TO FORMULATE AND EVALUATE EXTENDED-RELEASE TABLETS OF ETODOLAC (ETD)

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ABSTRACT

An ideal dosage form is the one which maintain the constant level of drug in the plasma during the entire period of treatment. The aim of the research was to formulate and evaluate extended-release tablets of ETD (etodolac). The etodolac (API) was obtained as gift sample from Bio-Leo analytical Lab, Prashanthinagar and other polymers of analytical grade form the certified suppliers only. The formulated tablets were gone through different evaluation parameters i.e., preformulation studies, weight variation, friability, hardness, disintegration & dissolution, in-vitro drug release, particle size, FT-IR & UV spectroscopy. In results, tablets were found excellent in all the parameters and optimum in the case of drug release. In concludes, that suitable analytical method based on UV-Visible spectrophotometer was developed for the model drug. λ_{max} *of 276 was identified for model drug in both 0.1 N HCL and PBS pH 7.0. By performing compatibility studies with DSC no interaction was confirmed. This study suggests that etodolac's extended-release tablets may be used in human beings after estimation of pharmacokinetics profiles in animal/human models.*

Key words: *Etodolac, HPMC, sustained release, in-vitro drug release,*

INTRODUCTION

An ideal dosage form is the one which maintain the constant level of drug in the plasma during the entire period of treatment [1]. According to the United States of Pharmacopoeia, the term "Modified Release Dosage Forms" is used to denote the dosage forms for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic objectives not offered by the conventional dosage forms [2][3]. According to Flynn, controlled release has been defined as "the use of whatever means possible, be it chemical or mechanical, to regulate a drug access rate to the body's central compartment, or in some cases, directly to the involved tissues" [4]. Controlled drug delivery system is produced when a polymer whether natural or synthetic is properly mixed with the active ingredient so that the drug is released in a predetermined manner [5].

NSAIDs are an important class of drugs that are used in the treatment of rheumatic arthritis and for reducing the associated pain and inflammation. These drugs are absorbed in stomach especially in the initial part of the small intestine. The concept of floating drug delivery systems can also be utilized to minimize the irritant effect of weakly acidic drugs in the stomach by avoiding direct contact with mucosa and improving the availability of the drug in the stomach for absorption. The present study is aimed to avoid the side effects of NSAID's by using floating drug delivery system [6].

Zhong Z and Guo Q have studied the Interpolymer complexes and miscible blends of poly (*N*-vinyl-2-pyrrolidone) with novolac resin and the effect of crosslinking on related behaviour. The nature of the solvent has a profound influence on the degree of interpolymer association. It was found out that the driving force in the formation of the interpolymer complexes between novolac and PVP is the hydrogen-bonding interaction between the hydroxyl of the novolac and the proton-accepting groups of PVP [7].

Etodolac

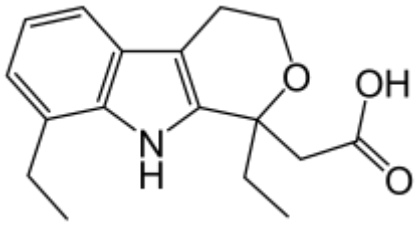

Fig. 1 Structure of etodolac

Mechanism of Action: NSAIDs, the anti-inflammatory effects of etodolac result from inhibition of the enzyme cycooxygenase (COX). This decreases the synthesis of peripheral prostaglandins involved in mediating inflammation. Etodolac binds to the upper portion of the COX enzyme active site and prevents its substrate, arachidonic acid, from entering the active site. Etodolac was previously thought to be a non-selective COX inhibitor, but it is now known to be 5 – 50 times more selective for COX-2 than COX-1. Antipyresis may occur by central action on the hypothalamus, resulting in peripheral dilation, increased cutaneous blood flow, and subsequent heat loss [8].

Dosage: Capsules: 200 and 300 mg;
Tablets: 400 and 500 mg;
Extended Release: 400, 500 and 600 mg.

Physicochemical Properties:

1. Description: slightly yellowish powder.

2. IUPAC Name: (RS)-2-(1,8-Diethyl-4,9-dihydro-3H-pyrano[3,4-b]indol-1-yl)acetic acid.

3. Molecular Formula: $C_{17}H_{21}NO_3$

4. Molecular Weight: 287.4 g/mol.

5. Solubility: Freely soluble in methanol, acetone. Insoluble in water.

6. Category: Anti-inflammatory Agents, Cyclooxygenase Inhibitors, Analgesics, Analgesics, Non-Narcotic, Antipyretics, Nonsteroidal Anti-inflammatory Agents (NSAIAs).

Pharmacokinetic Properties

1. Half-life ($t_{1/2}$): 7.3+ or - 4hours (biological).

2. Shelf-Life: 36 months.

3. Bioavailability: 80%

4. pH: 7.4

5. P^{Ka} : 4.65

6. Protein Binding: 100%

7. Route of Metabolism: Metabolized in liver

9. Volume of distribution: 390 mL/kg

Hydroxy Propyl Methyl Cellulose

Chemical Name:

Cellulose hydroxyl propyl methyl ether

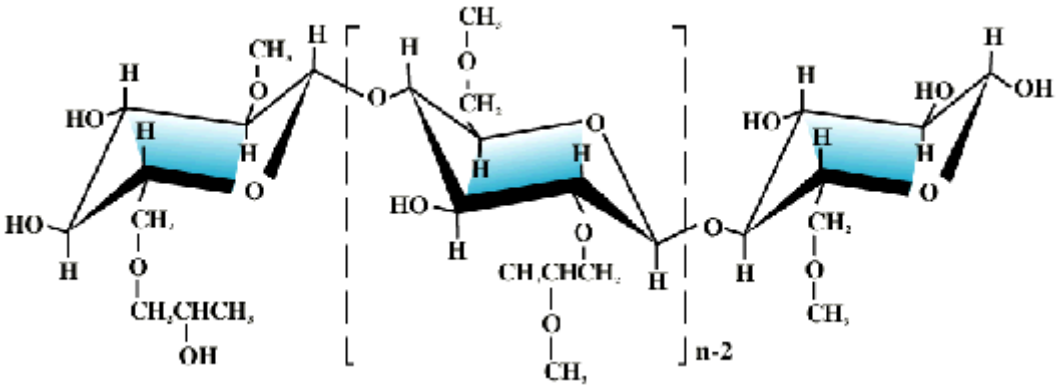

Fig. 2 Structure of HPMC

Lactose Monohydrate

Chemical Name **:**O-b-D-Galactopyranosyl-(1!4)-b-D-glucopyranose

Chemical Formula: C12H22O11

Chemical structure:

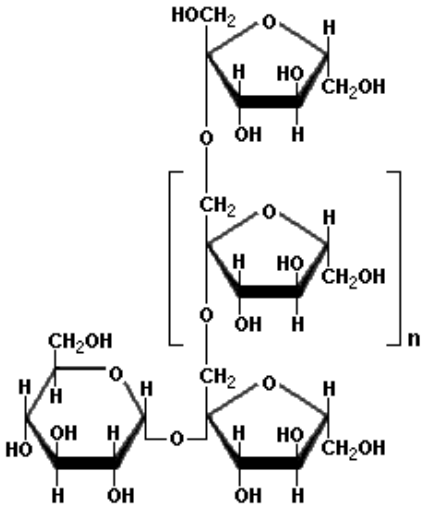

Fig. 3 Structure of Lactose Monohydrate

Physical state & appearance

Anhydrous lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous b-lactose and anhydrous a-lactose. Anhydrous lactose typically contains 70–80% anhydrous b-lactose and 20–30% anhydrous a-lactose.

Molecular Weight **:**342.3

Magnesium Stearate

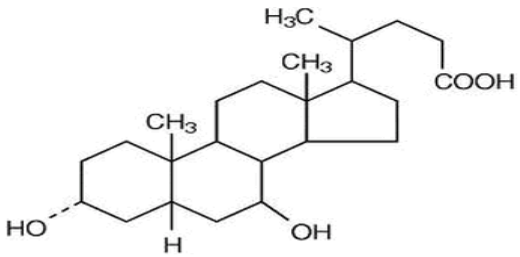

Fig. 4 Structure of Magnesium stearate

Chemical name

Octadecanoic acid magnesium salt

Functional category: Tablet and capsule lubricant.

Starch

- **Empirical Formula and Molecular Weight:**

  $(C_6H_{10}O_5)_n$ where n = 300 –1000.

- **Structural Formula:**

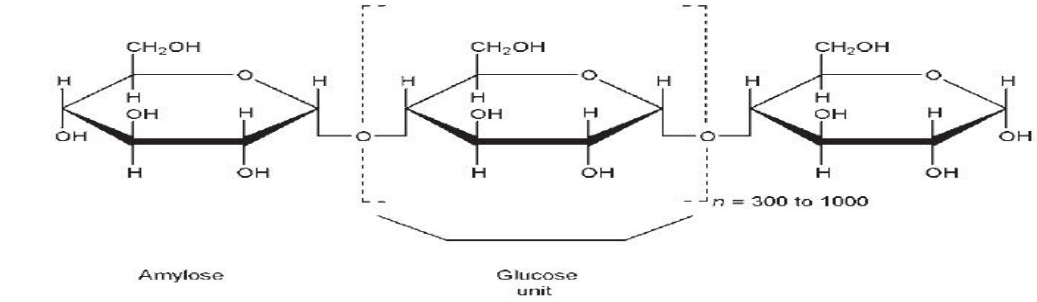

Fig. 5 Structure of Starch

Xanthan gum

Chemical Name and CAS Registry Number

Xanthan gum [11138-66-2]

Empirical Formula and Molecular Weight

(C35H49O29)n approximately 1×106, The USP32–NF27 describes xanthan gum as a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid, and is prepared as the sodium, potassium, or calcium
salt.

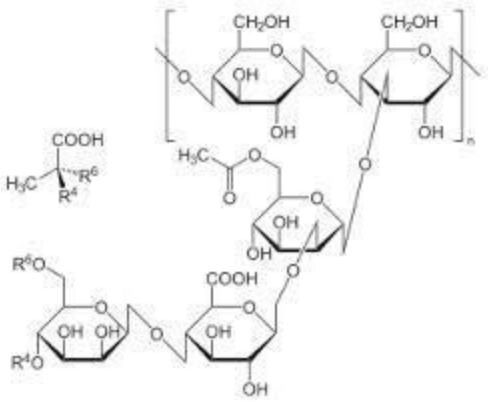

Fig. 6 Structure of xanthan gum

Chitosan

Chemical Name and CAS Registry Number

Poly-b-(1,4)-2-Amino-2-deoxy-D-glucose [9012-76-4]

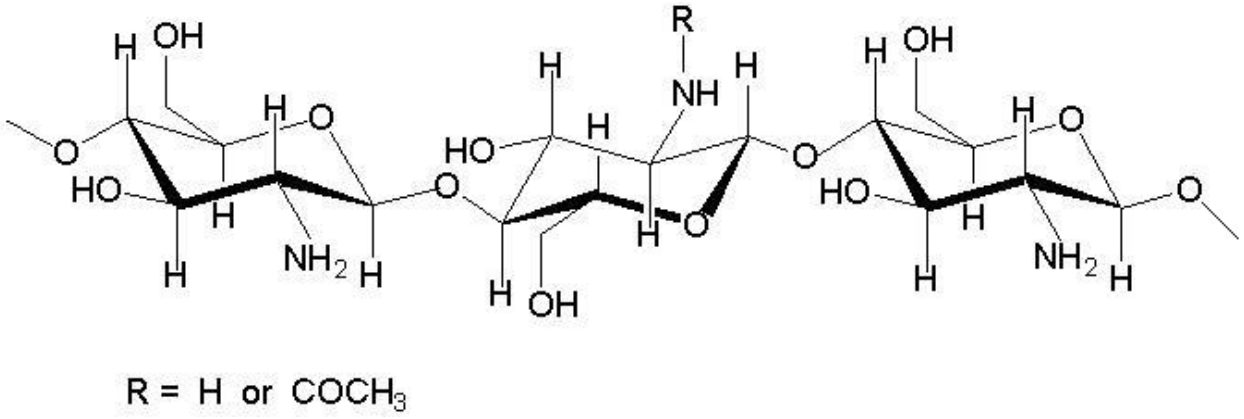

Fig. 7 Structure of chitosan

Surelease (Aqueous Ethylcellulose Dispersions)

Surelease is a platform of complete, extended release, aqueous coating systems utilizing ethylcellulose as the rate controlling polymer for drug release. The dispersions are a unique combination of film-forming polymer, plasticizer and stabilizers; that can be used for modified release and taste masking applications. This advanced technology provides reliable and reproducible release profiles that are consistent from the laboratory, to pilot and production scale processes.

Surelease has a shelf life of 18 months, from date of manufacture when properly stored.

MATERIALS AND METHODS

Materials

Table 1. List of materials

S.No	Material	Supplied
1	Etodolac	Gift sample from Bio-Leo analytical Lab, Prashanthinagar
2	Lactose	Drugs india, Hyderabad, Hyderabad
3	Starch	Drugs India, Hyderabad
4	HPMC K4M	Drugs India, Hyderabad
5	HPMC E5	Drugs India, Hyderabad
6	HPMC K100 LV	Drugs India, Hyderabad
7	Xanthangum	Drugs India, Hyderabad
8	Chitosan	Drugs India, Hyderabad
9	Surrelease	Drugs India, Hyderabad
10	Metalose	Drugs India, Hyderabad
11	Magnesium Stearate	Drugs India, Hyderabad
12	Aerosil	Drugs India, Hyderabad

Drug Evaluation

Different properties of the drug were evaluated before suitable excipients were chosen in order to develop a suitable matrix system.

Determination of λ_{max}

Procedure:

10mg of pure drug was taken and known concentration of drug solution was prepared by solubilizing in methanol then suitably diluting drug solution in Phosphate buffer pH 7 and in 0.1N HCl. The solutions were scanned from 200-400 nm against the reagent blank to fix absorption maxima. Spectrum of the model drug was obtained and λ_{max} of model drug was found to be 254 nm. Hence all further investigations were carried out at the same wavelength [9].

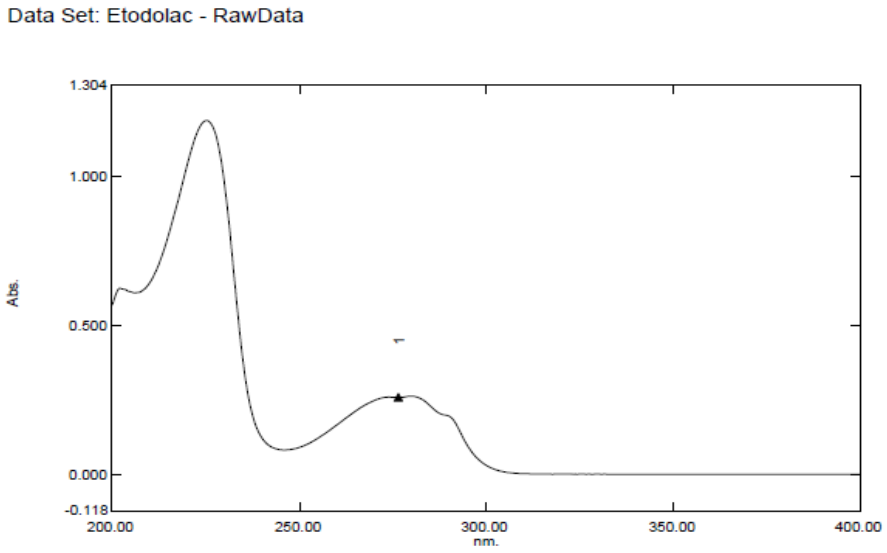

Fig. 8 Spectrum showing the λ_{max} of the model drug

Procedure for Calibration curve

Calibration Curve of model drug in PBS pH 7 and pH 1.2 by Double Beam UV Spectrophotometer

Solutions:

1. Standard Stock -100mcg/mL in PBS pH 7
2. Standard Stock -100mcg/mL in 0.1N HCl pH 1.2

From the stock solution, different aliquots were taken in series of 10mL volumetric flasks and volume made up with buffer to get a series of working standard solutions of concentrations, 2.5µg/mL, 5µg/mL, 7.5µg/mL, 10µg/mL 12.5µg/mL and 15µg/mL. The absorbance of samples was obtained spectrophotometrically against the reagent blank at 254nm. The calibration curves were constructed by plotting drug concentration versus the absorbance value at 254nm and the regression equation was computed.

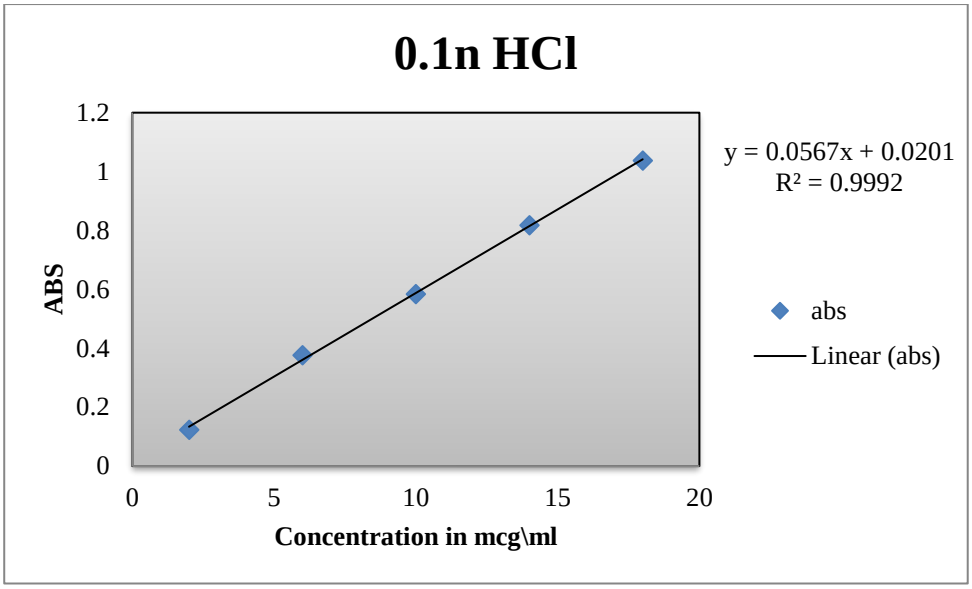

Fig. 9 Standard Curve of the model drug in pH 1.2

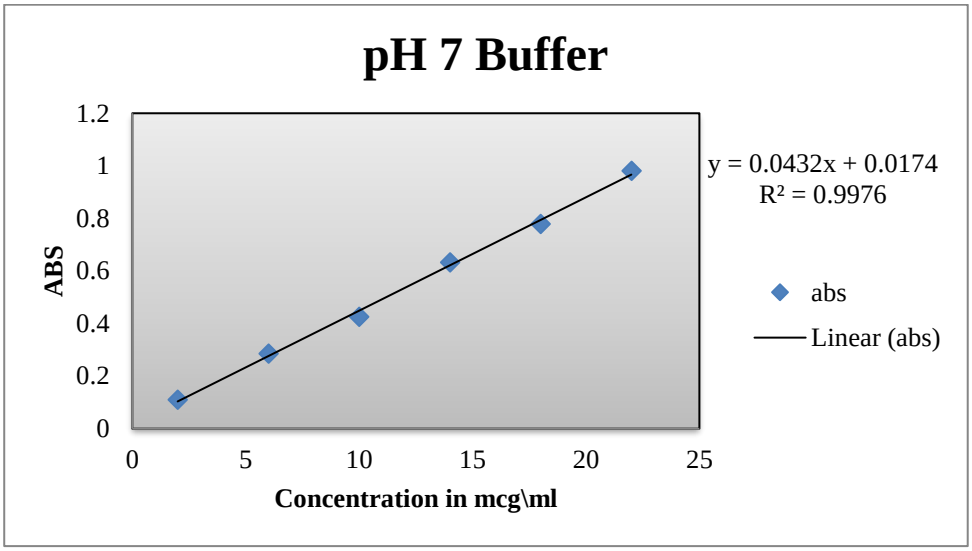

Fig. 10 Standard Curve of the model drug in pH 7

Particle size determination: Dry sieve analysis for particle size determination

Dry Sieving Method

Each test sieve was weighed to the nearest 0.1 g. An accurately weighed quantity of test specimen was placed on the top (coarsest) sieve, and lid was replaced. The nest of sieves was agitated for 5 minutes. Then each sieve was carefully removed from the nest without loss of material. Each sieve was reweighed, and the weight of material on each sieve was determined. The weight of material in the collecting pan was also determined in a similar manner. The nest of sieves were reassembled and agitated for 5 minutes. Each sieve was removed and weighed, as previously described. Upon completion of the analysis, the weights of material were reconciled. Total losses must not exceed 5% of the weight of the original test specimen.

Table 2. Particle size determination of model drug

Sieve Mesh Number	Sieve Size Opening(µm)	Mass of Sample Retained on Each Sieve(g)	Percentage of Sample Retained on Each Sieve (%)	Cumulative Percentage of Sample Retained on Each Sieve (%)
20	841	0.64	12.8	12.8
40	420	0.87	17.4	30.2
60	250	2.03	40.6	70.8
80	177	0.77	15.4	86.2
100	149	0.29	5.8	92.0
120	125	0.25	5.0	97.0
Pan	-	0.10	2.0	99.0

Inference

From the particle size distribution data, it was observed that the model drug has12.8 % of particles were around 841 microns and 30.2 % of particles were found to be around 420 microns, 92 % of API particles were found to be around 149 microns in size.

Solubility studies

Solubility studies were performed by taking solid dispersions of drug, PVP K90, β-cyclodextrin ratios (1:4, 1:5, 1:6, 1:4:2, 1:5:2, 1:6:2) in 250 mL of buffer and subjected to mechanical shaking at 200 rpm for 5 hrs. The resultant dispersions were collected and filtered through 0.45 µ filters and the concentration of drug was determined from absorbance at 254nm. The solubility was performed at various pH conditions pH 1.2, pH 4.5, pH 6.8, and water.

Table 3. Solubility data of pure drug

pH	Solubility (mg/mL)
Distilled water	1000mg
Acid buffer (pH 1.2)	786mg
Phosphate buffer (pH 7.0)	841mg

Inference

Solubility studies of pure drug showed that it is slightly soluble in water and aqueous buffers. Drug showed pH independent solubility with no significant difference in both the buffers.

Fourier Transform Infra-Red spectrum of model drug

FTIR was performed by KBr pellet method. Drug and KBr were taken in 1:100 ratios and ground in mortar for even distribution of sample and KBr. Then it was prepared in the form of disk by applying pressure of 5 tons for 5 min using a hydraulic press and subjected to IR. The software used was spectrum (version 6.1.0) in the wave number range of 400-4000 cm -1. The resolution is 4 cm -1.

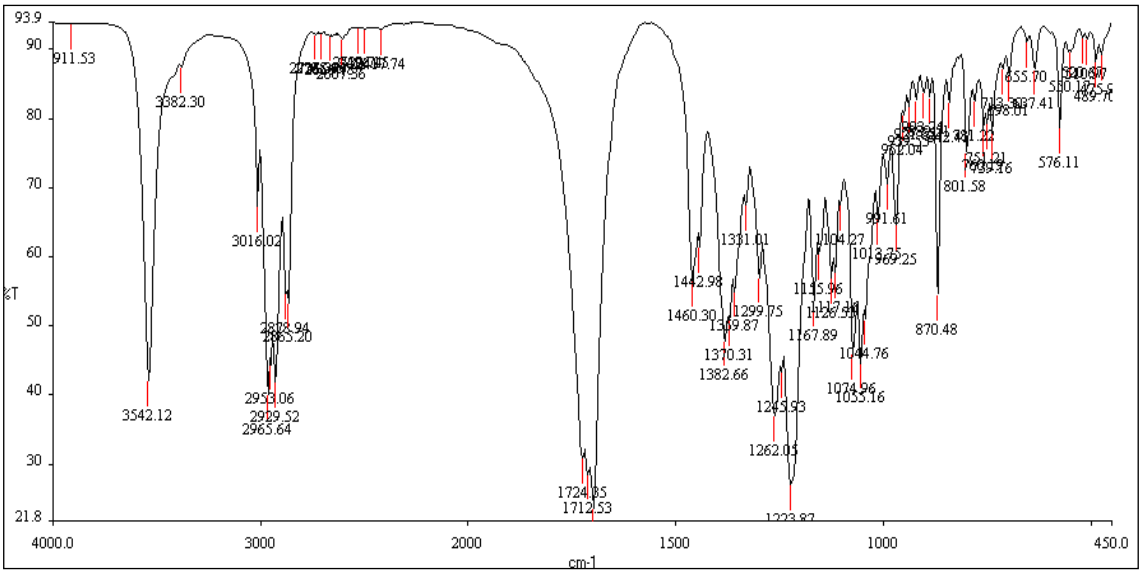

Fig. 11 FTIR Spectrum of model drug

Inference: Characteristic peaks of model drug were observed from FTIR peaks and summarized in Table 4.

Table 4. FTIR peaks and their functional groups of model drug

Functional Group	IR range (cm-1)	Peak observed (cm-1)
Usually sharp O-H	3200-3550	3542.12
		3382.30
= C-H & = CH2	3020-3100	3026.02
CH3, CH2 & CH	2850-3000	2953.06
		2929.52
		2865.20
C-H	2690-2840	2736.39
C=O (saturated aldehyde)	1720-1740	1724.35
C=O (saturated ketone)	1710-1720	1712.53
		1710.58
CH2 & CH3	1350-1470	1460.30
		1442.98
OH bending	1330-1430	1382.66
		1370.31
		1359.87
		1331.01
C=O	1210-1320	1299.75
		1262.05
O-H bonded	970-1250	1245.93
		1223.87
C-N	1000-1250	1167.89
O-H bonded	970-1250	1155.96

		1126.53
		1117.16
		1104.27
		1074.96
		1055.16
		1044.76
		1013.75
=C-H & = CH2	880-995	991.61
		969.25
		952.04
= CH2	780-850	842.41
		801.58

Powder and Flow Properties of API

Bulk density [10]

Bulk density was determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder (USP Method I).

Approximately 10 gm of test sample, M was introduced into 25 mL dry measuring cylinder without compacting. The powder was leveled carefully without compacting and read the unsettled apparent volume V0, to the nearest graduated unit. Bulk density was calculated, in g per mL, by the formula.

$$(M) / (V_o)$$

Generally replicate determinations are desirable for the determination of this property.

Tapped density

Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. After measuring the initial weight and volume, the cylinder was mechanically tapped, and volume readings were taken until little further volume change is observed.

Procedure: Cylinder containing the sample was tapped mechanically by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Unless otherwise specified, the cylinder was tapped 500 times initially and the tapped volume was measured, Va, to the nearest graduated unit. The tapping was repeated for an additional 750 times and the tapped volume was measured, Vb, to the nearest graduated unit. If the difference between the two volumes is less than 2%, Vb is the final tapped volume, Vf . It was repeated in increments of 1250 taps, as needed, until the difference between succeeding measurements is less than 2%. The tapped density was calculated, in g per mL, by the formula:

$$(M) / (Vf).$$

Generally, replicate determinations are desirable for the determination of this property.

Compressibility index [10]

The Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio.

Compressibility Index— Calculate by the formula:

Hausner's Ratio— Calculate by the formula:

Where V0 - Bulk volume

Vf - Tapped volume

Table 5. Scale of Flowability (USP)

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Determination of Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles.

Angle of repose was formed on a fixed base with a retaining lip to retain a layer of powder on the base. The base should be free of vibration. The height of the funnel was varied to carefully build up a symmetrical cone of powder. Care should be taken to prevent vibration as the funnel is moved. The funnel height should be maintained approximately 2–4 cm from the top of the powder pile as it is being formed in order to minimize the impact of falling powder on the tip of the cone. If a symmetrical cone of powder cannot be successfully or reproducibly prepared, this method is not appropriate. Angle of repose was determined by measuring the height of the cone of powder and calculating the angle of repose, from the following equation:

Table 6. Flow Properties and Corresponding Angles of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25-30
Good	31–35
Fair-aid not needed	36–40
Passable-may hang up	41–45
Poor-must agitate, vibrate	46–55

Flow Property	Angle of Repose (degrees)
Very poor	56–65
Very, very poor	>66

Table 7. Flow and powder properties of API

Parameters	API
Bulk density (gm/cm3)	2.05
Tapped density (gm/cm3)	2.37
Compressibility Index (CI) %	13.5
Hausner's ratio (HR)	1.15
Angle of repose (θ)	22.7

Inference

Flow and powder properties of API were fair hence tablets can be prepared by direct compression method.

Formulation Development Strategy

Following ingredients were selected for formulation development of matrix tablets based on literature search and pre-formulation studies.

Manufacturing process

Matrix tablets of the model drug were prepared by wet granulation process. Different grades of three different classes of rate retarding polymers-HPMC, Xanthan gum and Surelease and metalose were chosen. Starch and lactose was used as diluent. Magnesium stearate was used as lubricant. The method was chosen as direct compression.

Table 8. List of ingredients of formulation

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Etodolac	400	400	400	400	400	400	400	400	400	400	400	400
Lactose	45	45	45	15	15	15	15	35	35	35	35	35
Starch	40	40	40	40	40	40	40	40	40	40	40	40
HPMC k4m	100	--	--	30	30	30	30	30	30	30	90	80
HPMC E5	--	100	--	--	--	--	--	80	--	--	--	--
HPMC K100 LV	--	--	100	--	--	--	--	--	80	--	--	--
Xanthangum	--	--	--	100	--	--	--	--	--	--	--	30
Chitosan	--	--	--	--	100	--	--	--	--	--	--	--
Surrelease	--	--	--	--	--	100	--	--	--	80	--	--
Metalose	--	--	--	--	--	--	10	--	--	--	20	--

							0					
Magnesium stearate	10	10	10	10	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5
Total tablet weight	600	600	600	600	600	600	600	600	600	600	600	600

Evaluation of compressed tablets

Thickness and diameter

The shape and dimensions of compressed tablets were determined by the type of tooling used during the compression. Twenty tablets were randomly selected from formulations and thickness was measured using Vernier caliper. It was expressed in millimeter and average was calculated. The tablet thickness should be within the limits of ± 5%.

Weight variation

Uniformity of weight was determined by USP method. Twenty tablets were selected randomly and weighed. Average weight of the tablets was determined. These tablets were weighed individually and the weight variation was determined. The percent deviation was calculated using the following formula. The limits are mentioned in the below table as per USP.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Table 9: USP specification for tablet weight variation

Average weight of tablet	Percentage weight variation
130 mg or less	10 %
More than 130 mg and less than 324 mg	7.5 %
324 mg or more	5 %

Hardness

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. It indicates the ability of a tablet to withstand mechanical shocks while handling and transportation. Ten tablets were randomly selected from each formulation and hardness of the same was determined in terms of KP.

Friability

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This In-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation and shipment. About 6.5 g tablets (W initial) were transferred into Roche friabilator. The

friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were dedusted and weighed again (W final). The percentage friability was calculated by
The percent friability was determined using the following formula:

% Friability = 100 (1-$W_{initial}$/ W_{final})

$W_{initial}$= Initial weight of tablets

W_{final} = Final weight of tablets after 100 revolutions

% Friability of tablets less than 1 % are considered acceptable.

Estimation of drug content

Four tablets were powdered. The powdered sample equivalent to 10mg of drug was transferred to a 100ml volumetric flask. Required amount of pH 7.0 Phosphate buffer was added to dissolve drug and remaining volume was made up to 100ml with pH 7.0 Phosphate buffer, sonicate for 60 minutes and filter the solution. From the filtrate, 1ml was transferred to 10ml volumetric flask and the volume was made up to 10ml pH 7.0 Phosphate buffer. The sample was analyzed against blank by UV spectrophotometer at 249 nm.

$$\text{Assay} = \frac{\text{Drug content (practically)}}{\text{Drug content (Theoretically)}} \times 100$$

Drug excipients Compatibility

Thermal properties of drug & polymer (EUDRAGIT, HPMC, PEO grades) were investigated using a METTLER differential scanning calorimeter thermal analysis controller with an intracooler-2 cooling. About 3 to 5 mg of product was placed in perforated aluminum sealed 50-µl pans, and the heat runs for each sample was set from 20°C to 300°C at 20°C/min, under an inert environment using nitrogen. The apparatus was calibrated using pure metals like indium with known melting points and heat of fusion (ΔH fusion).

***In-vitro* drug release kinetic studies**

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order, first order, Higuchi square root and korsmeyerpeppas model. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test.

Zero Order Model

This model describes the systems where the drug release rate is independent of the concentration.

C=koT

Where, ko is zero order rate constant expressed in units of concentration/time

C is the amount of drug released at time t.

T is time

A graph of cumulative % drug released vs. time would yield a straight line with a slope equal to Ko and the intercept at the origin of the axes.

This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some trans-dermal system, as well as matrix tablets with low soluble drugs, coated forms, osmotic systems, etc. The pharmaceutical

dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

First Order Model:

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species

Release behavior generally follows the following first order equation:

Log C= Log Co-Kt/2.303

Where, C is the amount of drug dissolved at time t,

Co is the amount of drug dissolved at t=0 and

K is the first order rate constant.

A graph of Log cumulative of % drug remaining vs. time yields a straight line.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drugs in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi Model:

A form of the Higuchi Square Root law is given by equation

Q=Kt 1/2

K= constant reflecting the design variables of the system

A graph of cumulative % drug released Vs square root t yields a straight line.

The Higuchi square root equation describes the release from systems where the solid is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion.

Korsmeyer-Peppas Model:

Korsmeyer et al. derived a simple equation to describe the release of drug from polymeric system. To find out the mechanism of drug release first 60% of drug release data was fitted to this Korsmeyer-Peppas Model

$M_t/M_\infty = Kt^n$

Where, M_t/M_∞ is the fraction of drug released at time t,

K is the rate constant

n is release exponent

A graph of log cumulative of % drug release Vs log time yields a straight line.

The n value is used to characterize different release mechanisms as given in table below.

Table 10. Depiction of mechanism of release depending on diffusion exponent

Diffusion exponent(n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n <0.89	Anomalous(non-Fickian) diffusion
0.89	Case II transport
n> 0.89	Super Case II transport

For the developed formulations of model drug (n=3), dissolution tests were carried out in two media - 0.1 N HCl, and pH 7.0 phosphate buffer with under the following conditions given in table 20.

Table 11. Dissolution b/w acidic and alkaline medium

S.No	Parameters	Acidic medium	Alkaline medium
1	Dissolution apparatus	USP XXIV apparatus no. I (Basket type)	USP XXIV apparatus no. I (Basket type)
2	Temperature	$37^0C \pm 0.5^0C$	$37^0C \pm 0.5^0C$
3	Paddle speed	100 rpm	100 rpm
4	Dissolution medium	0.1 N HCl	pH 7.0 phosphate buffer
5	Volume of dissolution medium	900ml	900ml
6	Volume of sample removed	8 ml	8 ml
7	Volume of dissolution medium replaced (Sink)	8 ml	8 ml
8	Sampling interval	1 and 2 hr	3^{rd}hr to 12^{th}hr

Table 12. Dissolution parameters

The samples withdrawn were filtered through Millipore PVDF filters 0.45µM and drug content in each sample was analyzed after suitable dilution (if required) using a validated UV spectroscopic method at 249 nm.

RESULTS AND DISCUSSION

Optical density

The Table 13 depicts the optical density as below-

Table 13. Optical characteristics and precision of the proposed Method

	In pH 1.2	In pH 7
λmax (nm)	**276**	**276**
Correlation coefficient (r2)	**0.999**	**0.997**

Inference

The linear equation in pH 7: Absorbance = 0.043 x concentration (µg/ml) +0.017. Different standard concentration and their absorbance values were shown in the table --. At all the concentration levels the standard deviation (SD) was low. Goodness of fit of regression equation was supported by high regression value (0.999). Hence the developed method can be used for routine analysis of the drug in pharmaceutical formulations and for dissolution studies.

Drug excipients Compatibility Studies

Thermal properties of drug, polymer and solid dispersion were investigated using a METTLER differential scanning calorimeter thermal analysis controller with an intracooler-2 cooling. About 3 to 5 mg of product was placed in perforated aluminum sealed 50-µl pans,

and the heat runs for each sample was set from 20°C to 250°C at 20°C/min, under an inert environment using nitrogen. The apparatus was calibrated using pure metals like indium with known melting points and heat of fusion (ΔH fusion).

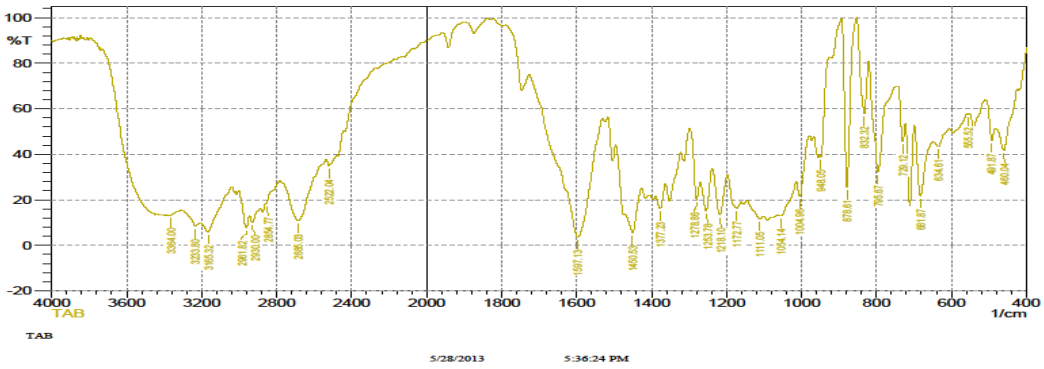

Fig 12. IR graph of Etodolac API

Characterization of lubricated blend

Table 14. Characterization of the blend

Formulation number	Bulk Density	Tapped Density	Carr's Index	Hausner ratio	Angle of repose
F1	0.52	0.65	20.02	1.25	34.2
F2	0.55	0.64	26.21	1.16	35.5
F3	0.49	0.57	14.04	1.163	33.2
F4	0.48	0.55	12.72	1.14	32.4
F5	0.5	0.58	13.79	1.16	33
F6	0.53	0.61	13.11	1.15	32.1
F7	0.49	0.55	10.9	1.12	33.5
F8	0.53	0.61	13.11	1.15	32.1
F9	0.53	0.66	19.69	1.24	31.8
F10	0.51	0.65	21.53	1.27	35.4
F11	0.54	0.61	11.47	1.12	32.5
F12	0.52	0.65	20	1.25	33.1

Characterization of lubricated tablets:

Table 15. Characterization of tablets

Formulation code	Weight variation	Hardness	Friability	Thickness	Content uniformity
F1	601	6.4	0.72	4.1	99.28

F2	598	6.3	0.68	4.15	97.16
F3	597	6.7	0.69	3.96	101.1
F4	599	6.6	0.66	3.99	97.68
F5	596	6.7	0.68	4.1	99.41
F6	599	6.9	0.65	4	98.19
F7	602	6.8	0.67	4.01	102.6
F8	601	7.1	0.65	4.12	99.5
F9	600	6.8	0.7	3.96	99.6
F10	598	6.7	0.68	3.98	98.4
F11	597	6.5	0.59	3.99	97.68
F12	604	6.7	0.52	4.11	97.06

Inference

The thickness of tablets was found to be between 3.96 –4.15mm. The hardness was found to be between 6.3-7.1 Kg/cm^2 , indicating satisfactory mechanical strength. The friability was below 1%, which is an indication of good mechanical resistance of the tablet. The percentage drug content was in the range 97-102% indicating uniformity of content of in the formulations.

Table 16. Dissolution Profiles of prepared matrix tablets

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	3.6	10.5	9.5	2.5	3.3	2.8	8.9	9.0	33.8	3.8	4.3	2.4
2	4.8	21.4	15.7	14.0	10.8	5.5	11.8	14.9	51.8	8.9	10.2	9.4
3	3.7	45.3	5.4	5.9	3.1	1.9	24.4	20.1	35.0	24.9	6.6	21.4
4	13.6	58.7	39.3	11.8	4.6	3.6	35.7	31.5	62.3	34.6	28.6	33.6
5	30.6	74.5	56.0	14.6	6.1	4.3	47.0	45.4	81.9	43.7	40.5	42.4
6	42.3	99.6	65.6	23.0	7.4	6.0	53.4	50.2	87.8	47.7	43.8	44.9
7	49.2	-	86.7	31.3	9.3	7.8	66.1	58.7	91.0	51.0	50.8	51.3
8	58.7	-	-	37.3	12.0	10.3	81.9	73.5	96.3	61.8	61.8	66.1
9	68.2	-	-	42.1	18.2	15.5	90.4	83.0	-	71.9	69.8	76.7
10	74.6	-	-	48.8	23.6	20.1	88.9	89.4	-	84.6	74.6	80.4
11	85.1	-	-	53.9	27.4	21.2	90.5	87.3	-	87.3	77.8	83.6
12	95.2	-	-	68.7	36.0	25.0	90.5	-	-	88.9	88.8	83.6

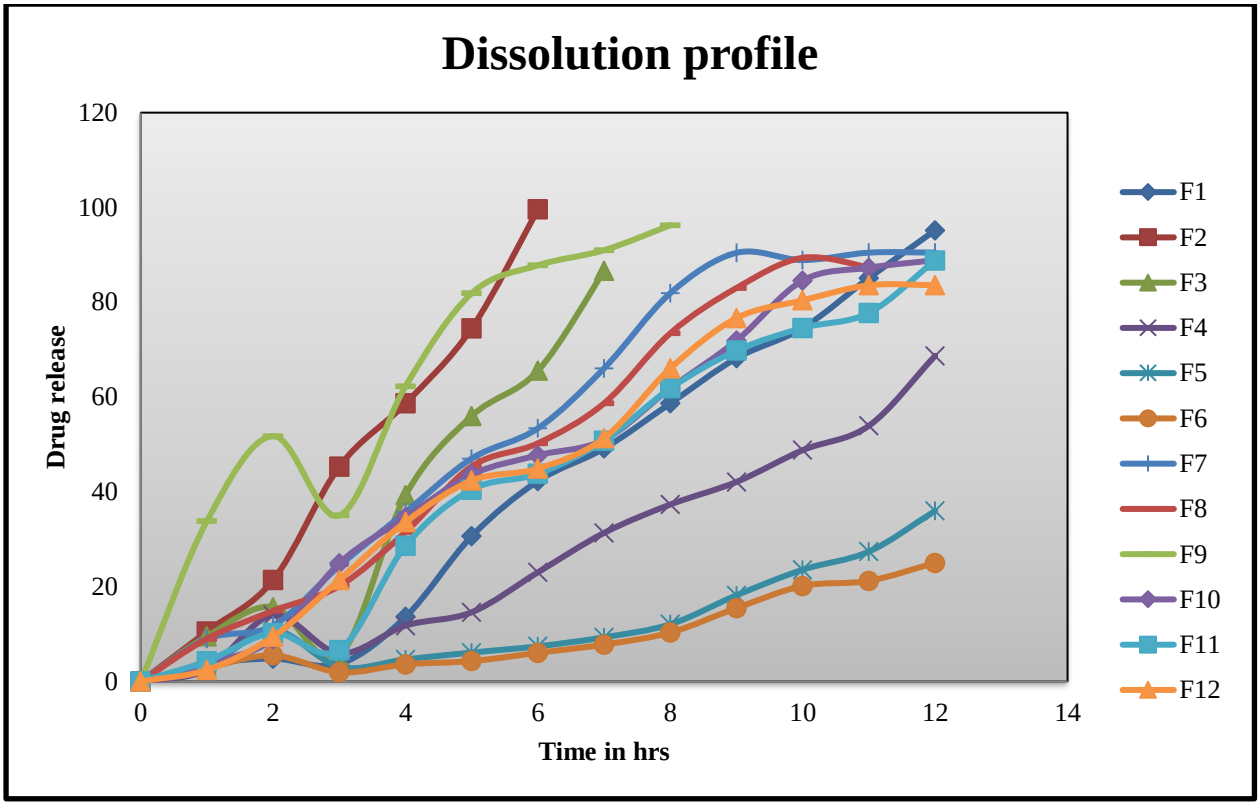

Fig. 13 Drug release

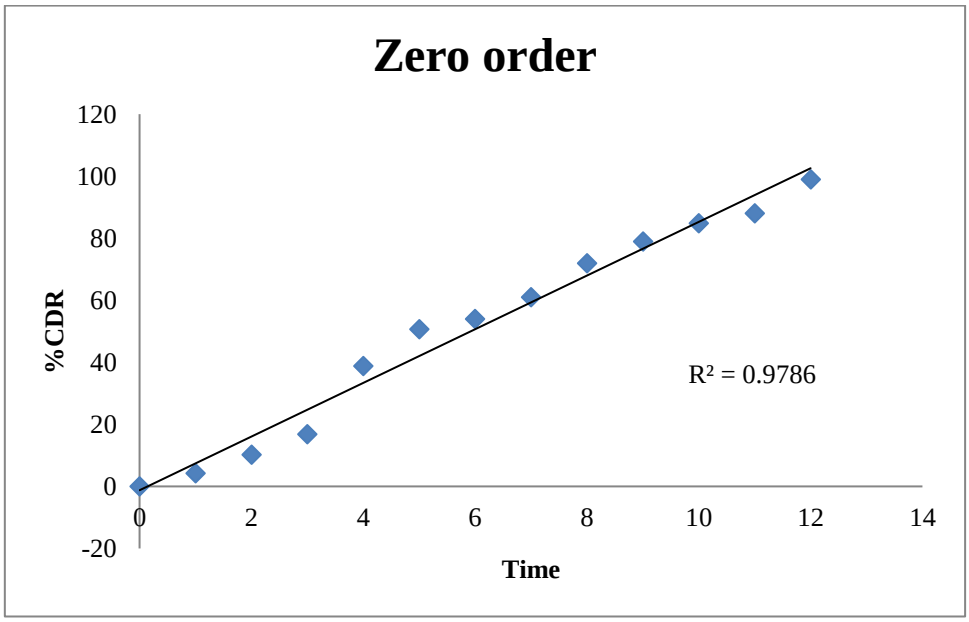

Fig. 14 Zero order plot for F11

Fig. 15 First order plot for F11

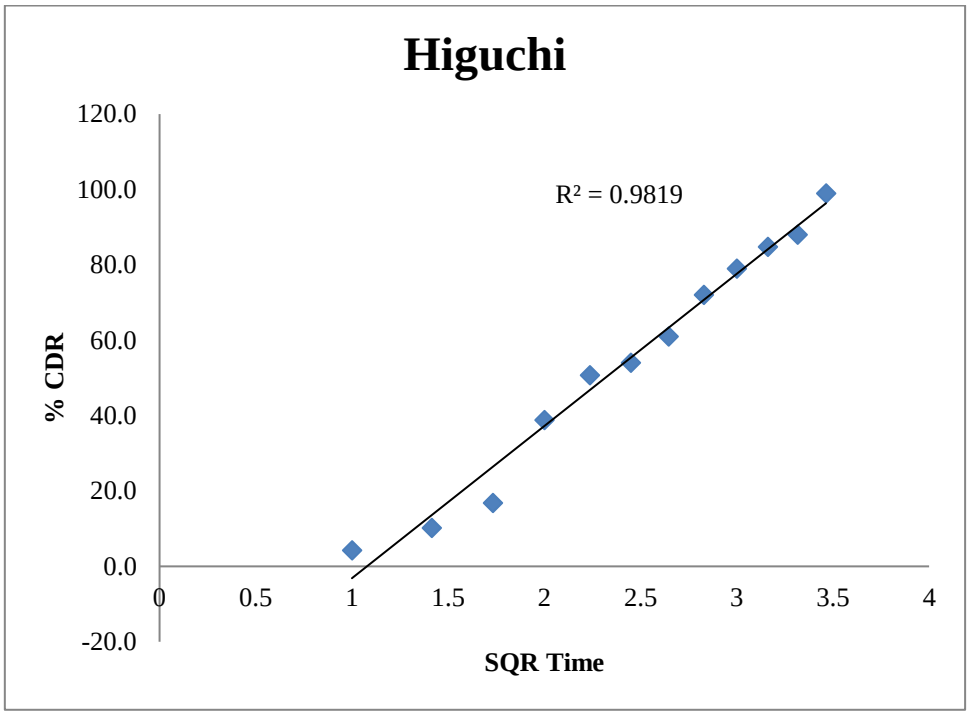

Fig. 16 Higuchi plot for F11

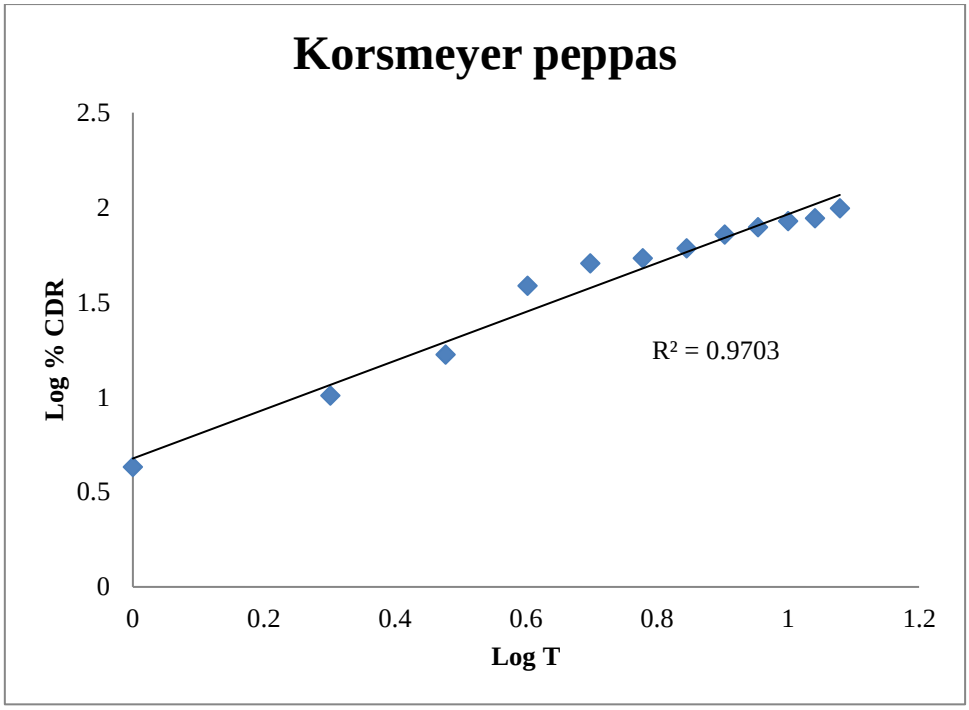

Fig. 17. Korsemeyer Peppas plot for F11

CONCLUSION

Conventional dosage forms have been used for decades for treatment of acute and chronic conditions. These forms promptly release the drug. In order to maintain the drug action/to maintain drug concentration in the therapeutically effective range, it would be necessary to administer a conventional dosage form in frequent intervals, several times in a day.

Suitable analytical method based on UV-Visible spectrophotometer was developed for the model drug. $\lambda_{max}$of 276 was identified for model drug in both 0.1 N HCL and PBS pH 7.0. By performing compatibility studies with DSC no interaction was confirmed. Prior to compression, drug and granules were evaluated for flow properties such as angle of repose, bulk density, tapped density, Compressibility index and Hausner's Ratio. Core tablets of model drug (F1 – F12) were successfully prepared by granulating drug, Mannitol SD200 & different grades of HPMC, Xanthan gum, Surelease and Magnesium stearate as excipients by direct compression method.The above lubricated blend was compressed into tablets.

This study suggests that etodolac’s extended-release tablets may be used in human beings after estimation of pharmacokinetics profiles in animal/human models.

FUNDING

Nil.

CONFLICT OF INTEREST

None.

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