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Formulation and Evaluation of Modified Release Etodolac Tablets Enhanced with Serratiopeptidase for Improved Anti-Inflammatory Efficacy

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ABSTRACT: This research focuses on creating and testing a modified release tablet that contains the non-steroidal anti-inflammatory medicine (NSAID) etodolac along with the proteolytic enzyme serratiopeptidase, which has fibrinolytic and anti-inflammatory qualities. Conventional NSAID therapy often results in gastrointestinal irritation, systemic toxicity, and frequent dosing requirements, leading to reduced patient compliance. The incorporation of Serratiopeptidase aims to enhance anti-inflammatory efficacy while mitigating gastrointestinal side effects and improving drug absorption. In order to achieve regulated medication release, hydrophilic and hydrophobic polymers are used in the formulation of modified release tablets. Various preformulation studies, including drug-excipient compatibility using IR and DSC, were conducted to ensure stability. The developed formulations were evaluated for physicochemical properties such as hardness, friability, weight change, and in vitro dissolving studies in order to determine the drug release profile. The goal is to achieve modified release of Etodolac while optimizing the enzymatic activity of Serratiopeptidase for enhanced therapeutic benefits.

Keywords: Serratiopeptidase, Formulation, Eudragit L-100, Anti-inflammatory agent, Evaluation, Etodolac.

INTRODUCTION

The intricate biological reaction of bodily tissues to pathogens, damaged cells, or irritants is known as inflammation (Gusev and Zhuravleva 2022; Medzhitov, 2008). It serves as a protective mechanism to eliminate the cause of the injury, eliminate necrotic cells, and initiate the healing process. (Tidball, 2005; Davies, 2000). However, many pathological problems, such as autoimmune disorders, cardiovascular diseases, and arthritis, are linked to excessive or chronic inflammation (Bennett, 2018; Mason and Libby 2015). Non-steroidal anti-inflammatory drugs, or NSAIDs, are frequently used to relieve inflammation and discomfort.Still, their conventional dosage forms present significant limitations, such as gastrointestinal irritation, systemic toxicity, and the requirement for frequent dosing (Fokunang *et al*., 2018; Lazzaroni and Bianchi Porro 2004; Morya, 2016, Thakur *et al*., 2018).

To address these limitations, modified release drug formulations have gained attention in pharmaceutical research (Wen and Jung 2015; Wang *et al*., 2022). By providing regulated, prolonged, or delayed medication release, modified release tablets increase therapeutic efficacy while reducing adverse effects (Lin and Kawashima 2012). This study uses Serratiopeptidase, a proteolytic enzyme having anti-inflammatory and fibrinolytic qualities, in the formulation of Etodolac, a popular NSAID (Nair, 2022). The combination aims to enhance anti-inflammatory effects, reduce gastrointestinal complications, and improve patient compliance by ensuring modified drug action (Patrignani *et al*., 2011).

Modified release drug delivery systems aim to optimize drug therapy by regulating the rate, timing, and location of drug release (Liu *et al*., 2016). These formulations can be classified as extended-release, controlled-release, and delayed-release systems, each serving specific therapeutic purposes. The advantages of modified release formulations include (Wheless and Phelps 2018):

- Reduced dosing frequency enhances adherence to prescribed therapy.
- Controlled drug release reduces peak plasma concentrations, thereby decreasing adverse effects.
- Prolonged drug release maintains a stable concentration in the bloodstream.
- Improved absorption profiles lead to better therapeutic outcomes.

By integrating modified release technology, this study aims to enhance the therapeutic efficacy of Etodolac while reducing its gastrointestinal side effects through the incorporation of Serratiopeptidase (Paul *et al*., 2017).

Etodolac is a selective cyclooxygenase-2 (COX-2) inhibitor belonging to the NSAID class (Kumagai *et al*., 2013). It is mostly used to treat rheumatoid arthritis, osteoarthritis, and other musculoskeletal conditions that cause pain and inflammation. Etodolac is rapidly absorbed after oral therapy, peaking in plasma concentrations within one to two hours (Brocks and Jamali 1994). It undergoes hydroxylation and

conjugation in the liver before being mainly removed by the kidneys, with an elimination half-life of 6 to 8 hours (Remmer, 1970).

The proteolytic enzyme serratiopeptidase, which is obtained from Serratia marcescens, is well-known for its mucolytic, fibrinolytic, and anti-inflammatory qualities. It functions by breaking down inflammatory mediators, facilitating tissue repair, and enhancing drug absorption. It decreases levels of bradykinin and histamine, thereby reducing pain and swelling (Wang and Thyagarajan 2022). It enhances permeability of biological membranes, leading to better bioavailability (Aungst, 1993). It works in combination with Etodolac to enhance overall anti-inflammatory action while reducing gastric irritation (Russell, 2001).

By formulating a modified release tablet with Serratiopeptidase, this study aims to develop a more effective anti-inflammatory therapy with improved safety and patient adherence (Patil *et al*., 2011; Sanap *et al*., 2023; Thakur Desai 2023; Yang *et al*., 2018).

This study hypothesizes that the incorporation of Serratiopeptidase into a modified release Etodolac formulation will:

- Enhance anti-inflammatory efficacy.
- Improve patient compliance by reducing dosing frequency.
- Reduce gastrointestinal side effects compared to conventional NSAID formulations.

The development of a modified release formulation combining Etodolac with Serratiopeptidase represents a promising approach to improving anti-inflammatory therapy (Romano *et al*., 2013). By utilizing controlled release technology, this study aims to address limitations associated with conventional NSAID therapy, providing a safer and more effective treatment option for chronic inflammatory conditions (Haley and von Recum 2019).

MATERIALS AND METHOD

Preformulation studies. Followings tests were performed in present study.

Organoleptic Characteristics: Using descriptive terms, the drug's color, odor, and taste were described and documented.

Solubility of Drug. The solubility was tested in 250 milliliters of 0.1N HCl, buffers with a pH between 2 and 8, and water. After carefully weighing the maximum dosage, it was moved to a different volumetric flask containing different solutions and sonicated for 30 minutes (Lawrence *et al*., 2004).

Particle Size Distribution

Particle size affects medication solubility, homogeneity of content, and powder flow for many active ingredients (Khadka *et al*., 2014) .The particle size of the API has been defined in order to guarantee consistent product quality (Kougoulos *et al*., 2011). Light scattering serves as the foundation for Malvern Master Seizer's particle size analysis. Both dry and wet procedures can be used to analyze the particles (Are, 2015).

Physico-Mechanical Characterization:

A. Bulk density. The bulk density of a powder is calculated by dividing its weight by its volume. The bulk density was determined by carefully pouring 20 grams of sample into a graduated cylinder that held 50 milliliters using a glass funnel (Abdullah and Geldart 1999). The occupied volumes of the samples were recorded. This is how the bulk density was calculated :

Bulk density = Weight of granules (in gm)/Bulk volume of granules (in ml).

B. Tapped density. The taped density was measured using the Electrolab density tester, which consists of a graded cylinder fixed on a mechanical tapping apparatus (Samineni *et al*., 2019). A carefully weighed sample of powder was carefully added to the cylinder using a funnel (Muzzio *et al.*, 1337). The sample is typically tapped 500, 750, or 1250 times after the first volume is noted, or until there is no further volume decline or the difference percentage is less than 2%. To guarantee repeatability, a sufficient number of taps should be used for the substance in question (Zanjani *et al*., 2007). After recording the volume, the taped density was calculated using the formula below:

Tapped density = Weight of granules (in gm)/Tapped volume of granules (in ml).

C. Compressibility Index. The compressibility index and the closely related Hausner ratio have emerged as the most straightforward, quick, and widely used techniques for forecasting the properties of powder flow in recent years (Barbosa-Cánova and Juliano 2005). The compressibility index and Hausner ratio were determined using a powder's bulk density and tapped density. The connection between flow properties and CI and HR is (Saker *et al*., 2019):

C.I.(%)=TD-BD/TD*100

D. Hausner's ratio. It is the ratio of bulk volume to tapped volume or tapped density to bulk density.

Hausner's ratio = tapped (density)/bulk (density)

E. Angle of Repose. The angle of repose has been used to characterize the flow properties of solids. Angle of repose is related to interparticulate friction, or the resistance to movement between particles (Ambrose *et al*., 2016). This is the maximum angle that can be formed between the horizontal plane and the surface of the granule or powder pile.

$\text{Tan } \Theta = h / r$

$\Theta = \text{Tan}^{-1} h / r$

Here, h = height, r = radius, Θ = angle of repose

A funnel was installed at a height of about 2–4 cm above the platform. A powder cone was created by slowly moving the loose powder along the funnel's wall (Wu and Cocks 2006). To determine the angle of repose, measure the height of the powder cone and the radius of the powder heap. Flow Characteristics and Associated Repose Angles

E. Sieve Analysis. An electromagnetic sieve is used to shake the sample through a sequence of successively ordered sieves (sieve numbers 20, 40, 60, 80, 100, and receiver). Weighing the portion of the material that is retained on each sieve allows us to calculate the percentage retained on each sieve (Kilmer and Alexander 1949).

Moisture content. The moisture content was ascertained using a halogen moisture analyzer. The compound's moisture content, which measures the percentage of water present, shouldn't be greater than 1.0% w/w (Mostafa and Salem 2015). One gram of medication was placed in the digital moisture balance device's plate. The temperature was set at 105°C and the gadget was ramped up to constant weight. Ultimately, the LCD panel read the drying % loss (Chandrasekaran *et al*., 2018).

Melting point determination: The melting point is the temperature at which a pure liquid and solid are in equilibrium. In practice, it is utilized as an equilibrium mixture under an external pressure of one atmosphere and is frequently referred to as normal melting points (Ge *et al*., 2013). The Thiel's tube method was used in this investigation to ascertain the liquid paraffin's melting point.

Differential scanning calorimetry. Differential scanning calorimetry (DSC) was used to determine the melting points of the serratiopeptidase sample used in this investigation and the drug etodolac. A duplicate sample of 5 mg was used for the DSC analysis, which was carried out in crimped aluminum sample pans over 50°C to 200°C at 5°C/min. Fig. 1 and 2 illustrated the DSC curve (Al-Qatami and Mazzanti 2022).

IR Absorption. To Conform the authencity of the sample, the IR scan has been taken as shown in Fig. 3 and 4. It was discovered that the reference sample and the IR spectra matched (Bevin *et al.*, 2066).

Preparation of Standard Curve. 100 mg of the medication was dissolved in 100 milliliters of phosphate buffer at a pH of 6.8 (1000 ug/ml) to create the stock solution (Mor and Heifets 1993). A sample containing 100ug/ml of drug was prepared from the stock solution and sample was scanned between 200-400 nm to determine λmax.

Calibration Curve of Etodolac in Phosphate pH 6.8. A tiny amount of methanol was used to dissolve 100 mg of carefully weighed etodolac in a 100 ml volumetric flask (Dutt *et al.*, 2017). 6.8 phosphate buffer was then used to increase the volume to 100 ml, and 6.8 Ph phosphate buffer was used to do further dilutions (Owen *et al*., 1969). Absorbance was measured at 274 nm in a series of standard solutions with 25–200 ug/ml of etodolac in comparison to a reagent blank. Every measurement of spectral absorbance was performed using a UV-visible spectrophotometer.

Approach-Trials: (Separate Granulation Combine Lubrication of Serratiopeptidase and Etodolac Monolayer Approach)

Table 1: Formula in Approach-I.

No.	Content (mg/tab)	F1	F2	F3
Serratiopeptidase part				
1	Serratiopeptidase	37.50	37.50	37.50
2	DCL 11	19.0	15.0	15.0
3	Aerosil-200	2.0	2.0	2.0
4	Sodium Lauryl Sulphate	5.0	5.0	5.0
5	Eudragit L-100	4.0	8.0	8.0
6	Isopropyl alcohol	q.s.	q.s.	q.s.
7	Acetone	q.s.	q.s.	q.s.
		67.50	67.50	67.50
Etodolac part				
1	Etodolac	400.0	400.0	400.0
2	Microcrystalline cellulose	13.34	13.34	13.34
3	Ac-di-sol	57.33	57.33	57.33
4	PVP K 30	13.33	13.33	13.33
5	Purified water	q.s	q.s	q.s
		484.0	484.0	484.0
Combine lubrication				
1	Etodolac granules	484.0	484.0	484.0
2	Serratiopeptidase granules.	67.5	67.5	67.5
3	Aerosil-200	6.5	6.5	6.5
4	Magnesium sulphate	6.5	—	—
5	Ac-di-sol	66.0	66.0	66.0
6	Primogel	19.5	19.5	19.5
7	Magnesium stearate	—	6.5	6.5
		650.0 mg	650.0 mg	650.0 mg
Film coating				
1	Ferric oxide red	—	—	**0.15**
2	Isopropyl Alcohol.	—	—	**q.s.**
3	Purified Talc	—	—	**2.925**
4	Dibutyl phthalate	—	—	**0.50**
5	Purified water	—	—	**q.s.**
6	HPMC 5cps	—	—	6.5
7	Titanium dioxide	—	—	**2.925**
Tablet average weight (in mg /tablet)		650.0 mg	650.0 mg	663.0 mg

When the Serratiopeptidase tablet was compressed, Formulation F1's surface was rough and showed some little sticking. Additionally, the enteric-coated Serratiopeptidase granules degraded within two hours in acidic media, indicating insufficient protection. It is advised to improve the compression properties of Serratiopeptidase granules by increasing their enteric coating and substituting magnesium stearate for magnesium sulphate.

After compression, Formulation F2 produced a tablet with a matte texture, and all physical characteristics were deemed acceptable. On the other hand, assay and dissolution values were found to be lower. To improve the formulation, it is recommended to apply a film coating on the tablet.

Formulation F3 exhibited satisfactory physical parameters; however, dissolution and assay values were found to be on the lower side. To address this issue, it is recommended to take batches using a new approach, specifically the inlay approach, to enhance drug release and overall formulation performance.

Dosage Form Development

Mono Layer Approach. Etodolac immediate release granules are lubricated with enteric serratiopeptidase granules. Etodolac has poor flow characteristics and an excessively high drug concentration, which makes it difficult to mix the material properly during blending and results in a very low material density. For this reason, direct compression is not the method of choice. Due to the several reprocessing steps required to obtain the necessary granule fraction, dry granulation or the roller compaction process is laborious. Therefore, moist granulation might be the preferred method. It must be shielded from stomach acid by serratiopeptidase. Granulation with an enteric polymer is hence the recommended method for serratiopeptidase. The simplest way to create a monolayer tablet is to add serratiopeptidase while the granules of etodolac are being lubricated.

Manufacturing Process. Each and every excipient was weighed. Medication weights were determined using the RM calculation. Step 1 involves sifting DCL 11, Aerosil-200, and SLS through a 40# filter and thoroughly mixing them in a polybag. In Step 2, Serratiopeptidase is sifted through a 40# sieve and blended with the previously prepared mixture in a polybag for 5 minutes. In Step 3, the obtained blend is granulated using an Eudragit L100 solution prepared in Acetone. The wet granules are filtered through an 8# sieve in step four, and they are then dried in a tray drier at 35°C until the loss on drying (LOD), as determined by an infrared (IR) moisture balance at 45°C, exceeds 2.0%. Step 1 involved passing MCC and Ac-di-sol through a 40-mesh sieve. A 20-mesh sieve was then used to filter the etodolac. Step 2 involved mixing these ingredients for 15 minutes at 100 rpm in a Rapid Mixer Granulator (RMG). Step 2: PVP K-30 was dissolved in filtered water while being constantly stirred. then used the binder solution made in Step 2 to granulate the mixture from Step 1. After passing through 8#, the wet granules were then dried in a Fluidized Bed Dryer (FBD) at 55°C until LOD NMT 3.0% (105°C IR moisture balance). The yield was calculated after the dry granules were run through 20#. After being sieved through 40#, Ac-di-sol, Primogel, and Aerosil-200 were combined with the two dried granules in an octagonal blender for ten minutes. Magnesium stearate was sieved through 40# and mixed with the mixture for two minutes in an octagonal blender.

Coating on Film: In a beaker, IPA and water were combined and thoroughly blended. Two portions of the mixture were separated. HPMC E-5 was introduced to one section while being stirred. In the other section, talc, ferric oxide red, and titanium dioxide were added while being stirred, and the mixture was homogenized for fifteen minutes. The two parts from Step 3 and Step 4 were then mixed together under stirring. Finally, the solution was passed through muslin cloth.

Table 2: Impeller Setting Parameters.

Time (sec)	Main impeller (rpm)	Chopper impeller (rpm)
600	100	-
120	100	-
240	150	100 (1min)

RESULTS AND DISCUSSION

Preformulation Studies

Organoleptic Properties. Etodolac is a white or nearly white, crystalline powder that has no fragrance, whereas serratio-peptidase is a grayish white to pale brown powder that has a noticeable odor. The procured sample of drug was similar in physical description.

Solubility of drug. The solubility of Etodolac in chloroform was found to be 1.0049gm/ml. it is soluble in chloroform.The solubility of Etodolac in alcohol was found to be 1.0053gm/ml. It is soluble in alcohol. The solubility of Etodolac in water was found to be 0.000103gm/ml. it is practically insoluble in water.

Serratiopeptidase was discovered to be soluble in distilled water at a rate of 1.0028 grams per milliliter. It is soluble in water forming clear solution. The solubility of Serratiopeptidase in alcohol was found to be 0.0105gm/ml. It is practically insoluble in alcohol. The solubility of Serratiopeptidase in ether was found to be 0.0100gm/ml. In ether, it is essentially insoluble.

Melting point: The sample of etodolac gave Melting point in the range of 145-148°C

Differential scanning calorimetry. Etodolac's DSC study revealed a distinct endothermic peak at 150.19°C. Serratiopeptidase's DSC examination revealed a peak at 75.65°C, which is the drug's melting point.

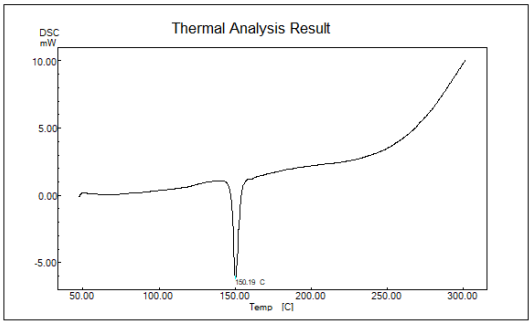

Fig. 1. DSC thermo gram of Etodolac.

IR spectra. To confirm the authenticity of the sample, the IR scan method has been taken as shown in Fig. 3. It was discovered that the infrared spectrum matched the reference spectrum.

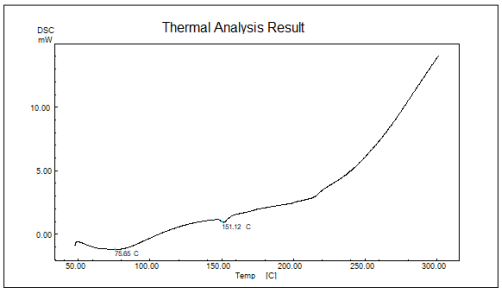

Fig. 2. DSC thermo gram of Serratiopeptidase.

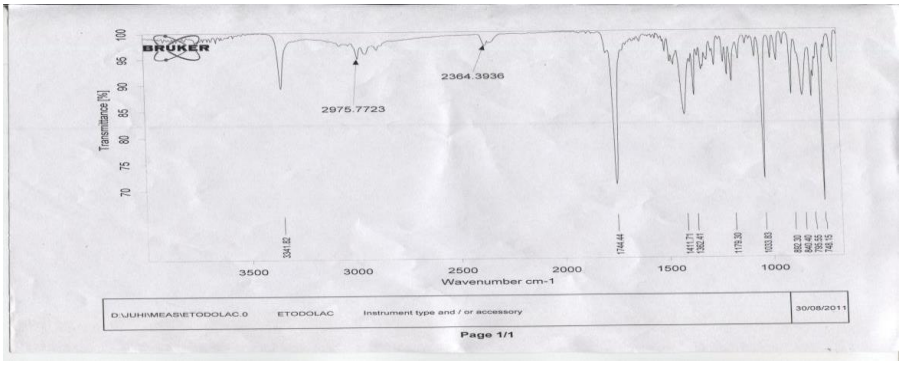

Fig. 3. Etodolac: IR absorption spectrum.

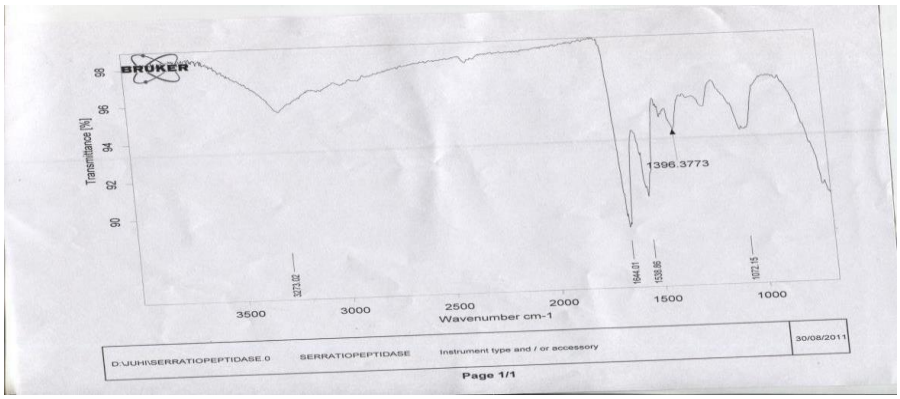

Fig. 4. Serratiopeptidase: IR absorption spectrum.

Table 3: Positions of some characteristic absorption of Etodolac.

Wave no. cm^{-1}	Characteristic absorption
1179.30	C-O stretching (ether) sharp peak
3341.81	N-H stretching
1744	COOH stretching
1411.70	C=C Stretching

Table 4: Positions of some characteristic absorption of Serratiopeptidase.

Wave no. cm^{-1}	Characteristic absorption
1538.85	C=C Stretching
3273.01	O-H Stretching
1644.00	C=O Stretching

Flow properties:

Table 5: Flow properties data of API (Etodolac and Serratiopeptidase).

Sr. No.	Parameters	Etodolac	Serratiopeptidase
1.	Tapped density(in gm/ml)	0.285	0.555
2.	Bulk density(in gm/ml)	0047	0026
3.	Compressibility index(%)	25.53	30.76
4.	Hausner's ratio	1.34	1.44

For the above data the mean compressibility index was found to be 25.53% and 30.76% for Etodolac and Serratiopeptidase respectively.

Thus it is evident that Etodolac exhibits poor flow property and Serratiopeptidase exhibits poor flow property and is necessary to add sufficient diluents to increase the flow and compressibility.

Loss on drying

Table 6: Data of loss on drying.

Drug	Limit	Result
Serratiopeptidase	NMT 5.0%w/w	3.35%
Etodolac	NMT 0.5% w/w	0.09%

Particle size distribution

Table 7: Data of Particle size distribution (by Malvern analyzer).

Drug	Particle size in µm (% of particles under size)	
Etodolac	90%	50%
	12 µm	6µm

API Characterization: Certificate of Analysis of Etodolac

Table 8: Certificate of Analysis of Etodolac.

Test	Specification		Result
Description	White, powdered crystalline.		Conforms
Solubility	It is soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol but insoluble in water.		Conforms
Water content	NMT 0.5%w/w		0.09%w/w
Residue on ignition	NMT 0.1%w/w		0.07%w/w
Limit of chloride	NMT 0.3 mg/g		< 0.3 mg/g
Heavy Metals	NMT 0.001 % w/w		0.07 %w/w
Chromatographic purity (By HPLC)	Any individual impurity	NMT 0.50%	0.07%
	Total impurity	NMT 2.0%	0.31%
Residual Solvents	Methanol	NMT 100ppm	Not detected
Assay (By Titration)	98.0% to 102.0% (on anhydrous basis)		99.8%
Partical size (By Malvern)	D90 : NMT 20µm D50 : NMT 10µm		12 µm 6 µm
Remarks: The sample confirms as per IP Specification			

API Characterization: Certificate of Serratiopeptidase

Table 9: Certificate of Analysis of Serratiopeptidase.

Test	Specification	Result
Description	Grayish white to pale brown powder with characteristic odour.	Conforms
Loss on Drying	5.00% w/w(NMT) (105°C for 1 hr)	3.35%
Solubility	Almost insoluble in alcohol and solvent ether, but soluble in water, yielding a clear solution.	Conforms
Assay	NLT 2300IU/mg	2350.5IU/mg
Microbial limits Pathogens	I. *E. coli* II. *Salmonella*	Absent Absent
Remarks: The sample confirms as per IP Specification		

Analytical Profile of Drug

Preparation of calibration curve. A diluted medication solution in phosphate buffer with a pH of 6.8 was subjected to a UV scan.

Calibration Curve - Etodolac

Table 10: Standard plot of Etodolac.

Concentration (in µg/ml)	Absorbing Power
nil	nil
25	0.049
50	0.180
75	0.311
100	0.446
125	0.569
150	0.687
175	0.812
200	1.026

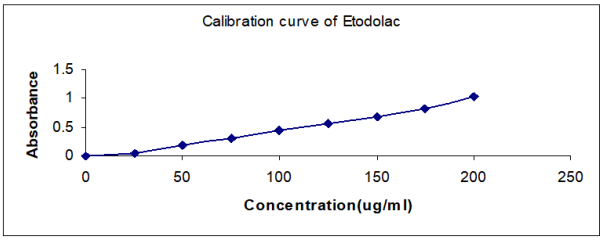

Fig. 5. Calibration curve – Etodolac (in phosphate buffer pH 6.8).

Table 11: Optical Characteristics and Precision Data.

Parameters	Values
Solvent	phosphate buffer
Wavelength	274nm
Beer's law(µg/ml)	0-200
calibration curve (Intercept)	0.0577
calibration curve (Slope)	0.0051
Coefficient of correlation	0.9905

Evaluation of Blend. The powder flow characteristics of the mixes, such as Hausner's ratio, bulk density, tapped density, and compressibility index, are evaluated.

Pre-Compression Properties of Lubricated Granules /Blend

Table 12: Precompression parameter of trails.

No.		Pre-Compressions parameter			
		Bulk density (g/ml)	Tapped Density (g/ml)	Compressibility index (%)	Hausner ratio
1.	**F1**	0.435	0.583	25.39	1.346
2.	**F2**	0.464	0.555	16.40	1.213
3.	**F3**	0.549	0.654	16.06	1.194

The size, propensity of particles to stick together and shape determine bulk density. The blend's bulk density ranges from 0.43 to 0.54 gm/ml The range of the tapping density was 0.55 to 0.65 gm/ml. The range of the compressibility index was 16.06 to 25.39 percent. Free flow materials are defined as those with a value of less than 20%. With a Hausner's ratio of 1.3 or below, the powder blend of every formulation demonstrated exceptional flowability. When the compressibility index was less than sixteen percent, the powder's flow properties were outstanding. This indicates the flow property of the blend were satisfactory.

Sieve Analysis As Comparison of All Trials:

Table 13: Sieve Analysis results of trials.

Trials	% Cumulative Retained					
	Sieve No.					
	20# 850 (µ)	40# 425 (µ)	60# 250 (µ)	80# 180 (µ)	100# 150 (µ)	Fines
F1	0.00	0.38	56.32	96.46	98.97	99.99
F2	0.00	0.48	54.65	95.12	99.98	99.98
F3	0.00	0.55	55.08	95.93	99.98	99.98

RESULT

The thickness, hardness, friability, weight variation, and disintegration time of the generated tablets were evaluated. The created tablet's average weight ranged from 651.3 mg to 663.5 mg. The tablet's thickness ranged from 6.19 to 6.29 mm. The prepared tablet's hardness ranged from 192 N to 229N. It was discovered that all of the formulations had friability levels below 0.1%. Serratiopeptidase tablets do not dissolve within two hours, while the disintegration times of Etodolac tablets ranged from five to six minutes.

Table 14: IPQC Parameter of Tablets.

Formulation	Thickness (mm)	Hardness (N)	Weight (mg)	D.T. (min.)	Friability (%)
F1	6.19	194	651.3	5-6	0.12
F2	6.20	192	651.6	5-6	0.14
F3	6.29	229	663.5	5-6	0.15

***In vitro* drug release profile.** In vitro drug release studies were conducted using the USP class II dissolving test apparatus at 37.0±0.5°C in phosphate buffer 6.8 pH at 75 rpm. The results of the in vitro drug release investigation are shown in the following table and graphic:

(a) Initial order release kinetics: log percentage of medication maintained against time

(b) Total drug release percentage over time (zero order release kinetics)

(c) Higuchi model: cumulative percentage of drug release vs square root of time

(d) log time (Korsemeyer Peppas model) v/s log mt/ma*1000

The medication release order was found to be F1>F3>F2.

The kinetic treatment was given to the gathered release data in order to identify the kind and sequence of release. Since the log percent medicines retained vs. time plot shows high linearity, the in vitro drug release profile makes it evident that all produced tablets have first-order drug release kinetics. Because the coefficient of determination of R^2 values and the values generated from n are near or within the range of 1 for Higuchi and Korsemeyer plots, the results demonstrate that the drug release from the tablets followed a diffusion-controlled mechanism.

Table 15: *In vitro* release data of tablets-zero order release.

Time (min.)	F3	F2	F1
0	0	0	0
5	9.42	7.96	7.93
10	12.43	11.24	12.53
15	27.49	23.47	33.21
20	46.54	47.28	53.04
25	63.35	66.44	68.52
30	73.53	75.65	80.26
35	78.73	80.14	85.22
40	86.00	81.65	87.61
45	91.53	89.37	94.64

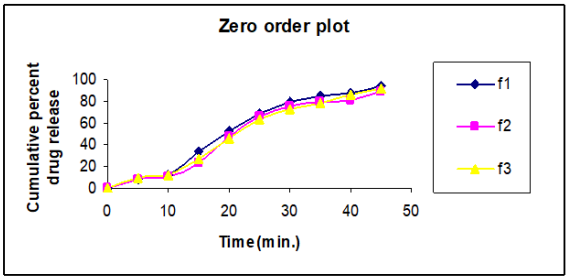

Fig. 6. *In vitro* release profile of tablets-zero order release.

Table 16: *In vitro* release data of tablets-first order release.

Time(min.)	F1	F2	F3
5 min	1.96	1.96	1.95
10 min	1.94	1.94	1.94
15 min	1.82	1.88	1.86
20 min	1.67	1.72	1.72
25 min	1.49	1.52	1.56
30 min	1.29	1.38	1.42
35 min	1.16	1.29	1.32
40 min	1.09	1.26	1.14
45 min	0.72	1.02	0.92

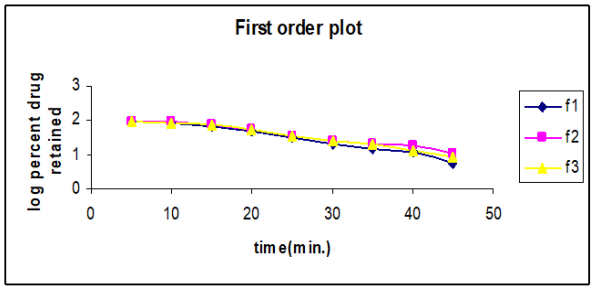

Fig. 7. Tablets' first-order release profile in vitro.

Table 17: Tablet release data in vitro: Higuchi plot.

Sqrt of Time (in min.)	F1	F2	F3
2.236	7.93	7.96	9.42
3.162	12.53	11.24	12.43
3.872	33.21	23.47	27.49
4.472	53.04	47.28	46.54
5	68.52	66.44	63.35
5.477	80.26	75.65	73.53
5.916	85.22	80.14	78.73
6.324	87.61	81.65	86.00
6.708	94.6	89.37	91.53

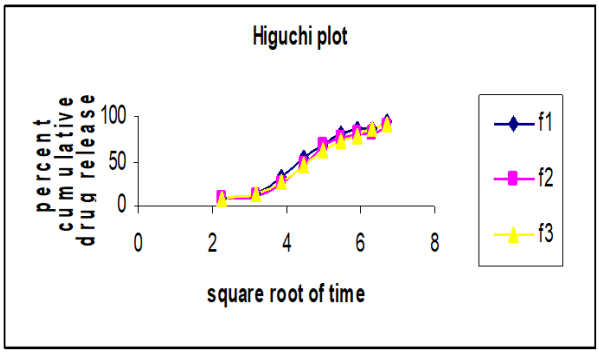

Fig. 8. Tablet release profile in vitro: Higuchi plot.

Table 18: Tablet release data *in vitro*-Korsemeyer plot.

Log time	F1	F2	F3
0.698	1.92	1.95	2.01
1	2.12	2.09	2.13
1.176	2.54	2.41	2.47
1.301	2.74	2.72	2.70
1.397	2.85	2.87	2.84
1.477	2.92	2.92	2.90
1.544	2.95	2.95	2.93
1.602	2.96	2.96	2.97
1.653	3	3	3

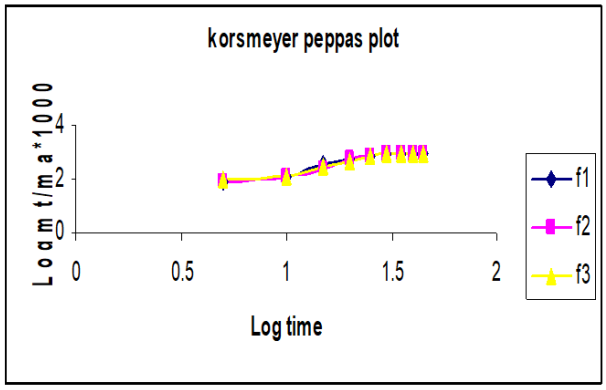

Fig. 9. *In vitro* release profile of tablets-korsemeyer plot.

CONCLUSIONS

The granules were prepared according to the formulation. The granules were characterized using the sieve analysis, LOD, bulk density, taped density, compressibility index, and Hausner ratio results of all experiments; the results demonstrated excellent flow behavior. In accordance with pharmacopeial requirements, the tablets in every trial underwent a number of evaluation tests, including weight fluctuation, friability, thickness, hardness, and disintegration time. The disintegration thickness, LOD and friability, and weight variation were all within acceptable bounds.

In F1: When the serratiopeptidase pill was compressed, a rough surface was seen. During compression, a slight sticking was noticed. In acidic media, enteric-coated Serratiopeptidase granules break down in two hours. Therefore, substitute magnesium stearate for magnesium sulphate and increase the enteric coat on serratiopeptidase granules.

In F2: Mate's completed tablet was seen when it was compressed. Every physical parameter was deemed adequate. Assay and dissolution on the lower side. Film coating was therefore applied to the tablet.

In F3: Every physical parameter was deemed adequate. Assay and dissolution on the lower side prompted us to redesign the formulation with a fresh twist, like the inlay tablet.

The tablet formulation with the drug release controlling polymer was the most successful, according to the experimental study mentioned above, since it showed zero order release kinetics, acceptable hardness, and a drug content and release profile (in a more controlled

manner over an extended period of time). Additionally, it offers a helpful tool to increase patient compliance and convenience.

FUTURE SCOPE

Future research can explore novel polymeric carriers for enhanced controlled release of Etodolac, optimizing its bioavailability. Advanced in vivo studies are needed to assess long-term efficacy and safety. Investigating synergistic effects with other enzymes may further enhance anti-inflammatory potential. Nanotechnology-based formulations could revolutionize targeted drug delivery and patient compliance.

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Conflict of Interest. None.

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