PH DEPENDENT, TIME DELAYED AND COMPRESSED TABLETS FOR COLON TARGETING

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ABSTRACT

The development of oral drug delivery systems capable of targeting specific parts of the gastrointestinal tract, such as the colon, has sparked widespread interest due to its potential to improve therapeutic efficacy while avoiding systemic side effects. In this paper, we describe a unique technique to colon targeting that uses pH-dependent, time-delayed, compressed tablets. To enable regulated medication release in the colon, the tablets were made with a combination of pH-sensitive polymers and excipients. Several formulations were created and tested for their physicochemical features, drug release profiles, and in vitro dissolving behaviour in simulated gastrointestinal settings. Our findings show that the designed tablets have pH-dependent dissolution behaviour, with minimum drug release in the stomach and small intestine, followed by progressive release in the colon.

Keywords: *compressed coated, Naproxen, Formulations, Drug, Excipients, IR, DSC.*

1. INTRODUCTION

Oral controlled - release formulations for the small intestine and colon have received considerable attention in the past 25 years for a variety of reasons including pharmaceutical superiority and clinical benefits derived from the drug - release pattern that are not achieved with traditional immediate or sustained release products. Colon targeted drug delivery would ensures direct treatment at the disease site, lower dosing and less systemic side effects. In addition to restricted therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation. For example, molecules that are degraded/poorly absorbed in the upper gut, such as peptides and proteins, may be better absorbed from the more benign environment of the colon.

Why colon targeted drug delivery needed

- Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.

- Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases.
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Cohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and Sulphasalazine (targeted).
- A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.
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Criteria for Selection of Drug for CDDS

The best Candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhoea, and colon cancer are ideal candidates for local colon delivery. Drug Carrier is another factor which influences CDDS**.** The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the system**.**

2. Materials and Methods

Naproxen, MCC, Magnesium stearate, cross povidone, sodium starch glycolate, Ethyl cellulose, Eudragit L 100, Ethyl cellulose.

METHOD OF PREPARATION:

STEP 1: FORMULATION OF NAPROXEN CORE TABLETS

The inner core tablets were prepared by using direct compression method. As shown in Tablet powder mixtures of Naproxen, microcrystalline cellulose (MCC), SSG, crospovidone, ingredients were dry blended for 20 min. Followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 200 mg of resultant powder blend was manually compressed using KBr hydraulic press at a pressure of 1 ton, with a 8mm punch and die to obtain the core tablet.

TABLE 1: PREPARATION OF CORE TABLETS BY USING DIFFERENT DISINTEGRATING AGENTS (FC1-FC6)

	FC1	FC2	FC3	FC4	FC5	FC6
Naproxen	10mg	10mg	10mg	10mg	10mg	10mg
Magnesium stearate	2mg	2mg	2mg	2mg	2mg	2mg
Microcrystalline cellulose	184mg	181mg	178mg	184mg	181mg	178mg
Cross Povidone	2%	3.5%	5%	-	-	-
Sodium starch Glycolate	-	-	-	2%	3.5%	5%
Total weight (mg)	200mg	200mg	200mg	200mg	200mg	200mg

STEP 2: FORMULATION OF COMPRESSION COATED TABLETS

The core tablets were compression coated with Eudragit L100 and Ethyl Cellulose with different ratios like(1:0, 0:1, 1:3, 3:1, 2:2, 2:3).Half of the quantity of the coating material was placed in the die cavity; the core tablet was carefully placed in the centre of the die cavity and was filled with the other half of the coating material the coating material was compressed using 13mm punch at a pressure of 5 tons for 3min using KBr hydraulic press.

TABLE 2: PREPARATION OF PRESS COATED TABLTES BY USING POLYMERS

FORMULATION CODE	EUDRAGIT & ETHYL CELLULOSE RATIOS (400mg)
FC1	1:0
FC2	0:1
FC3	1:3
FC4	3:1
FC5	2:2
FC6	2:3

EVALUATION PARAMETERS:

Evaluation of the Core and Compressed Tablet:

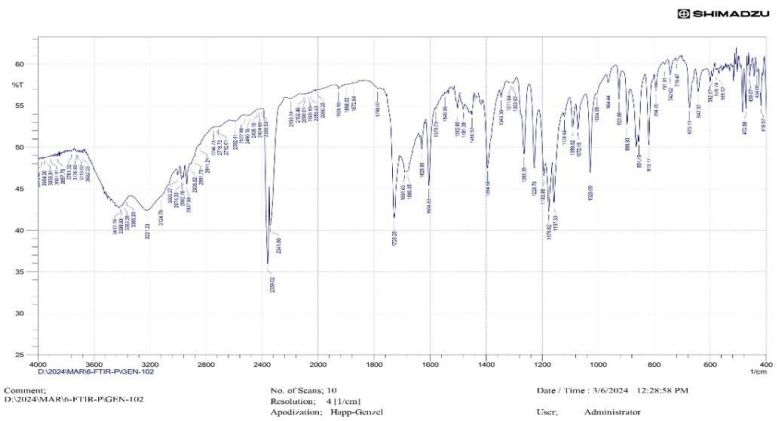

Fig 1: FTIR PURE DRUG OF NAPROXEN

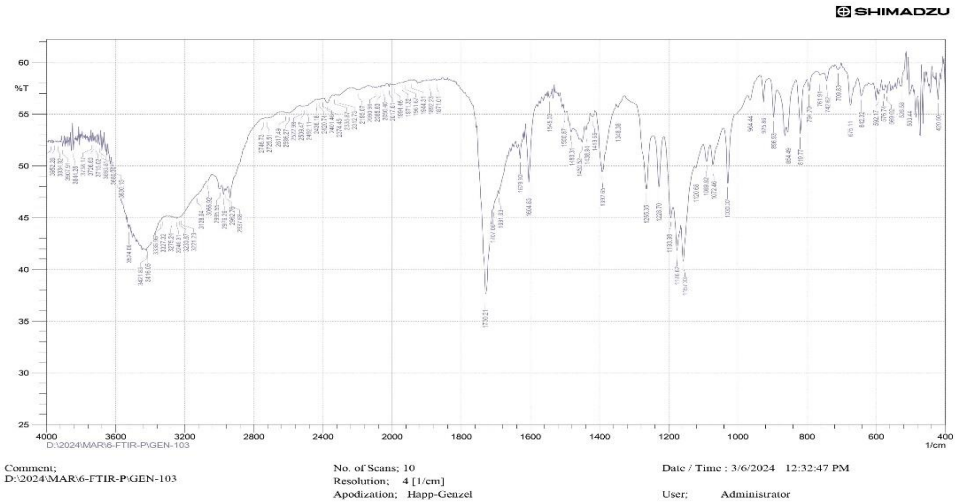

Fig: 2 FTIR OF CORE TABLET MIXTURE

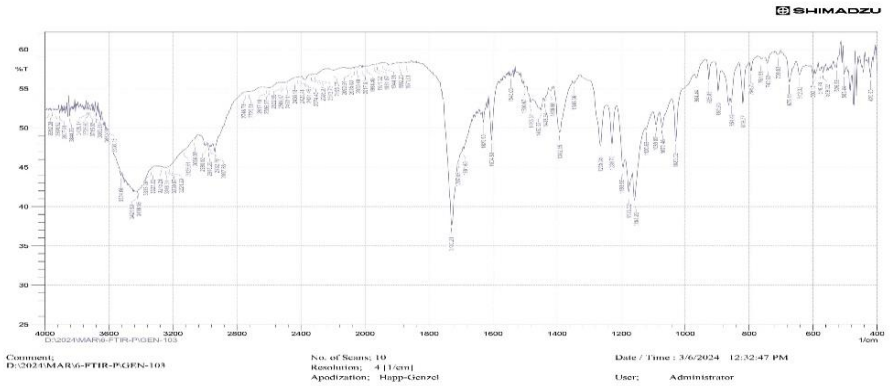

Fig:3 FTIR OF DRUG WITH POLYMERS

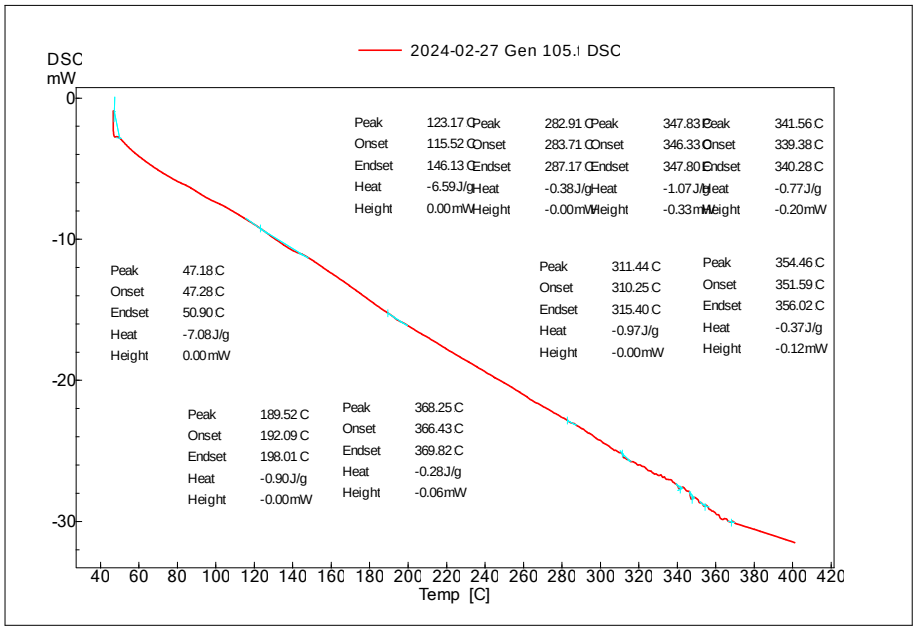

Fig: 4 DSC OF PURE DRUG

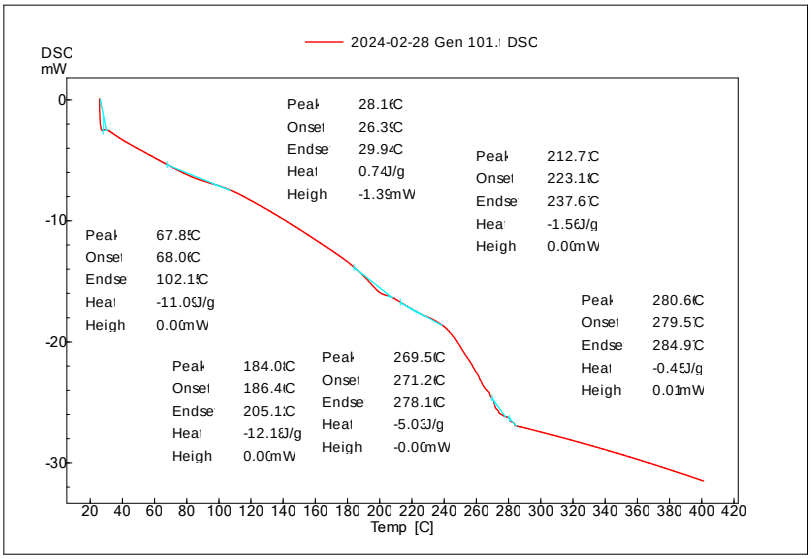

Fig: 5 DSC OF CORE TABLET MIXTURE

TABLE: 3 STANDARD CALIBRATION CURVE OF NAPROXEN IN pH 1.2, 6.8 & 7.4

Concentration mcg/ml	Absorbance in pH 1.2	Absorbance in pH 6.8	Absorbance in pH 7.4
2	0.101	0.042	0.364
4	0.204	0.128	0.418
6	0.289	0.221	0.481
8	0.389	0.289	0.522
10	0.453	0.354	0.601

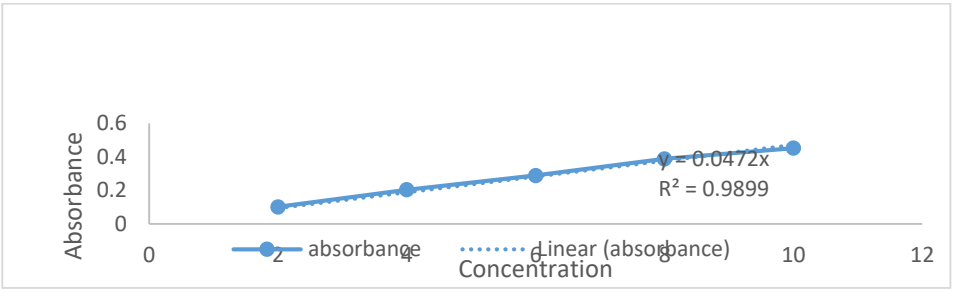

Fig: 6 STANDARD GRAPH OF NAPROXEN IN 0.1N HCl

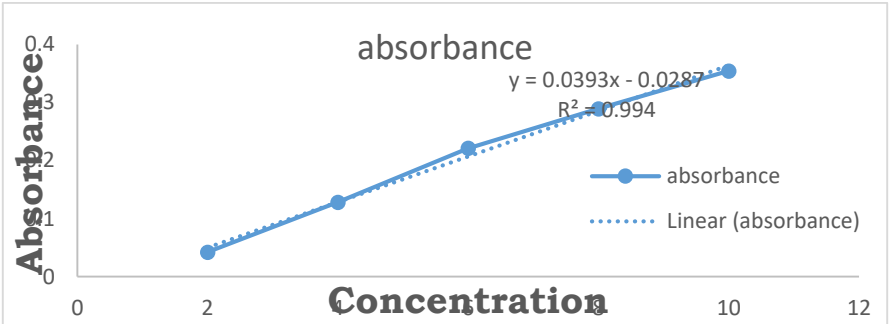

Fig: 7 STANDARD GRAPH OF NAPROXEN IN pH 6.8 BUFFER

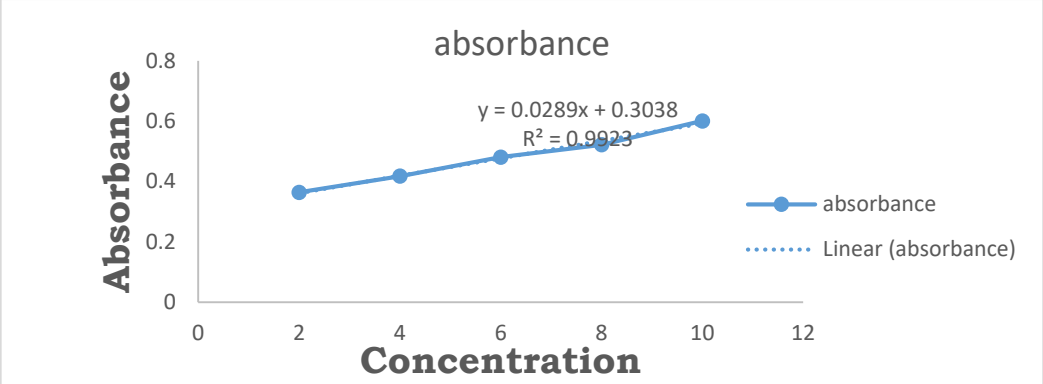

Fig: 8 STANDARD GRAPH OF NAPROXEN IN pH 7.4 BUFFER

TABLE: 4 PREFORMULATION STUDIES OF NAPROXEN

Formulation code	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	(%) Compressibility index	Hauser Ratio	Angle of Repose (θ)
F1	0.52±0.005	0.65±0.013	14.04	1.21	26.1±0.046
F2	0.55±0.009	0.64±0.007	12.72	1.16	28.6±0.0143
F3	0.49±0.011	0.57±0.009	13.20	1.15	27.2±0.0690
F4	0.48±0.007	0.55±0.009	12.72	1.14	24.1±0.044
F5	0.50±0.009	0.58±0.006	13.79	1.16	27.5±0.011
F6	0.53±0.005	0.61±0.007	13.11	1.15	26.8±0.055

TABLE 5: RESULTS FOR PRESS COATED TABLET PARAMETERS EVALUATION

S.no	Physical parameter	FC1	FC2	FC3	FC4	FC5	FC6
1	Weight variation (%)	599±1.24	601±3.52	598±5.18	599±2.28	601±1.14	599±2.52
3	Thickness (mm)	6.5±0.025	6.45±0.049	6.4±0.021	6.2±0.010	6±0.015	6.1±0.008
4	Friability %	0.62±0.02	0.68±0.04	0.55±0.04	0.54±0.08	0.62±0.06	0.58±0.04
5	Swelling index%	280	100	130	180	150	220
6	Hardness (Kg/cm^2)	6.8±0.122	7.0±0.080	7.2±0.124	6.8±0.100	6.8±0.198	6.4±0.124

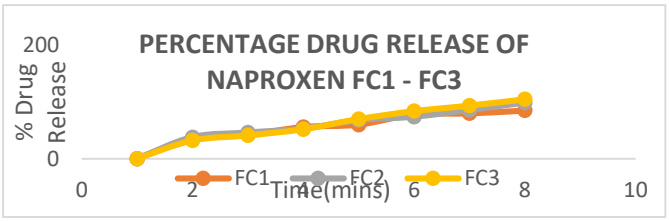

TABLE 6: CUMULATIVE % DRUG RELEASE OF NAPROXEN(FC1-FC6)

Time(mins)	FC1	FC2	FC3	FC4	FC5	FC6
5	36.12	38.12	32.14	25.11	27.12	32.12
10	42.14	46.15	41.18	36.18	34.21	40.32
15	56.23	53.19	52.15	49.13	48.14	52.13
20	60.18	68.12	70.12	55.12	57.24	68.15
30	78.14	74.16	84.19	62.18	66.18	74.18
45	80.17	86.12	94.01	70.12	78.12	82.14
60	85.12	99.11	105.13	84.00	86.11	91.22

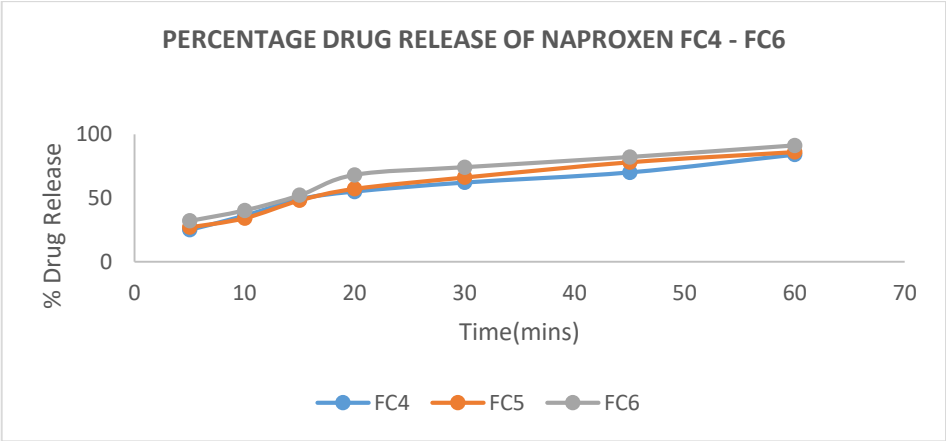

Fig: 9 PERCENTAGE DRUG RELEASE OF NAPROXEN (FC4-FC6)

TABLE: 7 PERCENTAGE DRUG RELEASE OF NAPROXEN

Dissolution time(hrs)	Compressed coated formulation code					
	FC1	FC2	FC3	FC4	FC5	FC6
0.1 N HCl						
1	-	-	-	-	-	-
2	1±0.22	2±0.32	1±0.25	3± 0.18	5.24± 0.14	2± 0.18
pH6.8						

4	6.3±0.34	4.2±0.14	6.14± 0.14	10.19± 0.24	7.32± 0.42	6.21± 0.28
6	10± 0.42	7.82± 0.13	18.15± 0.26	22.12± 0.28	10.15± 0.52	18.92± 0.12
pH 7.4						
7	22.5± 0.45	18.54±0. 24	27.18± 0.34	30.16± 0.36	28.14± 0.14	24.12± 0.56
10	38.5± 0.52	29.32±0. 65	36.14± 0.16	44.15± 0.54	34.32± 0.28	30.35± 0.64

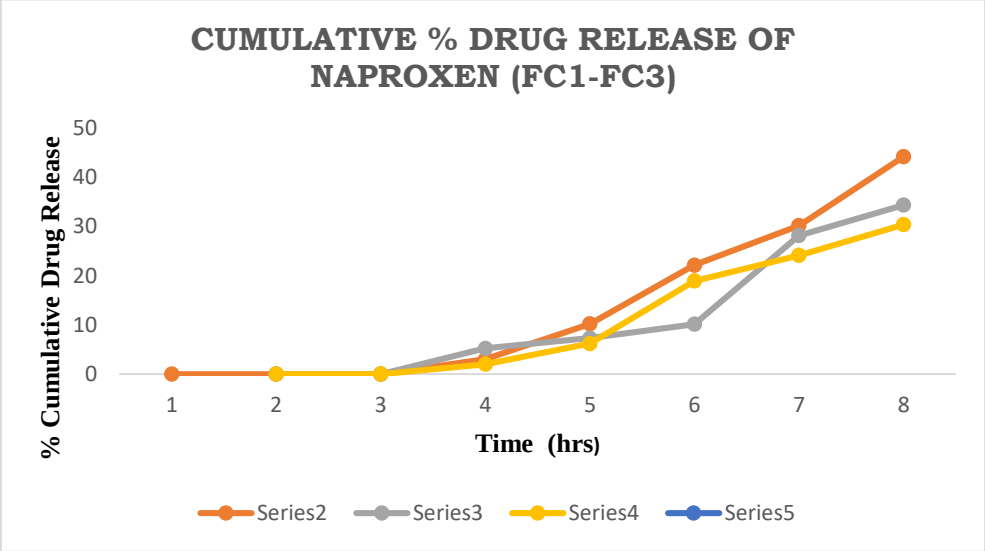

Fig: 10 CUMULATIVE % DRUG RELEASE OF NAPROXEN (FC1-FC4)

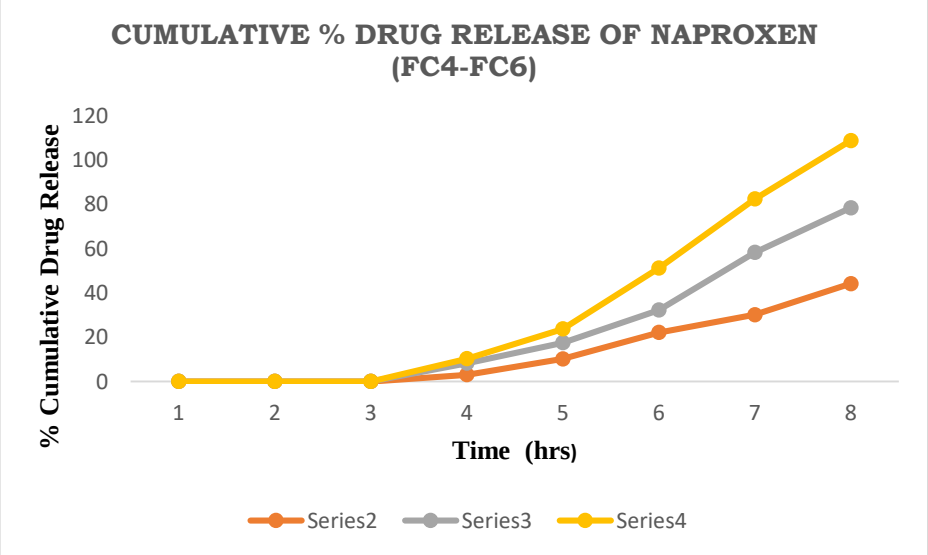

Fig 11: CUMULATIVE % DRUG RELEASE OF NAPROXEN(FC4-FC6)

6. RESULTS & DISCUSSION

From the experimental findings after formulation and evaluation of compressed tablets of Naproxen, it can be concluded that the

Pre-formulation studies indicate that the drug sample obtained was pure and does not show any incompatibilities with the excipients. Pre compression parameters were found suitable for tablet compression. Friability and hardness were within the pharmacopoeia limits.

Formulations (FC1-FC6) by using different disintegrating agents were prepared the drug release was observed from this one formula can be optimized as core tablet. After that (FC1-FC6) formulations drug release was observed in different Medias like 0.1N HCl, pH 6.8, pH 7.4 buffers. In 0.1N HCl the dissolution was carryout in 2 hrs. After that 4 hrs. In pH 6.8 phosphate buffer, remaining up to 3 hrs. Performed in pH 7.4 phosphate buffer. So, the lag time of drug release in 0.1N HCl 2hrs and in 6.8 phosphate buffer 4 hrs. in pH 7.4 buffers up to 3hrs. The percentage of eudragit increases drug releases was decreased. Based on the observations, it can be concluded that the formulated tablets of Naproxen using super disintegrates, release retardant polymers and different excipients was capable of exhibiting all the properties of compressed tablets. They are thus reducing the dose intake, minimize dose related adverse effects, costs and ultimately improve FC4 was consider to be optimized formulation as it showed % drug release 98.24 in 9 hrs.

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