BJMHR
British Journal of Medical and Health Research
Journal home page: www.bjmhr.com

Formulation & Evaluation of Nabumetone Enteric Coated Tablets

Dwarampudi Suma[1*], Medisetti Lalitha[1], Chirravuri S Phani Kumar[2]
1.Aditya College of Pharmacy, Faculty of Pharmaceutical Technology, Department of Pharmaceutics, Surampalem, India
2.VJ's College of Pharmacy, Faculty of Pharmaceutical Technology, Department of Pharmaceutics, Diwancheru, India.

ABSTRACT

Nabumetone is a non-steroidal anti-inflammatory agent preferred in the treatment of conditions and disorders associated with inflammation like osteoarthritis, rheumatoid arthritis and gout. The aim of the present study was to formulate HPMC matrix tablets coated with Eudragit S 100 and Eudragit L 100 for site-specific delivery of Nabumetone for treating spasms in colon. The use of enteric polymer Eudragit S 100 coated matrix tablets makes them able to release the drug at the particular pH of colonic fluid. The polymer Hydroxy propyl methyl cellulose K4M retards the drug release.

Keywords : Nabumetone, HPMC K4M, Eudragit L 100 & S 100, Enteric coated tablets

*Corresponding Author Email: chsphanikumar@gmail.com
Received 12 August 2016, Accepted 17 August 2016

Please cite this article as: Suma D *et al*., Formulation & Evaluation of Nabumetone Enteric Coated Tablets. British Journal of Medical and Health Research 2016.

INTRODUCTION

Numerous drug entities based on oral delivery have been successfully commercialized, but many others are not readily available by oral administration, which are incompatible with the physical and/or chemical environments of the upper gastrointestinal tract (GIT) and/or demonstrate poor uptake in the upper GI tract. Due to lack of digestive enzymes, colon is considered as suitable site for the absorption of various drugs. Over the past two decades the major challenge for scientist is to target the drugs specifically to the colonic region of GIT. Previously colon was considered as an innocuous organ solely responsible for absorption of water, electrolytes and temporary storage of stools. But now it is accepted as important site for drug delivery. Colonic drug delivery is a relatively recent approach for the treatment of diseases like ulcerative colitis, Crohn's disease, colorectal cancer and amoebiasis[1-5]. Colon-specific delivery systems are also gaining importance for the systemic delivery of protein and peptide drugs. Due to negligible activity of brush border membrane peptidase activity and less activity of pancreatic enzymes, the colon is considered to be more suitable for delivery of peptides and protein in comparison to small intestine. Besides this low hostile environment, the colonic transit time is long (20-30 hrs.) and the colonic tissue is highly responsive to the action of absorption enhancers. The longer residence time, less peptidase activity, natural absorptive characteristics and high response to absorption enhancers make the colon a promising site for the delivery of proteins and peptide drugs for systemic absorption. Colonic delivery can be accomplished by oral or rectal administration. Rectal dosage forms such as suppositories and enemas are not always effective since a high variability in the distribution of these forms is observed. Suppositories are only effective in the rectum because of the confined spread, and enema solutions can only offer topical treatment to the sigmoid and descending colon. Therefore, oral administration is preferred, but for this purpose, physiological barriers have to be prevailing over. Absorption or degradation of the active ingredient in the upper part of the GI tract is the major obstacle and must be circumvented for successful colonic drug delivery. The scientific frame work required for development of a successful oral controlled drug delivery dosage form consists of an understanding of three aspects of the system namely,

- The physicochemical characteristics of the drug
- Relevant GI anatomy and physiology
- Dosage form characteristics

MATERIALS AND METHOD

Nabumetone and all chemicals were gifted by SK Health Care Pvt. Ltd., Bollaram, Hyderabad.

METHODS

FT-IR Spectroscopy:

Infrared (IR) spectral matching studies are employed to detect any possible interaction between drugs and the polymers or excipients. In the present, the compatibility between the drug Nabumetone with HPMC, EL 100 K4M and ES100 were evaluated with help of FT-IR (PERKIN ELMER BX series 2.19 version). . The samples were scanned from 4000 to 400 cm $^{-1}$in FT-IR spectrophotometer. Similarly the IR spectra the individual drug wes also recorded. Physical appearance of the samples and appearance or disappearances of peaks in the spectra were observed to access any possible physical and chemical interaction.

Preparation of nabumetone core tablet:

Nabumetone and all other ingredients listed in Table except magnesium stearate, Talc were passed sieve no. 60 to get uniform size particles and weighed accurately. Finally, magnesium stearate, Talc (passed through a 60-mesh/250 micron screen) was introduced to the powder mixture. The final mixture was shaken manually for 5-10 min in a plastic bag. This powder was passed through the hopper of 16 station rotary tableting machine and punched into tablets using 8mm s/c. the process is similar for all core formulations, which are prepared by direct compression technique.

.Table 1: Various formulations tried for optimization of core tablets[6]

Ingredients	Amount (mg)
Nabumetone	500
HPMC K4M	25
Micro crystalline cellulose	59.5
Magnesium stearate	1
Talc	2
Total weight	600

Coating[7-9]**:**

Optimization of coating pan parameters:

The specifications of the coating pan used were

- Pan capacity 50 mg
- Pan diameter 5 inches
- Spray to bed distance 8 cm

- For the above specifications, the operating variables were found to be optimized between the following ranges.
  - Atomizing air pressure 10-15 psi
  - Temperature
  - Inlet air 35-45°
  - Tablet bed 50-55ºC

- Exhaust air 48-52ºC
- Pan speed 20-30 rev/min
- Flow rate 1-2 mL/min

Formulation: Optimization of the level of coating (in terms of total weight gain):Eudragit L-100:

Table 2: Composition of optimized Eudragit L-100 polymer coating solution

Ingredient	Amount/100mL
Eudragit L 100/S 100 (gm)	6
Triethyl citrate (mL)	2
Isopropyl alcohol (mL)	100
Talc (gm)	2

The various formulations tried were as follows.

Table 3: TWG of formulations coated with Eudragit L-100 and Eudragit S 100

Polymer	%TWG	Formulation Code
EL 100	5	EL a
	10	EL b
	15	EL c
	20	EL d
EL 100	5	ES a
	10	ES b
	15	ES c
	20	ES d

Evaluation of the tablets[10,11]:

Pre-compression parameters:

Prior to the compression, the powder blends of various batches were evaluated for their bulk and tapped density and from these values compressibility index and Hausner ratio were calculated. While the flow properties of the powder bled were accessed from the angle of repose. The evaluation parameters were studied before and after addition of lubricants to check and compare the inherent flow properties of powders.

Angle of repose:

The angle of repose of powder blend was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blend**.** The powder blend was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured & angle of repose was calculated using the following equation:

Tan θ = h/r

Where, h & r are the height & radius of the powder cone.

Bulk density:

Both bulk density (BD) & tapped density (TD) were determined. A quantity of 2 gm of

powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in the volume was noted. BD & TD were calculated using the following formulae: BD = weight of the powder / volume of the packing.

TD = weight of the powder / tapped volume of the packing.

Compressibility Index:

The Compressibility Index of the powder blend was determined by Carr's compressibility index. .

Carr's Index (%) = [(TD BD) x100] / TD

Where, TD=Tap Density & BD=Bulk Density.

Hausner's ratio:

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material. The ratio of tapped density to bulk density of the powders is Hausner's ratio. It is calculated by the following equation.

H = ρT / ρB

Where, ρT = tapped density & ρB = bulk density

POST COMPRESSION PARAMETERS:

Weight variation test:

Twenty tablets were randomly selected from each formulations and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight. The mean ± S.D. were noted. The tablets meet IP specifications if no more than 2 tablets outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Thickness measurement:

Randomly ten tablets were taken from each formulation and their thickness was measured using a screw gauge. The individual tablet was placed between two anvils of the screw gauge and sliding knob was rotated until the tablet was tightly fitted. The digital reading displayed was noted. The mean ±S.D. was noted. The tablet thickness should be controlled within a ± 5% variation of standard value.

Hardness:

The tablet hardness of different formulations was measured using the Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero was taken. The

upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded, and the zero force reading is deducted from it.

Friability:

The test is performed using a laboratory friability tester Roche friabilator 10 tablets were weighed and placed in a plastic chambered friabilator attached to a motor, which revolves at a speed of 25 rpm, dropping the tablets from a distance of 6 inches with each revolution. The tablets were subjected to 100 revolutions for 4 minutes. After the process, these tablets were dedusted and reweighed. Percentage loss of tablet weight was calculated. The limit for friability is NMT 1%.

% Friability = (W1 – W2) x 100/W1

Where, W1=initial weight of the 10 tablets before testing &

W2=final weight of the 10 tablets after testing

***In vitro* drug release study of tablets**

In-vitro drug release from matrix tablet was studied using USP II apparatus, with 900 ml of dissolution medium phosphate buffer pH 7.4 and rotated at 50 rpm. 5 ml aliquots were withdrawn at one hour interval from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 2 cm apart from bottom of the vessel. Suitable replacement with fresh medium was also made. Each sample solution was filtered through whatman filter paper No.4.The UV absorbance was measured at 332 nm by using (UV1700–Shimadzu) spectrometer after appropriate dilution by dissolution medium. Nabumetone concentrations in the samples were determined from the standard curve of the pure drug. The *in-vitro* dissolution study was performed up to 12 hours.

Same procedure was carried for coated tablets but *in-vitro* dissolution was tested in pH 1.2 buffer(upto 2 hours) followed by pH 6.8 phosphate buffer(up to 6^{th} hour) and in pH 7.4 phosphate buffer(upto 28^{th} hour) at different time intervals as stated in table 9 & 10.

Kinetic Analysis of Dissolution Data:

To analyze the *in-vitro* release data various kinetic models were used to describe the release kinetics.

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative % drug released versus log time.
5. Hixson-Crowell model - cubic root of unreleased fraction of drug versus time.

Zero order kinetics:

Zero order release would be predicted by the following equation:-

At = A0 – K0t

Where,At = Drug release at time‘t’, A0 = Initial drug concentration & K0 = Zero – order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order release kinetics, with a slope equal to K0.

First Order Kinetics:

First – order release would be predicted by the following equation:-

Log C = log C0 – Kt / 2.303

Where,C = Amount of drug remained at time‘t’, C0 = Initial amount of drug & K = First – order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant ‘K’ can beobtained by multiplying 2.303 with the slope values.

Higuchi’s model:

Drug release from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation.

Q = [D□ / □ (2 A - □Cs) Cst] ^{½}

Where, Q = Amount of drug released at time‘t’,

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

ε= Porosity of the matrix.

τ= Tortuosity.

t= Time (hrs) at which ‘q’ amount of drug is released.

Above equation may be simplified if one assumes that ‘D’, ‘Cs’, and ‘A’, are constant.

Then equation becomes:

Q = $Kt^{1/2}$

When the data is plotted according to equation i.e. cumulative drug release versus squareroot of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to ‘K’.

Korsmeyer equation / Peppa’s model:

To study the mechanism of drug release from the floating tablets of Stavudine, the release data were also fitted to the well – known exponential equation (Korsmeyer equation / Peppa’s law equation), which is often used to describe the drug release behavior from

polymeric systems.

$Mt / Ma = Kt^n$

Where, Mt / Ma = the fraction of drug released at time‘t’.

K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

And we get:

Log Mt / Ma = LogK + n Logt

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to ‘n’ and the ‘K’ can be obtained from y – intercept. For Fickian r**elease ‘n’** = 0.5 while for anomalous (non – Fickian) transport ‘n’ ranges between 0.5 and 1.0.

Table 4: Mechanism of Drug Release as per Korsmeyer Equation / Peppa’s Model

S. Non	value	Drug Release
1.	n <0.5	Fickian release
2.	0.5<n<1	Non-Fickian release
3.	n>1	Case II transport

RESULTS AND DISCUSSION

Characterization of Nabumetone pure drug:

Tablet 5: Characterization of pure drug

Angle repose (θ)	Compressibility Index	Result
24°18’	16.019%	good flow

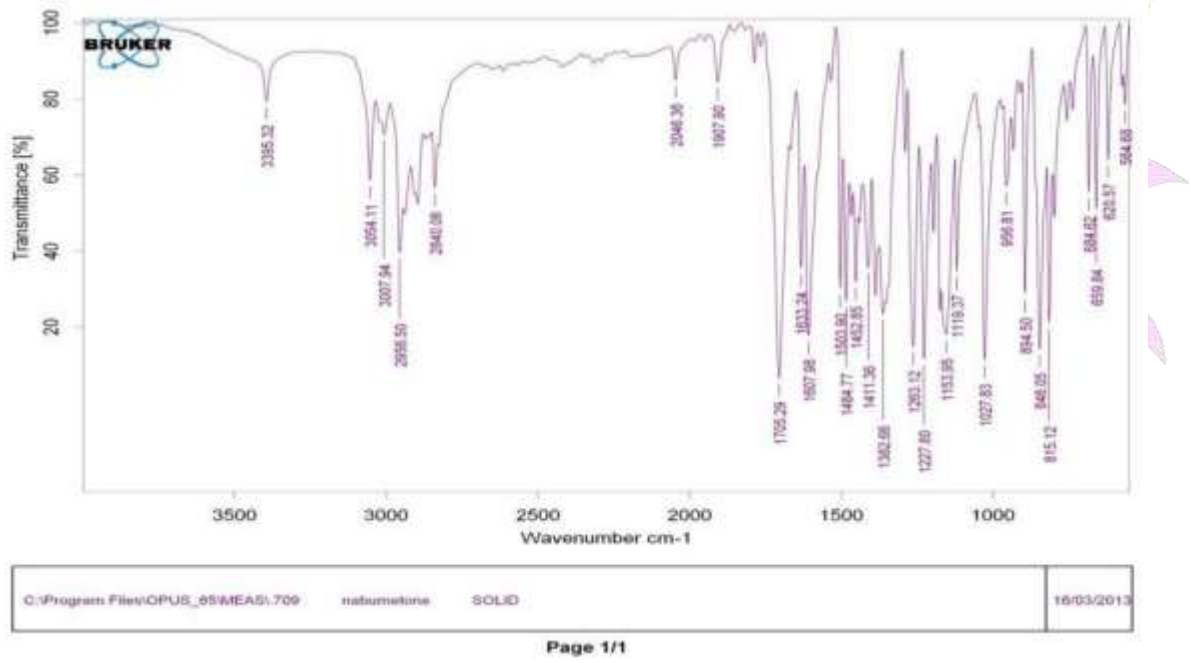

Figure 1: FT-IR Spectra of Nebumetone

Characterization of tablet blend:

Table 5: Characterization of tablet powder blend

Formulation Code	Angle of Repose(^{0})	Bulk ensity(gm/cm^3)	Carrs'Index(%)
Core Tablet	21^0 26 ± 1.84	0.51±0.037	13.88±0.28

Characterization of compressed core tablet:

Table 6: Characterization of compressed core tablet

Formulation Code	Thickness (mm)	Hardness (Kg/cm^2)	Weigh variation(mg)	Friability (%)	% Drug content
Core Tablet	4.77±0.1	6.17±0.29	601±1.36	0.14	99.7±0.16

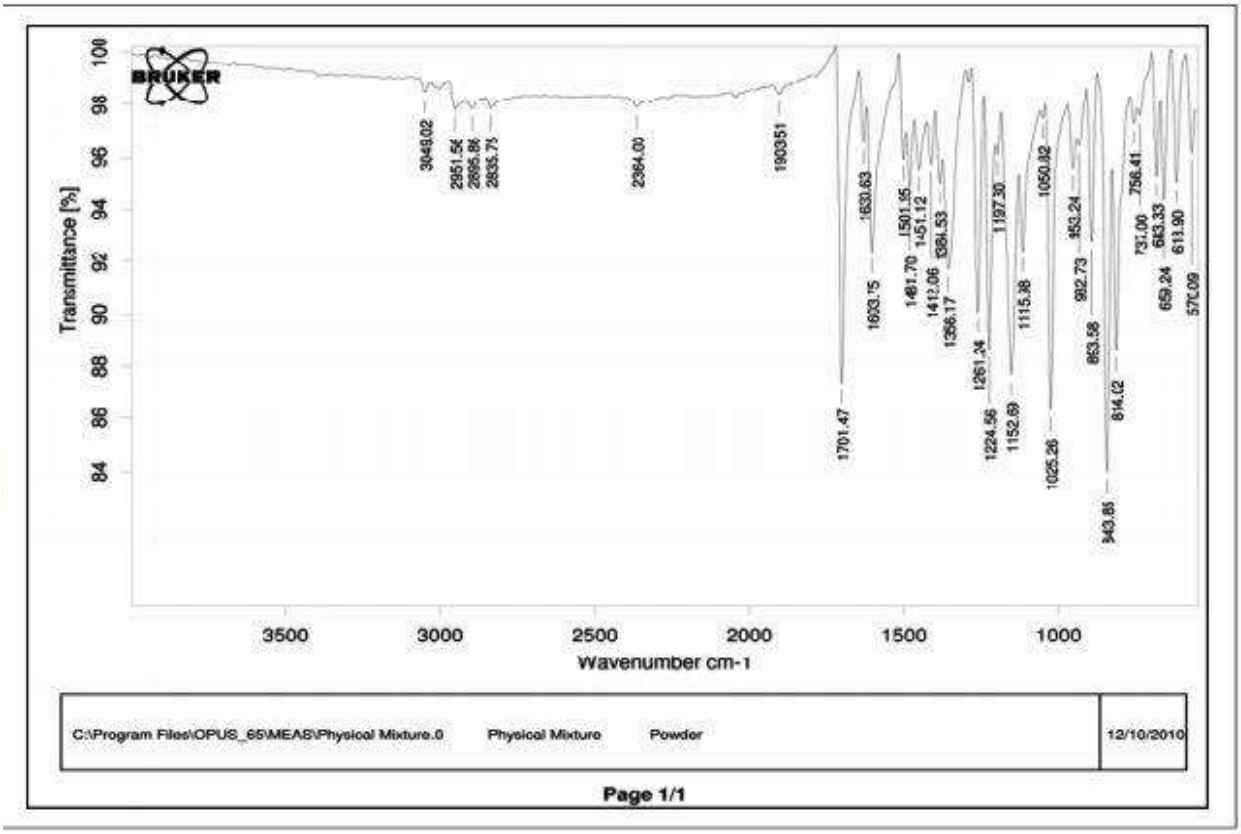

Figure 2: FT-IR Spectrum of Nabumetone, HPMC, EL100 & ES 100 polymers mixture

Table 7: Physical characteristics of coated formulations

Formulation Code	Thickness (mm)	Hardness (kg/cm^2)	% Drug content
Eudragit L 100			
EL a	5.88±0.05	7.8±0.3	98.64±0.43
EL b	6.0±0.04	7.3±0.2	101.31±0.29
EL c	6.13±0.02	7.6±0.1	99.94±0.46
EL d	6.28±0.05	6.9±0.3	99.83±0.68
Eudragit S 100			
ES a	5.94±0.06	7.6±0.18	101.49±0.72
ES b	6.07±0.01	7.5±0.33	101.27±0.43
ES c	6.18±0.05	7.1±0.15	101.27±0.45
ES d	6.32±0.01	7.5±0.12	101.33±0.27

***In vitro* drug release data of core tablet**

Table 8: Disso data of core tablet

Time in hours	Cumulative % drug release
0	0
0.5	8.015 ± 1.42
1	12.23 ± 1.53
2	15.9 ± 1.26
3	27.7 ± 1.63
4	34.48 ± 2.41
5	42.63 ± 2.11
6	55.3 ± 2.06
7	60.07 ± 2.62
8	65.7 ± 1.7
9	74.87 ± 1.07
10	80.7 ± 0.7
11	84.9 ± 1.9
12	90.23 ± 1.32

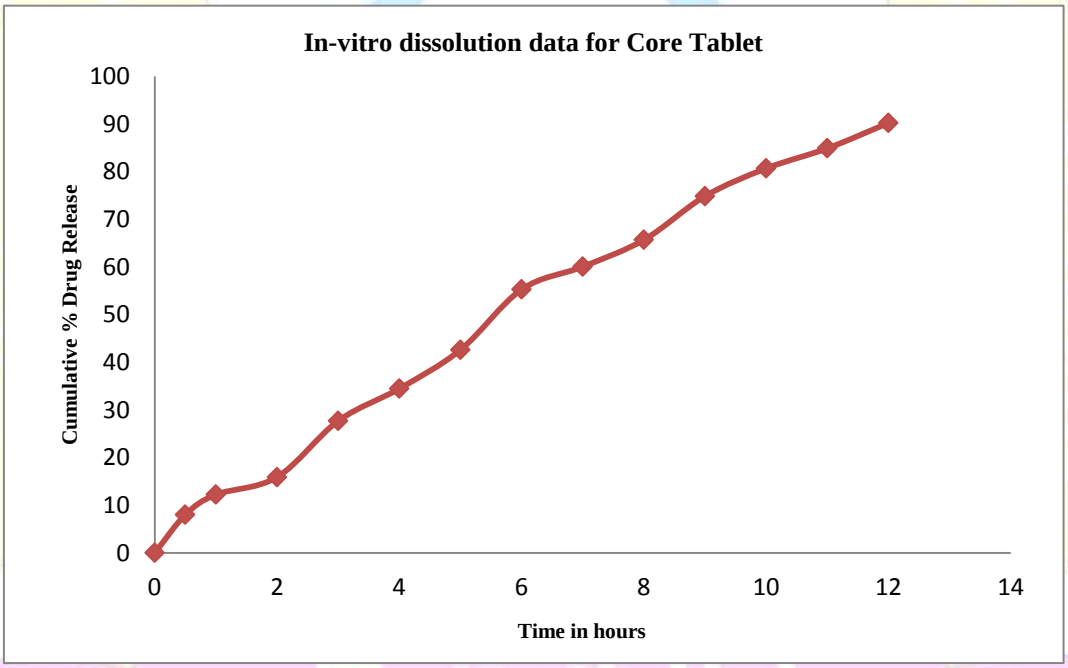

Figure 3 Cumulative percentage drug release of core tablets

Table 9: *In vitro* drug release

pH	Time (hr)	Cumulative amount of %drug released			
		EL a	EL b	EL c	EL d
1.2	0	0	0	0	0
	0.5	0.07±0.01	0.04±0.01	0.04±0.01	0.02±0.01
	1	0.5±0.01	0.09±0.01	0.07±0.01	0.07±0.01
	2	0.8±0.01	0.6±0.07	0.6±0.07	0.3±0.1
6.8	2.5	9.9±0.51	7.5±0.26	6.11±0.032	2.81±0.165
	3	15.96±1.08	12.1±0.7	9.3±0.08	4.31±0.07
	4	24.58±1.26	21.7±1.41	17.27±0.5	8.46±0.4
	5	33.58±1.04	28.3±0.81	21.29±0.88	12.9±0.825
7.4	6	41.68±1.06	36±1.05	29.57±0.88	23.05±0.955
	8	49.47±1.14	42.6±1.04	38.6±1.5	31.41±0.799

10	57.55±1.29	51.6±1.47	46.88±1.4	37.5±1.37
12	65.33±1.56	57.47±1.84	50.99±1.59	41.3±1.184
14	70.1±1.5	65.58±1.11	57.45±1.68	47.45±1.16
16	78.92±1.13	70.2±0.9	61.77±2.14	53.07±1.0
18	84.39±1.44	79.36±0.93	72.23±1.68	59.9±0.95
20	90.65±1.61	84.3±1.75	76.95±1.53	65.2±1.05
22	94.1±1.2	91.3±1.625	85.42±0.869	73.63±1.03
24	98.4±1.75	97.8±1.32	93.06±1.25	84.21±0.99
26	-	-	97.39±0.67	89.24±0.81

pro1file data for tablets coated with Eudragit L 100

Table 10: *In vitro* drug release pro1file data for tablets coated with Eudragit S 100

pH	**Cumulative % Drug Release**				
	Time (hr)	**ES a**	**ES b**	**ES c**	**ES d**
1.2	0	0	0	0	0
	0.5	0.3±0.04	0.2±0.06	0.4±0.03	0.2±0.01
	1	0.7±0.05	0.3±0.07	0.7±0.08	0.3±0.02
	2	1.6±0.1	1±0.07	0.9±0.043	0.5±0.01
6.8	2.5	4.12±0.165	3.07±0.032	1.34±0.04	1.1±0.1
	3	7.7±0.07	4.96±0.08	1.65±0.05	1.25±0.05
	4	11.5±0.4	7.7±0.5	3.5±0.26	2.46±0.08
	5	18.7±0.825	13.6±0.9	8.9±0.1	4.3±0.1
7.4	6	24.06±0.955	19.01±0.88	11.45±0.6	7.6±0.1
	8	38.6±0.799	30.17±1.5	23.19±0.49	13.96±0.23
	10	49.14±1.37	38.89±1.4	32.07±1.29	24.43±0.4
	12	54.75±1.18	51.07±1.59	42.42±1.56	33.21±0.56
	14	65.68±1.16	56.95±1.68	45.59±1.508	40.11±0.34
	16	73.41±1.008	64.17±2.14	57.68±1.13	44.51±0.81
	18	80.54±0.95	70.3±1.68	63.6±1.44	54.6±0.95
	20	83.86±1.05	76.15±1.53	69.74±1.61	61.86±1.6
	22	90.54±1.033	85.12±0.86	77.3±1.2	68.31±1.85
	24	94.17±0.99	90.13±1.25	87.1±1.75	75.66±1.75
	26	98.31±0.81	95.12±0.67	93.4±1.32	83.75±1.63
	28	-	-	98.07±1.89	88.4±2.1

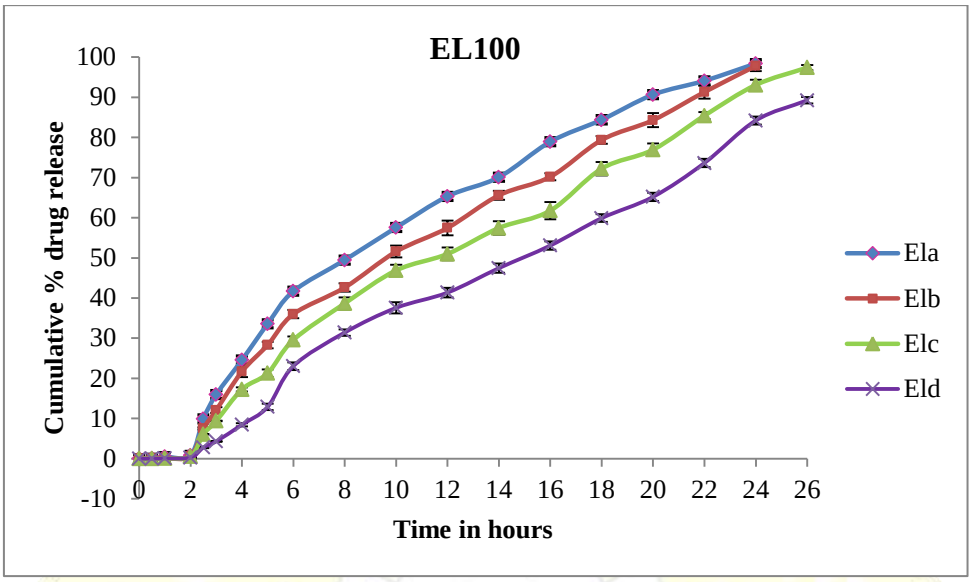

Figure 5: *In vitro* drug release profiles of tablets coated with Eudragit L- 100

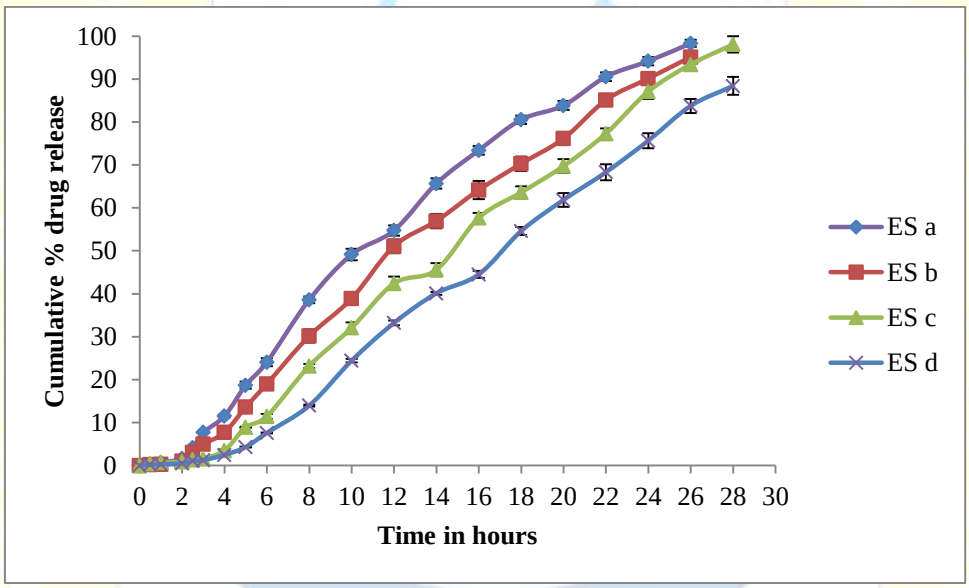

Figure 6: *In vitro* drug release profiles of tablets coated with Eudragit S- 100

***In-vitro* kinetic data:**

Table 11: *In-vitro* Drug release kinetics

Formulation Code	Zero order	First order	Higuchi	Korsmeyer-Peppas	Peppas (n)
ES c (R^2)	0.9901	0.8231	0.8957	0.9651	0.981

DISCUSSION

Site specific or targeted drug delivery system to the colon would ensure direct treatment at the disease site, lower dosing, fewer systemic side effects, minimizing extensive first pass metabolism of drugs.

Colon specific formulation could also be used to prolong the drug delivery. Due to a longer transit time than in the stomach, colonic absorption of poorly absorbed drugs can be improved. 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.

The aim of the present study was to formulate HPMC matrix tablets coated with Eudragit S 100 and Eudragit L 100 for site-specific delivery of Nabumetone for treating spasms in colon. The use of enteric polymer Eudragit S 100 coated matrix tablets makes them able to release the drug at the particular pH of colonic fluid. The polymer Hydroxy propyl methyl cellulose K4M retards the drug release.

There was no appearance or disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

The method employed for tabletting in this study was direct compression for which the powder blend should possess good flow. The optimum value for Carr's index (%) is upto 15%. Values for angle of repose (θ) less than or equal to 25^0 generally indicate free flowing material. By means of pilot studies it was found that pure nabumetone exhibited angle of repose value of 23.21± 0.52 ^{0} indicating good flow property. It was further supported by high Carr's index value of 17.24 ± 0.27 %. The tablet powder blend possessed good flow properties. Since, the flow properties of the powder mixture are important for the uniformity of dose of the tablets.

The tablets of different batches showed varied thickness i.e. 4.72±0 mm for core tablet and 5.88±0.05 to 6.32±0.01 mm for coated tablets, and hardness is 6.17±0.29 kg/cm^2 for core tablets and 6.9±0.3 to 7.8±0.3 kg/cm^2 for coated tablets. The friability is 0.14 % and weight variation 601.5±1.36, all are within the prescribed IP limits.

The drug content was found to be uniform (>75% according to IP 2007) within the batches of different tablet formulations.

The evaluation of release profile is recommended as an important tool in the development and optimization of drug formulations. Release studies of core tablet were carried out in pH 7.4 phosphate buffer. The drug release from core tablet (90.23%) was high at 12th hour, HPMC K4M has a substantial ability to swell and form a hydrogel in neutral medium hence the initial drug release takes place in SIF. Whereas the enteric polymers remain insoluble in the gastric pH and intestinal pH and thus controlling the release of drug within the desired range.

The second part of the formulation focused on the pH dependent polymeric coating of the HPMC tablets. The coating polymers were, Eudragit S-100 and Eudragit L-100, dissolves above pH 7.0 and pH 6 respectively, thereby protecting the drug from releasing from the

core before reaching the colonic region. Once the enteric coating dissolves, it is expected that drug release would be by controlled release of drug by polymer HPMC in the target area. Taking into account the dissolution profile of HPMC Nabumetone matrix tablets, the core tablet was an optimized formulation as its dissolution profile was according to the expected requirements of the study.

6% of Eudragit S 100 and Eudragit L 100 are enteric coated to achieve 5, 10, 15, 20% weight gain separately. The weight variation, hardness and the drug content of all the formulations was found to be within the official limit. From the dissolution data it was observed that all the formulations showed little or no significant release at pH 1.2 (i.e., <1% drug release). Release started in pH 6.8 buffer for all the formulations. This may be attributed to the fact that the threshold pH (pH at which dissolution occurs) of Eudragit L-100 is 6. The lag time for drug release in pH 6.8 buffer was found to be dependent on the level of coating 5, 10, 15 and 20% (coating level in TWG) corresponding to batches EL a, EL b, EL c and EL d respectively showed significant drug release (i.e., >20%) after a lag time of 4 hr., 5 hr., 5.5 hr. and 6 hr. respectively and drug release in pH 7.4 is >90% for EL a, EL b, in 24 hours and >90% for EL c in 26 hours and <90% for EL d in 26 hours.

Formulations coated with ES-100 TWG 15% and 20% showed no release in pH 6.8 buffer (i.e., <1% drug release). However the release for formulations coated with ES 100 TWG 5%, 10% started in 7.4 buffer. Also the lag time for drug release in pH 6.8-7.4 buffer was found to be dependent on the level of coating. 5, 10, 15, 20% (coating level in TWG) corresponding to batches ES a, ES b, ES c and ES d showed significant drug release (i.,e < 25%) after a lag time of 5 hr. (in pH 6.8 medium). Drug release in pH 7.4 buffer is >90% for ES a, ES b in 24 hours, >90% for ES c in 28 hours and <90% for EL d in 28 hours.

Formulation ES c coated with 15% TWG of Eudragit S- 100 showed the most desirable properties. EL c also performed better *in vitro* but ES c was considered more superior because of the former's dependence of GI transit for drug release and was not specific to pH of the colon. Hence ES c was considered as the optimized formulation for colonic drug delivery.

The mechanism of drug release from matrices containing swellable polymers is either purely diffusion or erosion controlled, while most systems exhibit a combination of these mechanisms. When hydrophilic matrix system enters an *in vitro* dissolution medium, drug particles initially pass into solution from the surface. The solid matrix also begins to swell as soon as hydration with solvent molecules, diffusion of the dissolved drug and erosion of viscous polymer layer and these in turn de aggregate into fine particles that also release their drug content by dissolution. The release mechanism is also influenced by porosity and

tortuosity of the matrix. In this study, drug release kinetics was evaluated by fitting with different models, zero-order, first-order, Higuchi, or Korsmeyer-Peppas. According to the Table 11, it is observed that ES c formulation was best fitted with zero order model indicating their release kinetics is not dependent on the concentration of drug in the depot. The drug release data were fitted to the power law or the Korsmeyer–Peppas equation. In this study, the Nabumetone release, in neutral medium, from HPMC tablets showed a good fit into the Korsmeyer-Peppas equation, indicating combined effect of diffusion and erosion mechanisms for drug release. It exhibited a correlation coefficient (r^2) greater than 0.98. In the case of matrix tablets, $0.45 < n$ corresponds to a Fickian diffusion mechanism and $n = 0.89$ indicates a purely relaxed controlled delivery which is referred to as Case II transport. Intermediate values $0.45 < n < 0.89$ indicate an anomalous behavior (non-Fickian kinetics corresponding to coupled diffusion/polymer relaxation). Occasionally, values of $n > 0.89$ have been observed, which has been regarded as Super Case II kinetics. The mechanisms of drug release is (super case-II), since they fitted well with Korsmeyer–Peppas models as their r^2 values in the range of 0.999 with n value above 1. This indicates that the drug release depends on swelling, relaxation and erosion of polymer with zero order release kinetics.

CONCLUSION

The ES c was considered as optimized formulation for its good extended release.

ACKNOWLEDGEMENT

Authors are very thankful to the managements of **Aditya group of pharmacy colleges**, Surampalem and **VJ's College of pharmacy**, Diwancheru (Rajamahendravaram) for providing all the facilities to carry-out thesis. And also sincerely thankful to **SK Health Care Pvt. Ltd.**, Bollaram(Hyderabad) for providind all the chemicals as well as drug to carry-out thesis as well as their great support.

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