ISSN 2349-7750

INDO AMERICAN JOURNAL OF

PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com *Research Article*

FORMULATION DEVELOPMENT & EVALUATION OF COLON TARGETED DOUBLE COATED TABLETS OF NIMESULIDE

Sampath*, Muneer Syed, D. Srinivasa Rao

Department of Pharmaceutics, K.C Reddy Institute of Pharmaceutical Sciences, Guntur, A.P.

ABSTRACT

Although the underlying mechanisms are still in the realm of speculation, accumulating evidence indicates that NSAIDs can lower the incidence of colorectal carcinomas. However, long-term uses of non-selective NSAIDs can lead to gastrointestinal toxicity from sustained inhibition COX-1. But one can overcome such problem by formulating them as colon specific delivery. In the light of this information, the present study was carried out to develop oral colon targeted drug delivery system for Nimesulide utilizing recently designed and patented system called CODES^{TM}, which consisted of a lactulose containing core over coated with both Eudragit E and Eudragit L designed to rapidly disintegrate in the colon, in order to give a new life for an existing banned drug. CODES^{TM} tablets were prepared by tabletting the granulation of Nimesulide and lactulose, followed with film coating. The prepared tablets were evaluated on the basis of various pharmacopoeial characteristics. The onset of Nimesulide release was found to dependent on the coating level of Eudragit E, and at Eudragit E coating level of 8% (coating weight gain), the onset of in vitro drug release was found to be optimum. It is concluded that Nimesulide can be targeted to hindgut by Novel approach of CODES^{TM} in a simple and economic way.

Keywords:*Nimesulide; NSAIDs, Colorectal Cancer; Colon Specific Delivery; Polymethacrylate polymers.*

Address for Correspondence:
K.C.Reddy Institute of Pharmaceutical Sciences,
Guntur, Andhra Pradesh.
E-mail: muneerkcrp@gmail.com

INTRODUCTION:

Colon specific diseases are often inefficiently managed by oral therapy, because most orally administered drugs are absorbed before arriving in the colon. Therefore, colon-specific drug delivery systems, which can deliver drugs to the lower gastrointestinal tract without releasing them in the upper GI-tract, can be expected to increase the quality of life for patients suffering from colon specific diseases. Treatment might be more effective if the drug substances were targeted directly on the site of action in the colon. Lower doses might be adequate and, if so, systemic side effects might be reduced.[1, 2]

CODES™ is a unique colon-specific drug delivery technology that was designed to avoid the inherent problems associated with pH or time-dependent systems. The design of CODES™ exploited the advantages of certain polysaccharides that are only degraded by bacteria available in the colon. This is coupled with a pH sensitive polymer coating. Since the degradation of polysaccharides occurred only in the colon, this system exhibited the capability to achieve colon delivery consistently and reliably. As schematically presented in **Fig. 1**, one typical configuration of CODES™ consists of a core tablet coated with three layers of polymer coatings.[3,4] From the literature it is shown that there are no colon targeted formulations of Nimesulide were present.[5]

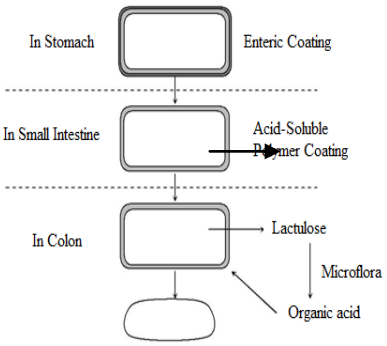


Figure No. 1: Schematics of the conceptual design of CODES™

Nimesulide is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration with a reported bioavailability of about 100%. Nimesulide is highly bound to plasma proteins about 99%. It is extensively metabolized in the liver and the major metabolite is pharmacologically active. So, the present study deals with the research work to develop and evaluate colon targeted double coated tablets of Nimesulide by solvent evaporation technique and also to characterize the double coated tablets for various parameters and calculate the release kinetics for optimized formulation.[6,7]

MATERIALS & METHODS:

Nimesulide was obtained from Emcure pharmaceuticals Ltd., Pune, Lactulose obtained from Solvay Pharma, Mumbai, HPMC (METHOCEL) E3 USP/EP Colorcon Asia Pvt. Ltd., Goa, and hydrochloric Acid, Isopropyl alcohol, Sodium Chloride etc are acquired from S.D. Fine-Chem Ltd., Mumbai.

Compatibility Studies:

Compatibility of the drug (Nimesulide) with excipients used to formulate our device was established by Infrared absorption spectral analysis. I.R. Spectral analysis of pure Nimesulide, pure excipients and combination of the drug with these excipients was carried out to investigate any changes in chemical composition of the drug after combining it with the excipients.

Fabrication of CODES™ for Nimesulide: [8,9]

The composition of a tablet core, acid-soluble coating layer, water-soluble layer and enteric coating layer of CODES™ containing Nimesulide are shown in Table 2. Lactulose, Nimesulide, magnesium oxide, microcrystalline cellulose and magnesium stearate were thoroughly mixed in a mortar with a pestle. Magnesium oxide was added for neutralization of Nimesulide, because an acidic drug such as Nimesulide would dissolve the acid-soluble coating layer. Microcrystalline cellulose and magnesium stearate are added for their usual purpose. Tableting was performed under a compression force of 1 tone using Hydraulic press. Initially, the tablet cores were coated with acid-soluble coating material, Eudragit E100. A coating solution was prepared by dissolving 8% (w/w) Eudragit E100 and 2% PEG 4000 in a mixture of ethanol and water (9:1).

A conventional pan pour coating machine under the following conditions performed coating: tablet bed temperature, 42 °C; and rotating speed of pan, 20 rpm. The amount of coating was 4, 8 and 12 % per tablet core, for formulation F1, F2 and F3 respectively. Later, the tablets were coated with water-soluble coating material, HPMC (METHOCEL)-E3 as an under coating layer. A coating solution was prepared by dissolving 10% (w/w) HPMC (METHOCEL)-E3 in water. The same coating machine under the following conditions performed coating: tablet bed temperature, 60.8 °C; and rotating speed of pan, 20 rpm. The amount of coating was 2 % per tablet core.

Finally, the tablets were coated with enteric coating material, Eudragit L100. A coating solution was prepared by dissolving 6% (w/w) Eudragit L100, 3% talc, and 1% (w/w) PEG 4000 in a mixture of ethanol and water (13:5). The same coating machine under the following conditions performed coating: tablet bed temperature, 42 °C; and rotating speed of pan, 20 rpm. The amount of coating was 6 % per tablet core.

Preformulation parameters: [10-12]

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced.

Angle of Repose: The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. Different ranges of flow ability are given in terms of angle of repose. Angle of repose is

calculated by formula:

$$r = (area/\pi)\ ½$$

$$\theta = \tan -1\ (h/r)$$

Bulk Density: Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another

Tapped density:

After carrying out the procedure as given in the measurement of bulk densitythe cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$Tap = M / V$$

Hausner ratio:

Hausner ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density. The relationship between Hauser's ratio and flow property.

Hausner ratio was calculated by using the formula.

Hausner Ratio = Tapped density / Bulk density

Post-Compression Parameters / Evaluation off Tablets: [13]

General appearance of Tablets:

Coated tablets were examined under a lens for the shape and color of the tablet, its overall elegance, uniformity, consistency, surface texture, odour, taste, etc.

Thickness and Diameter Test:-

Thickness and diameter test permits accurate measurement and provides information on the variation between tablets. Ten tablets were taken and the thickness and diameter was measured using a dial-caliper. The tablet thickness and diameter should be controlled within a 5% variation of a standard value.

Weight Variation Test:

Ten tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S. Pharmacopoeia allows a little variation in the weight of a tablet. In all the formulations the tablets weight is more than 80mg hence 10% maximum difference allowed.

Hardness Test:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. It expressed. The hardness of the tablets were determined using Monsanto Hardness Tester. The force needed to disrupt them by crushing in kg/cm2 expresses it. Ten tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability Test for uncoated tablets:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}).

Drug Content Uniformity Test:

Ten tablets were randomly selected, accurately weighed and average weight per tablet calculated. Tablets were ground individually to fine powder. Accurately weighed tablet powder, equivalent to 5 mg of Nimesulide was transferred to 100 ml volumetric flask. Powder was dissolved in 85 ml of 0.1 N sodium hydroxide and sonicated well to ensure complete solubility of the drugs. Then the volume was made up to 100 ml with 0.1N sodium hydroxide. Applying vacuum later filtered this solution. From this 1 ml of solution was withdrawn and volume made up to 100 ml by using 0.1 N sodium hydroxide solution. Absorbance of the sample solution was measured at 397nm, and concentration of drug in sample was calculated using standard calibration curve.

***In vitro* dissolution study:**

Dissolution testing was carried out on USP dissolution apparatus II (paddle) in 3 pH buffers - artificial gastric fluid (pH 1.2), artificial intestinal fluid (pH 6.8), and pH 5.0 buffer - that were prepared by combining appropriate amounts of sodium chloride with hydrochloric acid, potassium phosphate monobasic with sodium hydroxide, and citric acid with sodium phosphate dibasic, respectively. 2.5 % Polysorbate (Tween) 80 was taken as co-solvent in pH 5.0 buffer medium. All the solutions were degassed for 20 minutes before use. Table No. 1 summarizes the general conditions in this study.

Table No. 1: Summary of General Dissolution Conditions

Sr. No.	Parameter	Specifications
1.	Dissolution medium	Buffers (pH 1.2, 6.8, and 5.0)
2.	Temperature	37.0 ±0.5 °C
3.	Initial Volume	900ml
4.	Rotation speed	100rpm
5.	Drawn Volume	5ml
6.	Running time	1 hr in pH 1.2, 4 hrs in pH 6.8, and 4 hrs in pH 5.0.
7.	Medium replacement	Media refilling at 60 and 300 min.

RESULTS & DISCUSSION:

FT-IR Spectroscopy:

FTIR spectra obtained for Nimesulide, polymer and physical mixture presented in the **Fig. 2-7**. The characteristics peaks found in Nimesulide, physical mixture and formulations, hence it appears there was no chemical interaction between Nimesulide and polymer and it can be concluded that the characteristics bands of Nimesulide were not affected after successful load formulation of colon targeted double coated tablets

.

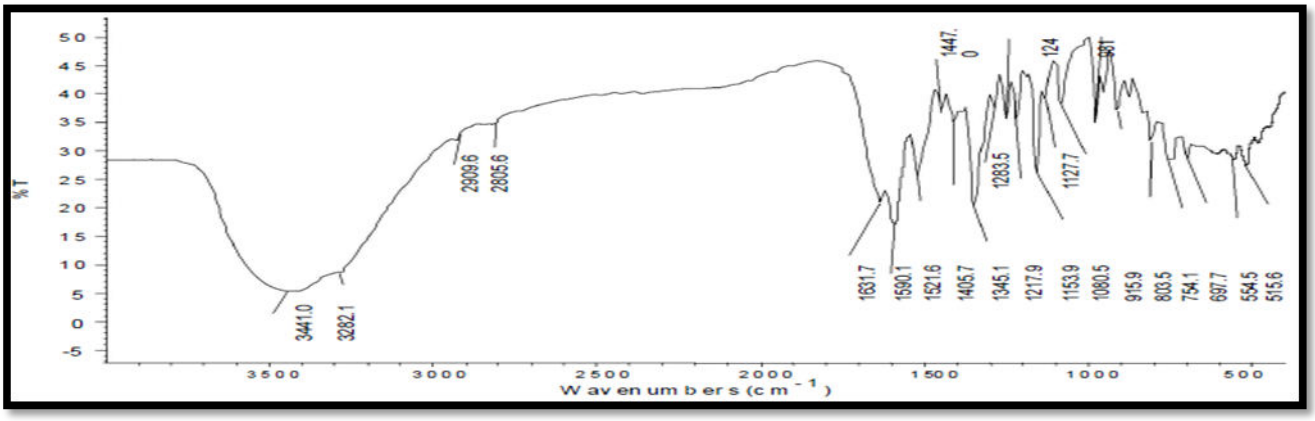


Figure No. 2: Infra Red Spectrum of Nimesulide

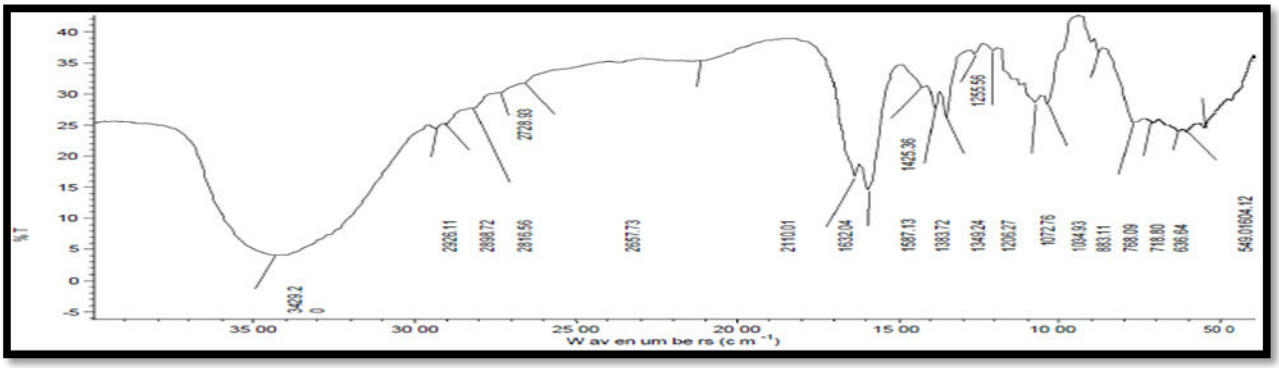


Figure No. 3: Infra Red Spectrum of Lactulose

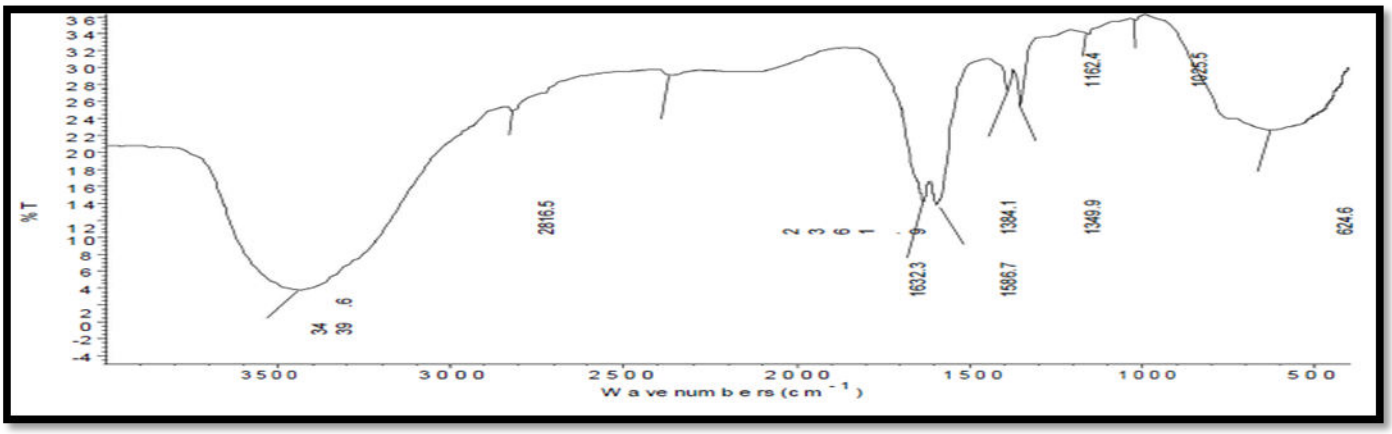


Figure No. 4: Infra Red Spectrum of Eudragit E 100

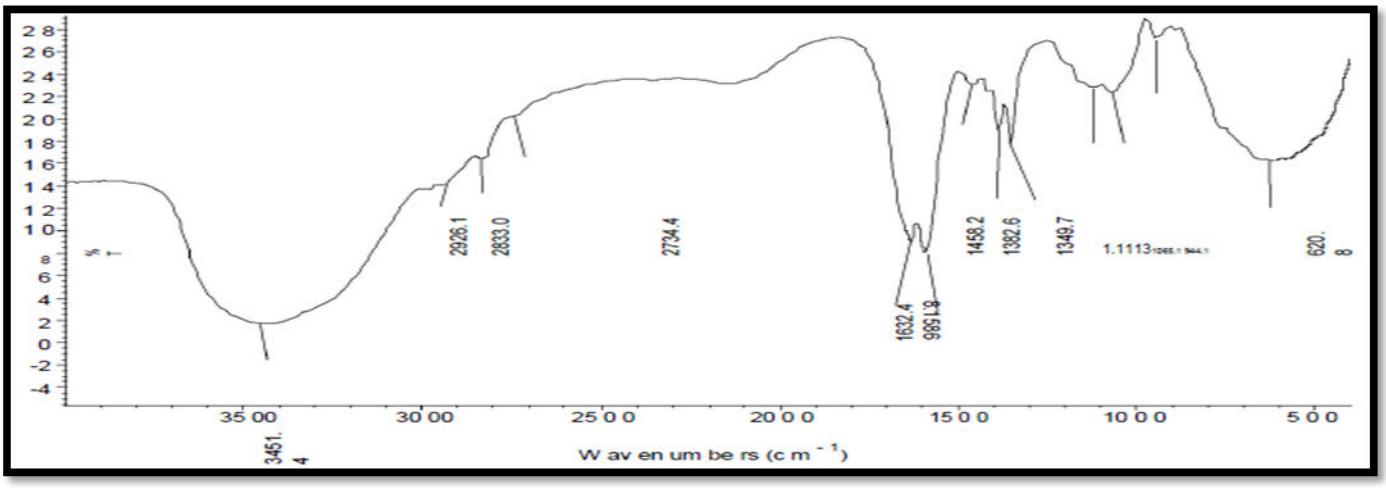


Figure No. 5: Infra Red Spectrum of HPMC (METHOCEL)

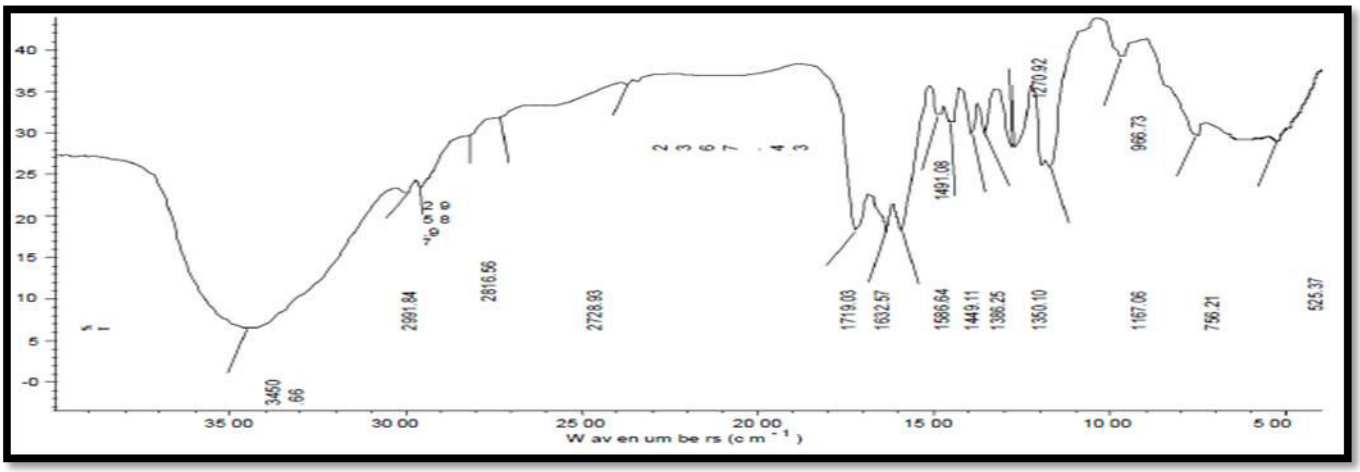


Figure No. 6: Infra Red Spectrum of Eudragit L 100

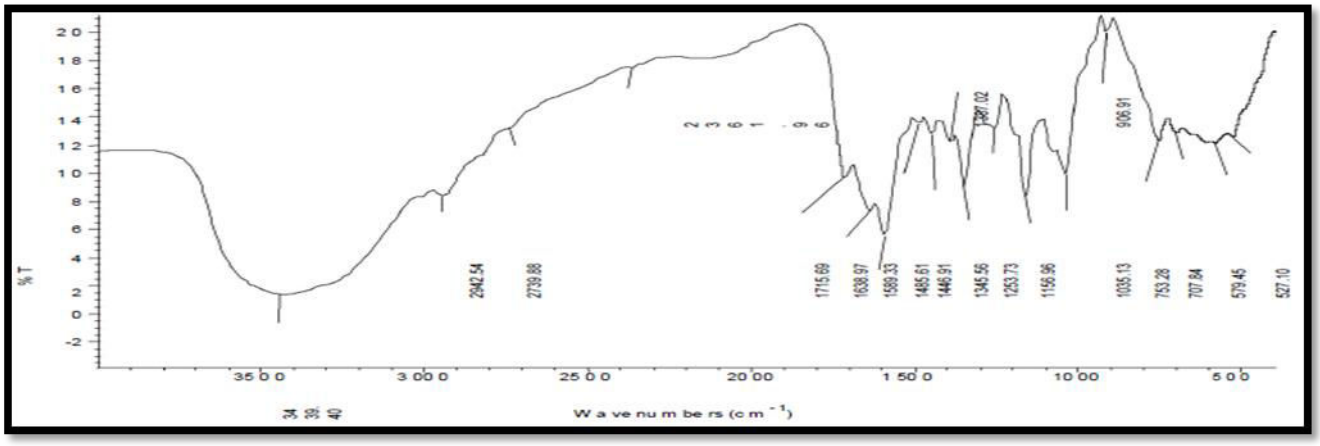


Figure No. 7: Infra Red Spectrum of Formulation

Tab le 2: Pre-Compression Parameters of Nimesulide

S. No.	Angle of Repose	LBD (gm/ml)	TBD (gm/ml)	Carr's Index (%)
1.	25.23	0.57	0.66	15.8
2.	25.55	0.58	0.67	15.51
3.	25.15	0.59	0.68	15.25
4.	25.36	0.55	0.64	16.36
5.	25.26	0.56	0.65	15.8
Mean	25.31^0	0.57	0.66	15.74
SD	0.15%	0.02%	0.02%	0.41%

Table 3: Post Compression Parameters Nimesulide

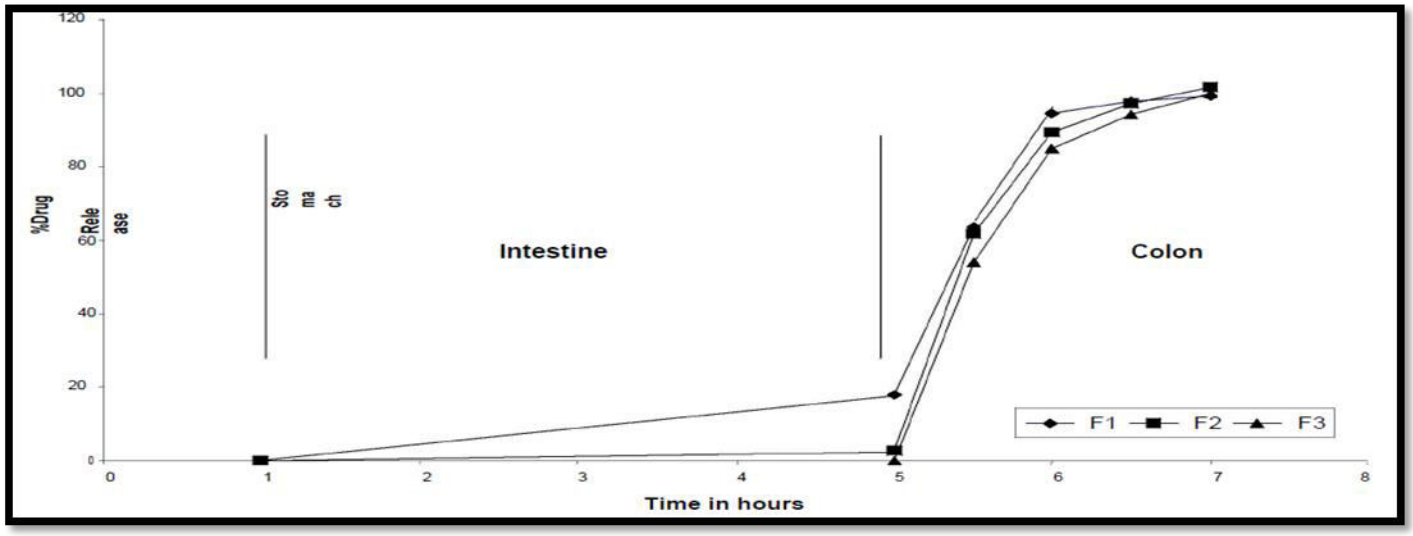
S. No	Formulation	Diameter	Thickness	Weight in mg/ tablet	Hardness
1	Uncoated	5	3.05	65	4
2	F1	5.35	3.15	73	4
3	F2	5.4	3.25	76	4
4	F3	5.5	3.3	79	4

***Table 4: In vitro* Dissolution Studies Nimesulide**

TIME (hr)	% DRUG RELEASE		
	F1	**F2**	**F3**
1	0	0	0
5	18	2.79	0
5.5	63.72	61.74	54
6	94.57	89.3	84.9
6.5	97.88	97.28	94.07
7	99.40	99.63	99.88

Sequential studies in three media were performed to evaluate the drug release characteristic of all formulations by paddle method according to the description in the Indian Pharmacopoeia (IP) 1996. The various parameters and *in vitro* release data for the various formulations of Nimesulide CODES^{TM} are provided in Tables 2-4. In the first dissolution media (pH 1.2) and the second dissolution media (pH 6.8), all formulations showed very small or negligible release for 1 and 4 total 5 (five) hours, respectively. Only formulation F1 had shown 18% drug release in the simulated intestinal fluid. All formulations disintegrated and released when the dissolution medium was replaced with the McIlvine buffer solution (pH 5). Formulation F3 had shown comparatively delayed disintegration. These results suggested that, there should be optimum acid soluble coat of Eudragit E 100 to protect in small intestine as well as for immediate release in the colon. From the drug release profile of formulation F2 found to be optimum one.

Plots of Cumulative Drug Release as a function of Time From the Novel Colon Targeted Nimesulide Tablets



CONCLUSION:

From the obtained results, it can be concluded that drug release and absorption of Nimesulide can be targeted on the colon by CODES system. Evaluation parameters like hardness and friability indicated that the tablets so prepared were mechanically stable and complied with necessary pharmacopoeial specifications. I.R. spectra revealed that, the drug and polymers are authentic and matches with the reference standard available and there is no interaction between polymers and drug. The onset of Nimesulide release depends on the coating level of Eudragit E. Eudragit E coating level of 8% (coating weight gain), the onset of *in vitro* drug release is optimum. Nimesulide CODES are found to be stable at 40^{o}C / 75 % RH when checked for 1 month of stability studies.

BIBLIOGRAPHY:

1. Katsuma M, Watanabe S, Kawai H, Takemura S, Masuda Y, Fukui M. Studies on lactulose formulations for colon-specific drug delivery. Int J Pharm 2002; 249:33-43.
2. Yang L, Chu JS, Fix JA. Colon-specific drug delivery: new approaches and *in vitro/in vivo* evaluation. Int J Pharm 2002; 235:1-15.
3. Katsuma M, Watanabe S, Takemura S, Sako K, Sawada T, Masuda Y, et al. Scintigraphic evaluation of a novel colon-targeted delivery system (CODESTM) in Healthy Volunteers. J Pharm Sci 2004; 93(5):1287-99.
4. Li J, Yang L, Ferguson SM, Hudson TJ, Watanabe S, Katsuma M, Fix JA. *In vitro* Evaluation of Dissolution Behavior for a Colon-Specific Drug Delivery System (CODES™) in Multi-pH Media Using United States Pharmacopeia Apparatus II and III. AAPS PharmSciTech 2002; 3(4) article 33. URL: http://www.aapspharmscitech.org
5. Watanabe S, Kawai H, Katsuma M, Fukui M. Colon specific drug release system. US patent application (09/183,339).
6. Jung YJ, Lee JS, Kim YM. Synthesis and *in vitro/in vivo* evaluation of 5-aminosalicyl-glycine as a colon-specific prodrug of 5-aminosalicylic acid. J Pharm Sci 2000; 89:594–602.
7. Takemura S, Watanabe S, Katsuma M, Fukui M. Human Gastrointestinal transit study of a novel colon delivery system (CODES™) using γ-scintigraphy. Proceedings of the International Symposium on Controlled Release Bioactive Material 2000; vol. 27.
8. Watanabe S, Kawai H, Katsuma M, Fukui M. Colon specific drug release system. US patent application 1998; (09/183,339).
9. Yang L, Watanabe S, Li J, Chu JS, Katsuma M, Yokohama S, Fix JA. Effect of colonic lactulose availability on the timings of drug release onset *in vivo* from a unique colon-specific drug delivery. Pharm Res 2003; 14:103-7.
10. Saha.N, Kranthi Kumar Y. Comparison of the %drug release of drug and polymers (pvp k30 and peg 6000) by using various buffers. Iajpr, 2014; 4(2): 815-819.
11. Takeuchi H, Yasuji T, Yamamoto H, Kawashima Y. Spray-dried lactose composite particles containing an ion complex of alginate-chitosan for designing a drycoated tablet having a time-controlled releasing function. Pharm Res 2000; 17:94.
12. Banker GS, Anderson NR, Tablets. In: Lachman L, Liberman HA, Kanid JL, Editors, The theory and practice of Industrial Phramacy. 3rd edn. Bombay: Verghese publishing house 1991:292-303.
13. Alderborn G. Tablets and compaction. In: Aulton ME, editor, Pharmaceutics: The Science of Dosage Form Design. 2nd edn. Rdinburgh: Churchill living stone. 2001: 417-23.