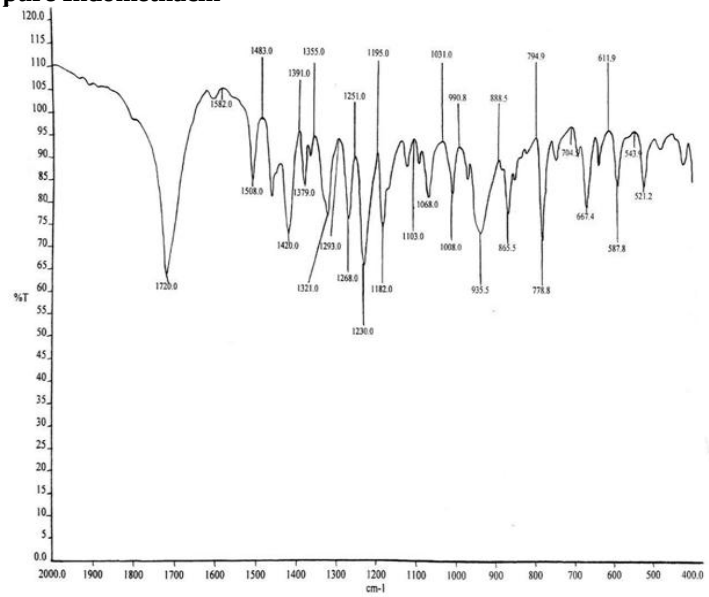
2. DRUG - EXCIPIENTS COMPATIBILITY STUDIES

S. No	Composition	Initial	After 15days	After 30days	Conclusion
1	Indomethacin	White	NCC	NCC	Complies
2	Indomethacin + Excipients	White	NCC	NCC	Complies

- **NCC-** No Characteristic Change.

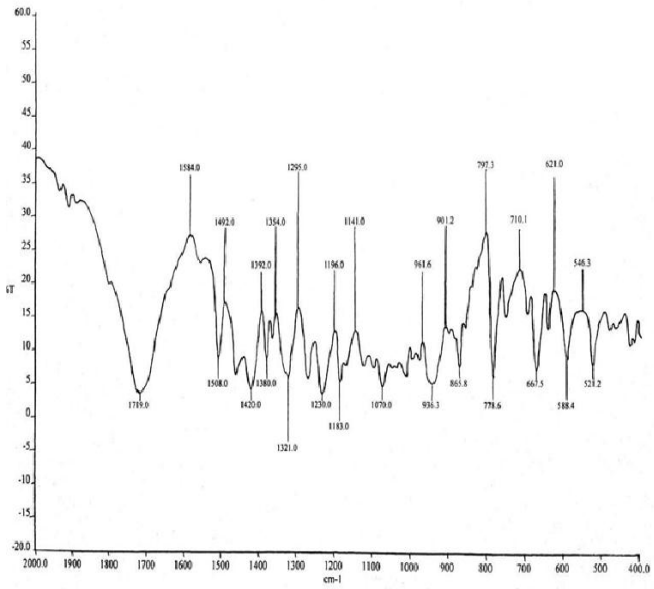
From the drug excipients compatibility study, it was observed that there was no characteristic change or interaction between drug and excipients. Thus it was concluded that the excipients selected for the formulation were compatible with Indomethacin.

2.1 FT-IR spectra of pure Indomethacin



S. No	Wave Number (cm^{-1})	Functional Group
1.	1720.0	C=O Stretching of carboxylic acid
2.	1420.0	C=C Stretching of Benzene
3.	1321.0	Methyl of alkane
4.	1230.0	Methylene of Benzene ring
5.	1068.0	C-O of carboxylic acid
6.	935.5	CH_2 bending vibration of alkane

2.2 FT-IR spectra of indomethacin with excipients



S. No	Wave Number (cm^{-1})	Functional Group
1.	1719.0	C=O Stretching of carboxylic acid
2.	1420.0	C=C Stretching of Benzene
3.	1380.0	Methyl of alkane
4.	1230.0	Methylene of Benzene ring
5.	1070.0	C-O of carboxylic acid
6.	936.3	CH_2 bending vibration of alkane

Pure Indomethacin spectra showed sharp characteristic peaks at 1720.0, 1420.0, 1321.0, 1230.0, 1068.0, 935.5 cm^{-1}. These peaks are also prominent in the FTIR spectra's of the physical mixtures containing Indomethacin and other excipients in the final formula. This indicates that there is no interaction between the drug and excipients from both Physical observation and FT-IR studies.

3. EVALUATION OF LUBRICATED POWDER BLEND

Formulation Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio	Angle ofrepose (degree)	Moisture content (%)
F1	0.35±0.02	0.40 ± 0.01	11.73±0.79	1.12 ±0.15	$29^0$58'±0.53	1.15 ± 0.05
F2	0.31±0.03	0.35 ± 0.05	12.10±0.54	1.13 ±0.28	$33^0$23'±0.35	1.28 ± 0.02
F3	0.37 ± 0.01	0.42 ± 0.06	13.63±0.38	1.13 ±0.12	$30^0$96'±0.19	1.42 ± 0.02
F4	0.38 ± 0.07	0.40 ± 0.08	11.57±1.05	1.14± 0.85	$31^0$26'±0.60	1.21 ± 0.06
F5	0.35 ± 0.10	0.44 ± 0.06	12.60±0.86	1.12 ±0.74	$29^0$35'±0.48	1.33 ± 0.03
F6	0.41± 0.06	0.46± 0.01	12.98±0.65	1.13 ±0.24	31^0.05'±0.25	1.15 ± 0.02

All values are expressed as mean ± standard deviation, n=3

- The bulk density and tapped density of all formulations were measured by using graduated measuring cylinder. The bulk density was found in the range of 0.31- 0.41gm/cm^3. The tapped density was between 0.35-0.46 gm/cm^3. Both are within the acceptable limits.
- If the compressibility index of the powder is between 11 and 15, it shows good flow character; here all the formulations exist in the range between 11.73-13.63. It indicates that the granules showed good flow character.
- The result showed that the Hausner ratio of all the formulations was between 1.12-1.14, if the Hausner ratio lies between 1.12-1.18, it shows good flow behavior of the granules or powder. The result indicates good flow property of the granules.
- If the angle of repose is within 35^0, it indicates good flow property of the granules. The result showed that the angle of repose of all the formulations was between 29^0-33^0.It proved that the flow properties of all formulations are good.

4. EVALUATION OF FINISHED PRODUCT (UNCOATED)

Parameters	F1	F2	F3	F4	F5	F6
Average weight(mg)	275±1.18	275±0.89	275±2.00	275±0.61	275±2.68	275±0.21
Thickness (mm)	3.4± 0.16	4.2±0.09	4.7± 0.14	5.9± 0.12	5.7±0.01	5.9 ± 0.16
Hardness (kg/cm^2)	12.6 (± 0.15)	9.4 (± 0.22)	6.2(± 0.30)	5.2(± 0.32)	6.0(± 0.30)	5.8(± 0.11)
Friability (%)	0.36	0.41	0.39	0.31	0.35	0.33
Disintegration time (min)	-	24'46''	17'42''	14'45''	8'42''	7'18''
Assay (%)	99.34	99.2	98.51	99.85	99.53	100.21

All values are expressed as mean ± standard deviation, n=3

- The thickness of the tablets was in the range of 3.4 to 5.9 mm. This is due to the upperand lower punch adjustments during compression process.
- The prepared tablets in all the trials possessed good mechanical strength with sufficient hardness in the range of 12.6 to 5.2 kg/cm^2.
- The friability of the tablets was found to be within 1%. All the above trail formulationshave passed the friability test.
- The average weight of all the formulations was found to be 275 mg. It is within the permissible range.
- The percentage of drug content was found among different batches of the tablets and ranged from 98.5 to 100.21 which were within the acceptable limits.

5. EVALUATION PARAMETERS OF INDOMETHACIN ENTERIC COATED TABLET

Trial	Thickness(mm)	Weight variation(mg)	Disintegrationtime(min)	Assay (%)	Drug release(%)
F6	6.0 ± 0.02	292±0.21	218'63'' ±1.98	99.92 ± 0.08	98.51

All values are expressed as mean ± standard deviation, n=3

Indomethacin tablet of the above trial (F6) was satisfied of all the parameters. It was coated by using enteric coating method. The coated tablets were evaluated for the following parameters including thickness, disintegration test, weight variation, assay and *in-vitro* studies.

6. COMPARATIVE DATAS OF UNCOATED AND ENTERIC COATED INDOMETHACINTABLETS

Trial	Thickness (mm)	Weight variation (mg)	Assay (%)	Drug release (%)
F6 Uncoated	5.9 ± 0.16	276±5	100.21±0.12	99.69 at 12 hrs
F6 Enteric coated	6.0±0.02	292±5	99.92 ± 0.08	98.51 at 24 hrs

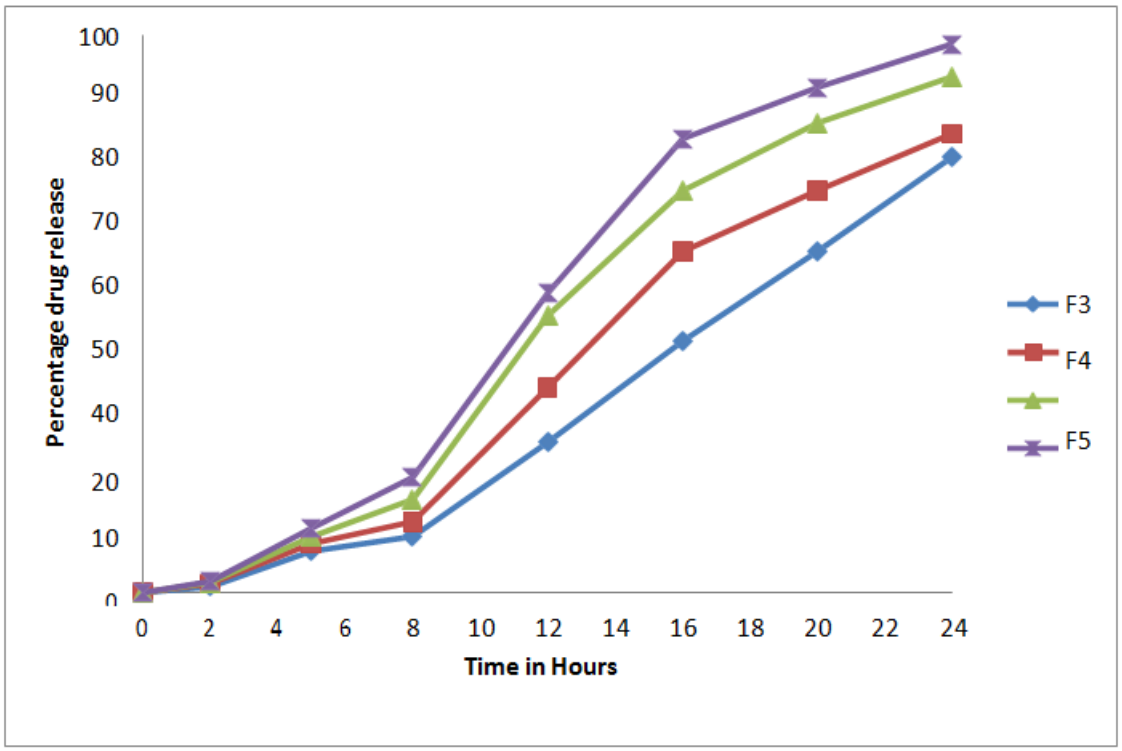
All values are expressed as mean ± standard deviation, n=3

Indomethacin Enteric coated tablets were compared with the same trial of uncoated Indomethacin tablets. The thickness of enteric coated tablets was found to be more than uncoated tablets. Weight variation was increased in enteric coated tablets than the uncoated tablets. This is due to the coating of core tablet.

7. *IN-VITRO* DISSOLUTION PROFILE OF ENTERIC COATED TABLETS

DissolutionMedia	Samplingtime	Cumulative% drug release in different trials			
		F3	F4	F5	F6
Simulated gastric fluid(0.1 HCL)	2 Hrs	1.07	1.60	1.83	2.00
Simulated Intestinal Fluid (7.4pH Phosphatebuffer)	5 Hrs	7.43±0.32	8.804±0.13	10.09±0.78	11.58±0.13
	8 Hrs	10.09±0.78	12.74±0.43	16.76±0.13	20.72±0.43
	12 Hrs	26.97±0.52	36.82±1.35	49.76±0.57	53.80±0.78
	16 Hrs	45.18±0.95	61.24±0.52	72.21±0.95	81.51±0.57
	20 Hrs	61.24±0.57	72.19±0.43	84.31±0.57	90.71±0.95
	24 Hrs	78.22±0.78	82.43±0.57	92.65±0.95	98.51±0.78

Graphical representation of *in-vitro* drug release



F1: The method used in this trial is direct compression. The concentration of Eudragit S 100 used was 80 mg/unit, Ethyl cellulose concentration was 60mg/unit. Lactose DCL 21 was 50mg/unit. And the concentration of Talc and magnesium stearate used was 5mg/unit. The hardness of the tablet were crossed the specification limit.

F2: Same as procedure of F1. But in this formulation the concentration of Eudragit S100 and Ethyl cellulose was decreased to 60 mg/unit and 55mg/unit. And diluent concentration increased to 75mg/unit. The hardness of this formulation were better than the above formulation but the time required to disintegrate tablets were crossed the specification limit.

F3: The hardness were achieved. But the time required to disintegrate tablets were crossed the specification limit. In this formulation the concentration of Eudragit S100 and Ethyl cellulose was decreased to 50 mg/unit and 40 mg/unit to reduce the hardness of the tablets. And the diluent concentration increased to 100mg/unit. This formulation was selected for coating. And the tablets were subjected to *in-vitro* dissolution study. The release

was found to be 78.22±0.78 at 24hrs.

F4: In trial 4 the concentration of Eudragit S100 and Ethyl cellulose was further decreased to 35mg/unit and 25mg/unit and increased the Lactose DCL21 concentration to 130mg/unit. The disintegration time of tablet was better than the above formulations but crossed the limits. The tablets were subjected to *in-vitro* dissolution study.

F5: The concentration of Eudragit S100 and Ethyl cellulose was further decreased to 20mg/unit and 15mg/unit and increased the Lactose DCL21 concentration to 154mg/unit. The concentration of Magnesium stearate was increased to 6mg/unit to improve the lubrication of granules. The disintegration time of tablet was found to be within the limit. The triethyl citrate was used in the enteric coating part, to give better flexibility to the polymer. The tablets are subjected to *in-vitro* dissolution study. The percentages of drug release were found to be 92.65±0.95 at 24 hrs. It was better than the earlier trials.

F6: The concentration of Eudragit S 100 and Ethyl cellulose was further decreased to 14mg/unit and 10mg/unit and increased the Lactose DCL21 concentration to 165mg/unit. The tablets of this trial are subjected to *in-vitro* dissolution study. The percentage of drug release showed 98.51±0.78 at 24 hrs. This trial was taken as confirmatory trial and subjected as stability studies.

7. STABILITY STUDIES

7.1 Physical parameters

Stability studies for post compression parameters of (F-6) enteric coated tablets.

Post compressionParameters	Storage condition: 40^0C± 2^0C /75±5%RH			
	Initial	1st month	2nd month	3rd month
Description	White coloured Enteric coatedtablet	White coloured Enteric coatedtablet	White coloured Enteric coatedtablet	White coloured Enteric coatedtablet
Average weight (mg)	292±0.21	292.38 ± 0.003	292.52 ± 0.006	292.67 ± 0.04
Disintegration time(minutes)	219’63’’±0.03	219’13’’±0.08	220’ 38’’±0.08	221’ 7’’ ±0.05

*All the values are expressed as mean’s, n=3.

The F-6 formulation of enteric coated tablets was carried out for the stability study. It was kept at 40^0C± 2^0C/75±5%RH. It revealed that there were no significant changes in color but slight increase in average weight and disintegration time. The sample was tested at one month interval.

8. *IN-VITRO* DRUG RELEASE AND ASSAY

Formulation	Time inhrs	Storage condition 40^0C±2^0C /75±5%RH					
		In-vitro drug release (%)				Assay (%)	
		Initial	1 month	2 month	3 month	Initial	After Stability
F6	24	98.51	98.31	97.42	97.28	100.21	100.1

The F6 formulation of enteric coated tablets was carried out for the stability study, it was kept in 40^0C± 2^0C /75±5% RH for the period of three months. Percentage of drug release and assay was determined. The data’s does not showed much variation during stability studies. The results revealed that the product was stable.

CONCLUSION

In conclusion, preformulation studies confirmed the absence of interaction between the active pharmaceutical ingredient (API) and excipients. Indomethacin matrix tablets were successfully formulated using the direct compression method with appropriate excipient quantities. The tablets met pharmacopoeia standards in terms of pre-compression and post-compression parameters. Enteric polymer Eudragit FS 30D was used to coat the tablets via pan coating. Among all batches, formulation F6 exhibited optimal drug release, with 98.51% release at 24 hours. Formulation F6, an enteric coated matrix tablet of Indomethacin, holds promise as a treatment for ulcerative colitis, offering protection in acidic conditions and rapid release in intestinal pH, without gastric irritation or ulcers.

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