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Development and Characterization of Modified Release Tablet Etodolac with Proteolytic Enzyme Serratiopeptidase

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Abstract: Developing and characterizing a modified-release tablet is the main goal of this project which contains Etodolac, a selective NSAID, and Serratiopeptidase, a proteolytic enzyme known for its anti-inflammatory and fibrinolytic properties. The objective is to design a formulation that provides modified drug release, reduces gastrointestinal side effects, and enhances therapeutic efficacy. A polymer-based matrix system was utilized to control drug release, and various formulation strategies were employed to optimize the tablet composition. Stability studies, in vitro drug release profiles, and physicochemical parameters were used to assess the created formulation. These results demonstrated that the modified-release tablet maintained consistent drug levels over an extended period, improving patient compliance and minimizing side effects. The synergistic action of Etodolac and Serratiopeptidase offers a promising alternative for managing chronic inflammatory conditions, paving the way for further research into advanced drug delivery systems.

Keywords: Serratiopeptidase, Proteolytic Enzyme, Development, Etodolac, Characterization

INTRODUCTION

The development of modified-release drug formulations has gained significant attention in the pharmaceutical industry due to their ability to improve drug efficacy, enhance patient compliance, and reduce dosing frequency [1]. Combining proteolytic enzymes with nonsteroidal anti-inflammatory medicines (NSAIDs) to improve treatment results is one such potential strategy [2]. Etodolac, a widely used NSAID, and Serratiopeptidase, a proteolytic enzyme, have demonstrated potential synergistic effects in inflammation

management and pain relief. This research focuses on the formulation, development, and characterization of a modified-release tablet containing Etodolac and Serratiopeptidase to provide therapeutic action while minimizing gastrointestinal side effects associated with NSAID therapy [3].

NSAIDs are commonly prescribed for their analgesic, anti-inflammatory, and antipyretic effects [4]. Among them, rheumatoid arthritis, osteoarthritis, and other inflammatory diseases are commonly treated with etodolac, a selective cyclooxygenase-2 (COX-2) inhibitor. Unlike non-selective NSAIDs, Etodolac exhibits a reduced tendency to cause gastrointestinal irritation and ulceration. However, its short half-life necessitates frequent dosing, which can lead to patient non-compliance. Thus, the development of a modified-release formulation can offer slow drug action, minimizing dosing frequency and improving therapeutic efficacy [5].

Serratiopeptidase, an enzyme derived from the Serratia species, has been extensively used in clinical practice for its anti-inflammatory, fibrinolytic, and mucolytic properties [6]. It works by breaking down inflammatory mediators and reducing edema, thereby complementing the action of NSAIDs. When co-administered with NSAIDs, Serratiopeptidase has been shown to enhance drug penetration, reduce inflammation, and accelerate tissue healing [7]. This synergistic effect makes the combination of Etodolac and Serratiopeptidase a promising candidate for developing an advanced therapeutic formulation.

The conventional dosage forms of Etodolac require frequent administration to maintain effective plasma concentrations, leading to fluctuations in drug levels and potential adverse effects [8]. Modified-release formulations are designed to provide controlled drug release, maintaining steady-state drug levels over an extended period. This approach not only improves patient adherence but also enhances therapeutic outcomes by ensuring consistent drug exposure and minimizing peak-trough fluctuations [9].

The combination of Etodolac with Serratiopeptidase in a modified-release dosage form represents an innovative approach in pain management and inflammation control. The results of this study may help create new therapeutic approaches for long-term inflammatory diseases, giving patients a safer and more efficient option for care [10]. Furthermore, the successful formulation of a modified-release tablet can pave the way for future research into combination drug therapies for improved patient outcomes [11].

This study aims to bridge the gap between conventional NSAID therapy and advanced drug delivery systems by formulating and characterizing a modified-release tablet of Etodolac and Serratiopeptidase [12].

MATERIALS AND METHODOLOGY

Preformulation studies

Before beginning a formulation development activity, a thorough evaluation of the full physicochemical profile of the available active components is the first stage in any formulation activity [13]. The preformulation activity's main goals are to give formulation techniques a logical foundation, increase the likelihood that a product will be successfully formulated, and eventually offer a foundation for improving the quality and performance of drug products. The core of such data is a stability evaluation of the

drug excipients [14]. Preformulation concerns become crucial prior to starting the real experimental run.

The initial stage in the logical development of a pharmacological substance's dosage form is preformulation research [15]. Creating a portfolio of data on the drug material that may be used to create various dosage forms is the aim of preformulation studies. Preformulation is the study of the physical and chemical characteristics of the medicinal ingredient both by itself and in combination with excipients [16]. Preformulation studies are intended to find the excipients and physicochemical characteristics that could affect the final product's pharmacokinetic-biopharmaceutical characteristics, manufacturing process, and formulation design.

Followings testy were performed in present study

Organoleptic Characteristics

Using descriptive terms, the drug's color, odor, and taste were described and documented [17].

Drug's Solubility The solubility was examined in water, buffers with a pH between 2 and 8, and 250 milliliters of 0.1N HCl [18]. The maximum dosage was precisely weighed, transferred to a separate volumetric flask with various solutions, and then sonicated for half an hour.

Particle Size Distribution

Particle size affects medication solubility, homogeneity of content, and powder flow for many active ingredients [19]. To ensure consistent product quality, the API's particle size has been described. Light scattering serves as the foundation for Malvern Master Seizer's particle size analysis. Both wet and dry methods can be used to analyze the particles.

Physico-Mechanical Characterization:

A. Bulk density:

The weight of powder divided by its volume is known as its bulk density. By carefully pouring 20 grams of sample via a glass funnel into a 50 milliliter graduated cylinder, the bulk density was ascertained [20]. The samples' occupied volumes were noted. The bulk density was computed as follows:

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

B. Tapped density:

The Electrolab density tester, which comprises of a graduated cylinder mounted on a mechanical tapping device, was used to measure the taped density [21]. A funnel was used to properly introduce a precisely weighed sample of powder to the cylinder. After noting the starting volume, the sample is usually tapped 500, 750, or 1250 times until either no more volume drop is observed or the difference percentage is less than 2%. For the substance in question, a sufficient number of taps should be used to ensure reproducibility [22]. Volume was recorded, and the following formula was used to get the taped density.

Tapped density = Weight of granules (gm)/Tapped volume of granules (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. The bulk density and the tapped density of a powder were

used to calculate the compressibility index and the Hausner ratio. flow property's relationship to HR and CI [23].

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

D. Hausner's ratio:

It is the proportion of tapped density to bulk density or bulk volume to tapped volume.

$$\text{Hausner's ratio}=\text{tapped density/bulk density}$$

E. Angle of Repose:

The flow characteristics of solids have been described using the angle of repose [24]. Interparticulate friction, or the resistance to movement between particles, is associated with angle of repose. This is the greatest angle that can exist between the granule or powder pile's surface and the horizontal plane.

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

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

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

At a height of roughly 2-4 cm above the platform, a funnel was mounted. The loose powder was gradually moved along the funnel's wall until a powder cone formed. Measure the height of the powder cone and the radius of the powder heap to find the angle of repose [25].

Sieve Analysis

The sample is shaken through a series of sequentially ordered sieves (sieve numbers 20, 40, 60, 80, 100, and receiver) using an electromagnetic sieve. The fraction of the sample retained on each sieve is weighed, and the percentage retained on each sieve is calculated [26].

Moisture Content

A halogen moisture analyzer was used to determine the moisture content [27]. The moisture content shouldn't be higher than 1.0% w/w. moisture content of the compound measure the % content of water present in the compound. About 1 gm of drug was taken in the plate of digital moisture balance instrument [28]. Temperature was set at 105 °C and instrument was run up to constant weight. Finally drying percentage loss was read out from the display panel.

Melting point determination

The temperature at which a pure liquid and solid are in balance is known as the melting point [29]. It is commonly referred to as normal melting points and is used in practice as an equilibrium mixture at an external pressure of 1 atmosphere. The current study employed the Thiel's tube method to determine the melting point of liquid paraffin [30].

Differential scanning calorimetry

The melting point of the medication etodolac and the serratiopeptidase sample utilized in this study were ascertained using differential scanning calorimetry (DSC). The DSC analysis was performed using a duplicate sample of 5 mg in crimped aluminium sample pans over 50˚ to 200˚C at 5˚C/min. The DSC curve is shown in figure 1 and 2 [31].

IR Absorption

To Conform the authencity of the sample, the IR scan has been taken as shown in figure 3 and 4. It was discovered that the reference sample and the IR spectra matched.

Preparation of Standard Curve

The medicine's stock solution was made by dissolving 100 mg of the drug in 100 milliliters of phosphate buffer (pH 6.8)(1000ug/ml). A sample containing 100ug/ml of drug was prepared from the stock solution and sample was scanned between 200-400 nm to determine λ_{max}.

Calibration Curve of Etodolac in Phosphate pH 6.8

In a 100 ml volumetric flask, 100 mg of precisely weighed etodolac was dissolved in a small amount of 6.8 pH phosphate buffer. The volume was then increased to 100 ml using 6.8 phosphate buffer, and additional dilutions were made using 6.8 pH phosphate buffer. At 274 nm, absorbance was measured against a reagent blank in a series of standard solutions containing 25–200 ug/ml of etodolac. Every measurement of spectral absorbance was performed using a UV-visible spectrophotometer.

Table 1: Formula in Approach- (Inlay Tablets)

S. No.	Content (mg/tab)	F1	F2	F3	F4	F5	F6	F7
Serratiopeptidase part								
1.	Serratiopeptidase	37.5	37.5	37.5	37.5	37.5	37.5	37.5
2.	DCL 11	30.0	50.5	50.5	50.5	50.5	50.5	50.5
3.	Aerosil-200	5.0	5.0	5.0	5.0	5.0	5.0	5.0
4.	Magnesium stearate	--	3.0	3.0	3.0	3.0	3.0	3.0
5.	Sodium Lauryl Sulphate	4.0	4.0	4.0	4.0	4.0	4.0	4.0
6.	Magnesium sulphate	3.0	--	--	--	--	--	--
Avg wt of tablet (Core)		**80.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**
Seal coat								
7.	Hydroxy propyl methyl cellulose 5cps	--	--	3.0	1.50	1.50	1.50	1.50
8.	Poly Ethylene Glycol 6000	--	--	0.3	0.15	0.15	0.15	0.15
9.	Purified talc	--	--	0.3	0.15	0.15	0.15	0.15
10.	Titanium dioxide	--	--	0.40	0.20	0.20	0.20	0.20
11.	Methylene chloride	--	--	q.s.	q.s.	q.s.	q.s.	q.s.
12.	Iso propyl alcohol	--	--	q.s.	q.s.	q.s.	q.s.	q.s.
Avg wt of tablet (Seal coated)				**104.0**	**102.0**	**102.0**	**102.0**	**102.0**
Enteric coat								
13.	Hypromellose pthalate-55	--	8.0	8.480	8.320	8.320	8.320	8.320
14.	Dibutylpthalate	--	0.8	0.848	0.832	0.832	0.832	0.832
15.	Titanium dioxide	--	0.5	0.424	0.416	0.416	0.416	0.416
16.	Purified talc	--	0.5	0.424	0.416	0.416	0.416	0.416
17.	Ferric oxide red	--	0.2	0.215	0.216	0.216	0.216	0.216
18.	methylene chloride	--	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
19.	Iso propyl alcohol	--	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Avg wt of tablet (Enteric coated)			**110.0**	**114.4**	**112.2**	**112.2**	**112.2**	**112.2**
Etodolac part								
20.	Etodolac	--	**400.0**	**400.0**	**400.0**	**400.0**	**400.0**	**400.0**
21.	Lactose monohydrate	--	44.0	39.6	57.8	55.8	51.8	51.8
22.	Cross povidone	--	40.0	20.0	20.0	20.0	20.0	20.0
23.	Sodium lauryl sulphate	--	--	--	4.0	6.0	10.0	10.0
24.	PVP K30	--	20.0	16.0	16.0	16.0	16.0	16.0
25.	Purified water	--	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Lubrication								
26.	Ac-di-sol	--	--	24.0	24.0	24.0	24.0	24.0
27.	Purified talc	--	10.0	10.0	10.0	10.0	10.0	10.0
28.	Magnesium stearate	--	3.0	3.0	3.0	3.0	3.0	3.0
29.	Colloidal silicon dioxide	--	3.0	3.0	3.0	3.0	3.0	3.0
Avg wt of etodolac part			520.0	520.0	540.0	540.0	540.0	540.0
Avg wt of Inlay tablet (Core)			**630.0**	**630.0**	**650.0**	**650.0**	**650.0**	**650.0**

Film coat								
30.	Hydroxy propyl methyl cellulose 5cps	--	--	--	--	9.750	9.750	9.750
31.	Poly Ethylene Glycol 6000	--	--	--	--	0.975	0.975	0.975
32.	Purified talc	--	--	--	--	0.975	0.975	0.975
33.	Titanium dioxide	--	--	--	--	1.000	1.000	1.000
34.	Ferric oxide red	--	--	--	--	0.300	0.300	0.300
35.	Methylene chloride	--	--	--	--	q.s.	q.s.	q.s.
36.	Iso propyl alcohol	--	--	--	--	q.s.	q.s.	q.s.
Avg wt- Inlay tablet (Coated)		--	--	--	--	**663.0**	**663.0**	**663.0**

Dosage Form Development

Inlay Approach

Serratiopeptidase enteric coated tablet surrounded by Etodolac immediate release granules to form Inlay tablet.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. Hence, direct compression is not the method of choice. Dry granulation or the roller compaction process is cumbersome owing to the repeated reprocessing stages involved to get the desired granule fraction. Therefore, moist granulation might be the preferred method. It must be shielded from stomach acid by serratiopeptidase. Therefore, the preferred technique for Serratiopeptidase is a directly compressible tablet covered with an enteric polymer. When compared to tab-in-tab, the formulation of an inlay tablet was determined to be simpler because it contained a serratiopeptidase enteric coated tablet encircled by lubricated etodolac granules.

Features of Experiment

Serratiopeptidase via direct compression using DCL-11 as a diluent and Tablets are round and simple on both sides, compacted with a punch 6.50 mm s/c. Etodolac is granulated wet in water using the binder PVPK-30. The tablets were then circular and plain on both sides, compressed with a punch 13.5 mm s/c. Tablets and all initial physical and chemical criteria were confirmed to be good. charged in accordance with ICH Guidelines for a stability study

MANUFACTURING PROCESS

- Each and every excipient was weighed. Medication weights were determined using the RM calculation.
- Part of serratiopeptidase:
- In an octagonal blender, sift Serratiopeptidase, DCL 11, Aerosil-200, and SLS through 40#, then mix for 10 minutes.
- In an octagonal blender, sift the magnesium stearate through 40# and combine with the mixture above for two minutes. LOD NMT 2.0% (IR moisture balance at 45°C).
- • Using the proper punch size, compress the lubricated blend.
- Film coat the tablets.
- Enteric coat the tablets.

Etodolac part

- **Step-1:-** Sift Etodolac through 8#. Then sift Lactose monohydrate, Cross povidone, Sodium lauryl sulphate through 40#. For 10 minutes at 100 rpm, mix it in RMG.
- **Step-2:-** Dissolve PVP K-30 in specify quantity of Purified water under continuous stirring.
- **Step-3:-** Granulate the step-1 by using step-2 binder solution.

Table 2: Granulation Parameter

Operation	Time	Main impeller	Chopper impeller
Dry mixing	10 min	100	Off
Binder addition	3 min	120	Off
	3 min	150	Off
Wet mixing	4 min	150	250 (1 minute)

- **Step 4**: Dry the wet granules in a Fluidized Bed Dryer (FBD) at 55°C until LOD NMT 3.0% after passing them through 8#.(IR moisture balance at 105°C)
- **Step 5**: Determine the yield by passing the dry granules through 20#.
- **Step 6**: In an octagonal blender, sift the Aerosil-200, Talc, and Ac-di-sol through 40# and combine with the dried granules for 10 minutes.
- **Step 7**: In an octagonal blender, sift magnesium stearate through 40# and combine with the mixture above for two minutes.
- **Step 8**: Use a tab-in-tab compression machine to compress inlay tablets using an enteric-coated serratiopeptidase tablet and an etodolac lubricant blend.

Film coating part

•Step 1: Put water and IPA in a beaker and well mix.
• Step 2: Separate it into two sections.
• Step 3: Add HPMC E-5 to one part while stirring.
• Step 4: Add ferric oxide red, talc, and titanium dioxide to the other section while stirring. After 15 minutes, homogenize it.
• Step 5: Stir the two components of steps three and four together.
• Step 6: Use muslin cloth to filter this solution.

Enteric coating part

•Step 1: Put water and IPA in a beaker and well mix.
• Step 2: Separate it into two sections.
• Step 3: Add HP-55 to one section while stirring.
• Step 4: Add ferric oxide red, talc, and titanium dioxide to the other section while stirring. After 15 minutes, homogenize it.
•Step-5:- Mix the two parts of step-3 & step-4, under stirring.
•Step-6:- Pass this solution through muslin cloth.

Evaluation parameters of the blend of Etodolac and Serratiopeptidase tablets

Sieve analysis, LOD, bulk density, taped density, compressibility index, and Hausner ratio were used to analyze the granules.

Parameters of Compression:

The lone rotary compression machine was used for compression. After packaging, the tablet's hardness would be adjusted as much as possible to resist transit.

Table 3: Compression process parameters

Punch Description	**13.5 mm s/c, round plain on both sides**
Hardness	140-160N
Weight of tablet	663.0 mg
Thickness	5.6mm
Number of punches used	Double punch

RESULTS AND DISCUSSION

Preformulation Studies

Organoleptic Properties

Serratio-peptidase is a grayish white to pale brown powder with a distinct smell, while etodolac is a white or almost white, crystalline powder with no smell. The procured sample of drug was similar in physical description.

Solubility of drug

Etodolac

- 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 .

- It was discovered that etodolac was 0.000103 grams per milliliter of water. It is essentially water insoluble.

Serratiopeptidase

- • 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

Sample of etodolac gave Melting point in the range of 145-148˚C

Differential scanning calorimetry:

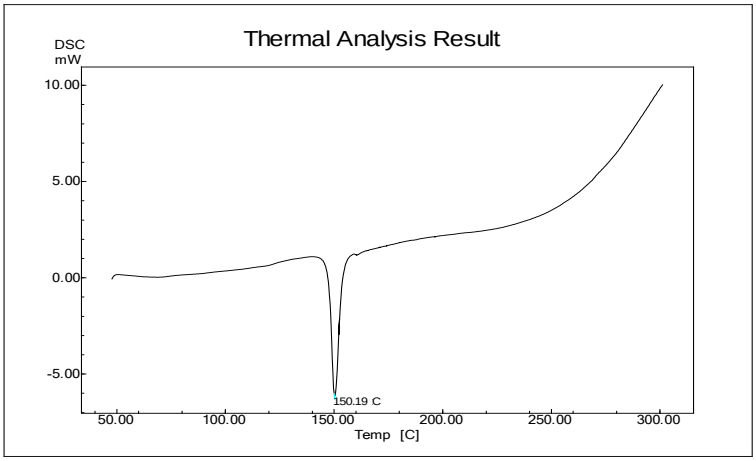

Figure 1: DSC thermo gram of Etodolac

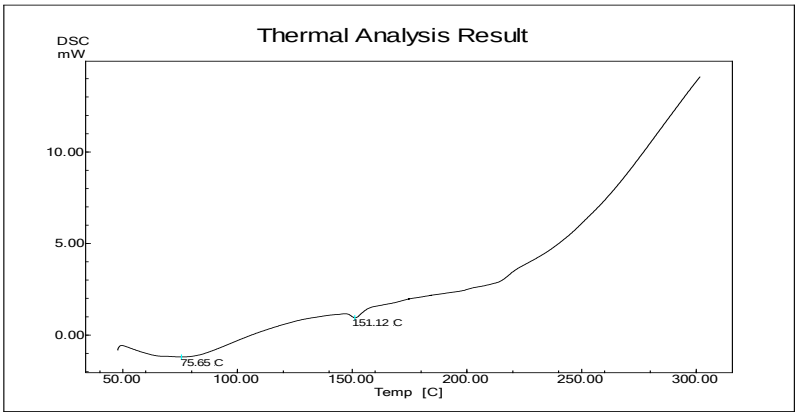

Figure 2: DSC thermo gram of Serratiopeptidase

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.

By IR spectra

The IR scan method was used to verify the sample's authenticity, as seen in the figure, and the IR spectrum was determined to match the reference spectrum.

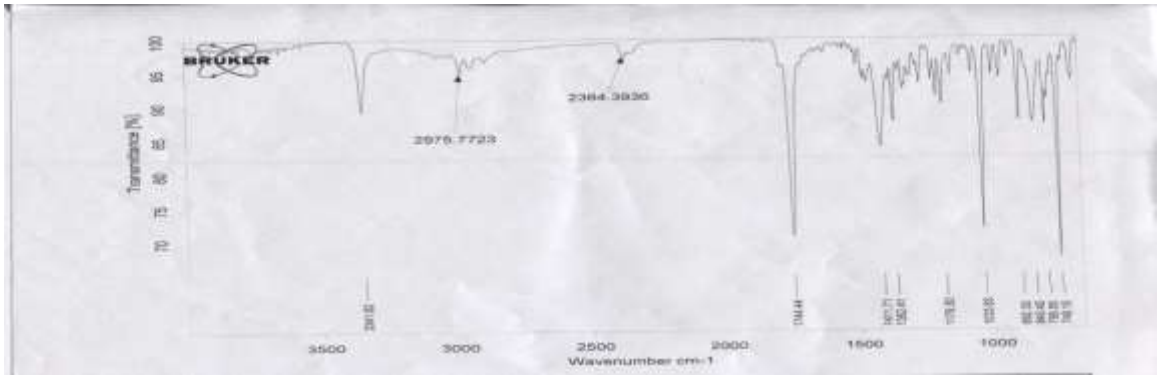

Figure 3: IR absorption spectrum - Etodolac

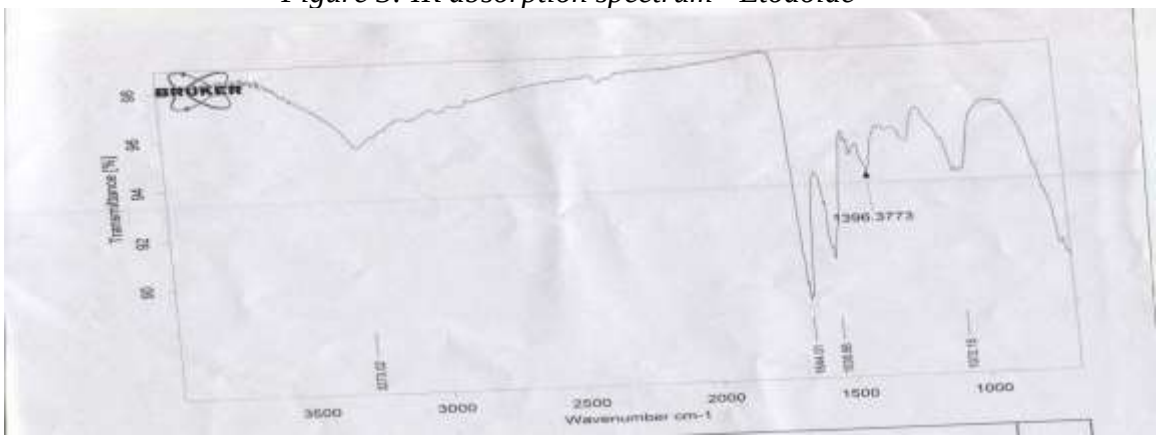

Figure 4: IR absorption spectrum -Serratiopeptidase

Table 4: Positions of some characteristic absorption of Etodolac

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

Table 5: 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 6: Flow properties data of Etodolac and

S.No.	Parameters	Etodolac	Serratiopeptidase
1	Tapped density(gm/ml)	0.285	0.555
2	Bulk density(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 7: Data of loss on drying

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

Particle size distribution

Table 8: 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 9: 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
Heavy Metals	NMT 0.001 % w/w		0.07 %w/w
Residue on ignition	NMT 0.1%w/w		0.07%w/w
Water content	NMT 0.5%w/w		0.09%w/w
Limit of chloride	NMT 0.3 mg/g		< 0.3 mg/g
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 10: Certificate of Analysis of Serratiopeptidase

Test	**Specification**	**Result**
Description	Grayish white to pale brown powder with characteristic odour.	Conforms
Solubility	Soluble in water forming a clear solution, practically insoluble in alcohol and in solvent ether.	Conforms
Loss on Drying	NMT 5.00% w/w (105^0C for 1 hr)	3.35%
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:

Calibration curve preparation

A UV scan was performed on a diluted drug solution in phosphate buffer with a pH of 6.8.

Etodolac - Calibration Curve

Table 11: Standard plot - Etodolac

S.No.	**Concentration (in µg/ml)**	**Absorbency**
1	nil	nil
2	25	0.049
4	50	0.180
5	75	0.311
6	100	0.446
7	125	0.569
8	150	0.687
9	175	0.812
10	200	1.026

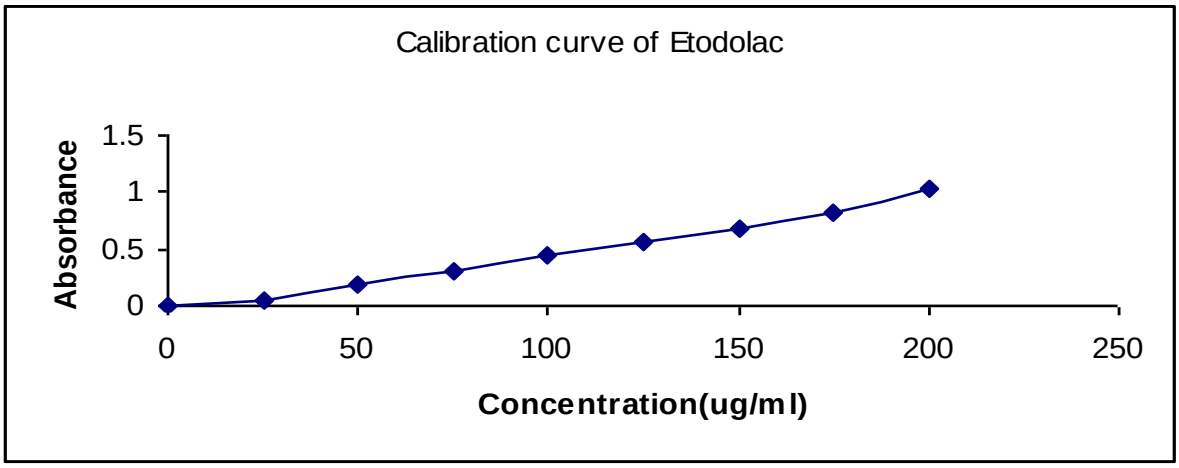

Figure 5: Etodolac- Calibration curve(in phosphate buffer pH 6.8)

Table 12: Optical Characteristics and Precision Data

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

Evaluation of Blend:

The blends' bulk density, tapped density, compressibility index, and Hausner's ratio are assessed for powder flow properties.

Pre-Compression Properties of Lubricated Granules /Blend:

Table 13: Precompression parameter of trails.

Sr.	**Formulations**		**Pre-Compressions parameter**		
		Hausner ratio	**Bulk density (g/ml)**	**Tapped Density (g/ml)**	**Compressibility index (%)**
1	**F1**	1.330	0.464	0.555	18.43
2	**F2**	1.234	0.549	0.654	18.99
3	**F3**	1.126	0.459	0.565	15.49
4	**F4**	1.263	0.417	0.526	20.83
5	**F5**	1.095	0.452	0.495	18.69
6	**F6**	1.042	0.612	0.637	4.0
7	**F7**	1.087	0.610	0.663	8.0

The size, shape, and propensity of particles to stick together determine bulk density. The blend's bulk density ranges from 0.41 to 0.61 gm/ml. The range of the tapping density

was 0.49 to 0.66 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 1.2 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 14: Sieve Analysis results of trials

	% Cumulative Retained					
	Sieve No.					
	20#	40#	60#	80#	100#	Fines
Trials	850(µ)	425(µ)	250(µ)	180(µ)	150(µ)	
F1	0.00	0.48	54.65	95.12	99.98	99.98
F2	0.00	0.55	55.08	95.93	99.98	99.98
F3	0.00	0.55	60.60	92.29	99.75	99.75
F4	0.00	0.46	67.51	89.67	99.99	99.99
F5	0.00	0.67	66.65	95.23	99.98	99.98
F6	0.00	0.35	62.23	94.23	99.98	99.98
F7	0.00	0.47	62.13	93.86	99.99	99.99

Evaluation of tablets

The produced tablets' thickness, hardness, friability, weight fluctuation, and disintegration time were all assessed. The created tablet's average weight ranged from 80.5 mg to 663.5 mg. The tablet's thickness ranged from 2.91 to 6.23 mm. The prepared tablet's hardness ranged from 65N to 127N. It was discovered that all of the formulations had friability levels below 1%. Serratiopeptidase tablets do not dissolve within two hours, while the disintegration times of Etodolac tablets ranged from five to six minutes for core tablets and six to seven minutes for coated tablets.

Table 15: IPQC Parameter of Tablets

Formulation	Thickness (mm)	Weight (mg)	Hardness (N)	D.T. (min.)	Friability (%)
F1	2.91	80.5	65	9-10	0.15
F2	6.18	630.8	89	5-6	0.14
F3	6.15	629.5	101	6-7	0.10
F4	5.95	650.5	126	5-6	0.95
F5	6.10	664.3	123	5-6	0.95
F6	6.00	663.0	127	5-6	0.93
F7	6.23	663.2	124	6-7	0.97

***In vitro* drug release profile**

The USP class II dissolving test device was used for *in vitro* drug release tests at 37.0±0.5˚c in phosphate buffer 6.8 pH at 75 rpm.

The drug release sequence was determined to be F7>F6>F5>F4>F3>F2.
To determine the kind and order of release, the kinetic treatment was applied to the collected release data. It is clear from the *in vitro* drug release profile that all produced tablets have first-order drug release kinetics since the plot of log percent pharmaceuticals retained vs time exhibits strong linearity. The results show that the drug release from the tablets followed diffusion because the coefficient of determination of R2 values and the values derived from n are close to or within the range of 1 for Higuchi and Korsemeyer plots.

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

Time (in min.)	F2	F3	F4	F5	F6	F7
5	10.75	10.66	10.53	10.79	10.92	10.31
10	12.66	12.30	12.21	12.43	12.52	16.71
15	23.96	23.83	23.65	23.96	28.55	28.29
20	46.40	46.27	45.61	52.14	61.10	60.48
25	65.42	70.19	70.10	70.24	73.78	80.14
30	75.69	75.69	75.51	82.54	85.51	86.76
35	82.74	83.85	83.72	90.26	90.46	91.66
40	89.89	90.56	91.04	94.42	94.66	96.04
45	91.71	93.62	94.59	97.17	98.43	98.97

Table 17: *In vitro* release data of tablets-first order release

Time (in min.)	F2	F3	F4	F5	F6	F7
5	1.95	1.95	1.95	1.94	1.95	1.95
10	1.9	1.94	1.94	1.94	1.94	1.92
15	1.88	1.88	1.88	1.88	1.85	1.85
20	1.72	1.73	1.73	1.67	1.58	1.59
30	1.38	1.38	1.38	1.24	1.16	1.12
35	1.23	1.20	1.21	0.98	0.97	0.92
40	1.00	0.97	0.95	0.74	0.72	0.59
45	0.91	0.80	0.73	0.45	0.1	0.009

Table 18: *In vitro* release data of tablets-Higuchi plot

Sqrt of Time (min.)	F2	F3	F4	F5	F6	F7
2.236	10.75	10.66	10.53	10.79	10.92	10.31
3.162	12.66	12.30	12.21	12.43	12.52	16.71
3.872	23.96	23.83	23.65	23.96	28.55	28.29
4.472	46.40	46.27	45.61	52.14	61.10	60.48
5	65.42	70.19	70.10	70.24	73.78	80.14
5.477	75.69	75.69	75.51	82.54	85.51	86.76
5.916	82.74	83.85	83.72	90.26	90.46	91.66

6.324	89.89	90.56	91.04	94.42	94.66	96.04
6.708	91.71	93.62	94.59	97.17	98.43	98.97

Table 19: *In vitro* release data of tablets-korsemeyerpeppas plot

Log time	F2	F3	F4	F5	F6	F7
0.698	2.06	2.05	2.04	2.04	2.04	2.01
1	2.13	2.11	2.11	2.10	2.10	2.22
1.176	2.41	2.40	2.39	2.39	2.46	2.45
1.301	2.70	2.69	2.68	2.72	2.79	2.78
1.397	2.85	2.87	2.86	2.85	2.79	2.90
1.477	2.91	2.90	2.90	2.92	2.87	2.94
1.544	2.95	2.95	2.94	2.96	2.93	2.96
1.602	2.99	2.98	2.98	2.98	2.98	2.98
1.653	3	3	3	3	3	3

Table 20: Fit of various kinetic models for tablets

Formulations	Zero order		First order	
	K (mg.min^{1})	R^2	K (min.^{1})	R^2
F1	-	-	-	-
F2	2.30	0.961	0.064	0.970
F3	2.35	0.955	0.070	0.966
F4	2.36	0.958	0.073	0.959
F5	2.47	0.950	0.090	0.957
F6	2.48	0.938	0.098	0.944
F7	2.49	0.932	0.108	0.939

Table 21: Fit of various kinetic models for tablets

formulations	Higuchi model		Korsemeyer model	
	K(mg.min $^{1/2)}$	R^2	N	R^2
F1	-	-	-	-
F2	21.69	0.957	1.206	0.941
F3	21.89	0.947	1.166	0.933
F4	22.04	0.948	1.170	0.937
F5	23.13	0.945	1.193	0.930
F6	23.04	0.943	1.185	0.923
F7	23.06	0.939	1.145	0.950

Stability studies: The formulation F7 was used for the stability tests. For one month, the formulation was kept in a stability chamber at accelerated temperatures (40°C ± 2°C/75% RH ± 5% RH). Tablets were examined for appearance, dissolution time, hardness, friability, thickness, and disintegration time following the stability period.

All of the formulation's parameters during the test period did not significantly change when the tablets were stored under accelerated storage conditions.

No alterations in appearance, thickness, hardness, friability, or disintegration time were discovered during the stability analysis in the F7 batch. The following table lists the modifications to the test and dissolving formulation that were discovered.

Assay for batch F7 before stability study and after stability studies

Table 22: Assay profile for stability study (Etodolac)

S.No.	% Assay(before stability)	% Assay(after stability)
1.	97.5	101.8
2.	97.6	101.3
3.	98.6	96.6
Minimum	97.5	96.6
Maximum	98.6	101.8

Table 23: Assay profile for stability study (Serratiopeptidase)

S. No.	% Assay(before stability)	% Assay(after stability)
1.	225.4	168.4
2.	215.0	161.9
3.	197.0	155.3
Minimum	225.4	168.4
Maximum	197.0	155.3

A summary of the dissolution profiles of batch number F7 before and after stability is provided.

Table 24: *In vitro* dissolution profile for stability study (Etodolac)

Percentage of drug released		
Time (min.)	**Before stability**	**After stability**
5	10.31	9.91
10	16.71	15.87
15	28.29	27.90
20	60.48	60.21
25	80.14	78.93
30	86.76	87.01
35	91.66	90.79
40	96.04	95.95
45	98.97	98.02

Assay, in-vitro dissolution investigations, hardness, thickness, disintegration time, and appearance did not show any notable alterations.

CONCLUSION

In the present study inlay tablets of an anti-inflammatory drugs was formulated and evaluated.

Tablets prepared by monolayer approach shows less dissolution as compared with tablets formulated with Inlay approach.The formulations with the highest medication release were F5, F6, and F7. Based on the discussion above, it was determined that the

formulation made using the inlay approach exhibits superior drug release and disintegration time compared to other formulations..

REFERENCES

1. Gujral G, Kapoor D, Jaimini M. An updated review on modified release tablets. Journal of Drug Delivery and Therapeutics. 2018 Jul 14;8(4):5-9.
2. Henrotin YE, Michlmayr C, Rau SM, Quirke AM, Bigoni M, Ueberall MA. Combination of enzymes and rutin to manage osteoarthritis symptoms: Lessons from a narrative review of the literature. Rheumatology and Therapy. 2022 Oct;9(5):1305-27.
3. Dorożyński P, Kulinowski P, Jamróz W, Juszczyk E. Geometry of modified release formulations during dissolution—influence on performance of dosage forms with diclofenac sodium. International Journal of Pharmaceutics. 2014 Dec 30;477(1-2):57-63.
4. Fokunang C, Fokunang ET, Frederick K, Ngameni B, Ngadjui B. Overview of non-steroidal anti-inflammatory drugs (nsaids) in resource limited countries. Moj Toxicol. 2018;4(1):5-13.
5. Murugesan S, Gowramma B, Lakshmanan K, Reddy Karri VV, Radhakrishnan A. Oral modified drug release solid dosage form with special reference to design; an overview. Current Drug Research Reviews Formerly: Current Drug Abuse Reviews. 2020 Jun 1;12(1):16-25.
6. Bhagat S, Agarwal M, Roy V. Serratiopeptidase: a systematic review of the existing evidence. International Journal of Surgery. 2013 Apr 1;11(3):209-17.
7. Cacabelos R, Torrellas C, Carrera I, Cacabelos P, Corzo L, Fernández-Novoa L, Tellado I, C Carril J, Aliev G. Novel therapeutic strategies for dementia. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2016 Mar 1;15(2):141-241.
8. Budsberg SC, Johnston SA, Schwarz PD, DeCamp CE, Claxton R. Efficacy of etodolac for the treatment of osteoarthritis of the hip joints in dogs. Journal of the American Veterinary Medical Association. 1999 Jan 15;214(2):206-10.
9. Navon N. The Accordion Pill®: unique oral delivery to enhance pharmacokinetics and therapeutic benefit of challenging drugs. Therapeutic delivery. 2019 Jul 1;10(7):433-42.
10. Tabas I, Glass CK. Anti-inflammatory therapy in chronic disease: challenges and opportunities. Science. 2013 Jan 11;339(6116):166-72.
11. Salave S, Patel P, Desai N, Rana D, Benival D, Khunt D, Thanawuth K, Prajapati BG, Sriamornsak P. Recent advances in dosage form design for the elderly: a review. Expert opinion on drug delivery. 2023 Nov 2;20(11):1553-71.
12. Rodríguez LA, Tolosa LB. Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population. Gastroenterology. 2007 Feb 1;132(2):498-506.
13. Kesisoglou F, Panmai S, Wu Y. Nanosizing—oral formulation development and biopharmaceutical evaluation. Advanced drug delivery reviews. 2007 Jul 30;59(7):631-44.

14. Chaudhari SP, Patil PS. Pharmaceutical excipients: a review. Int J Adv Pharm Biol Chem. 2012 Jan;1(1):21-34.
15. Bharate SS, Vishwakarma RA. Impact of preformulation on drug development. Expert opinion on drug delivery. 2013 Sep 1;10(9):1239-57.
16. Chaurasia G. A review on pharmaceutical preformulation studies in formulation and development of new drug molecules. Int J Pharm Sci Res. 2016 Jun 1;7(6):2313-20.
17. Mennella JA, Spector AC, Reed DR, Coldwell SE. The bad taste of medicines: overview of basic research on bitter taste. Clinical therapeutics. 2013 Aug 1;35(8):1225-46.
18. Sant VP, Smith D, Leroux JC. Novel pH-sensitive supramolecular assemblies for oral delivery of poorly water soluble drugs: preparation and characterization. Journal of controlled release. 2004 Jun 18;97(2):301-12.
19. Shah UV, Karde V, Ghoroi C, Heng JY. Influence of particle properties on powder bulk behaviour and processability. International journal of pharmaceutics. 2017 Feb 25;518(1-2):138-54.
20. Abdullah EC, Geldart D. The use of bulk density measurements as flowability indicators. Powder technology. 1999 Mar 3;102(2):151-65.
21. Patel RD, Raval MK, Pethani TM, Sheth NR. Influence of eutectic mixture as a multi-component system in the improvement of physicomechanical and pharmacokinetic properties of diacerein. Advanced Powder Technology. 2020 Apr 1;31(4):1441-56.
22. Gleaves JT, Ebner JR, Kuechler TC. Temporal analysis of products (TAP)—a unique catalyst evaluation system with submillisecond time resolution. Catalysis Reviews Science and Engineering. 1988 Feb 1;30(1):49-116.
23. Akseli I, Hilden J, Katz JM, Kelly RC, Kramer TT, Mao C, Osei-Yeboah F, Strong JC. Reproducibility of the measurement of bulk/tapped density of pharmaceutical powders between pharmaceutical laboratories. Journal of Pharmaceutical Sciences. 2019 Mar 1;108(3):1081-4.
24. Guo Y, Wassgren C, Ketterhagen W, Hancock B, Curtis J. Discrete element simulation studies of angles of repose and shear flow of wet, flexible fibers. Soft Matter. 2018;14(15):2923-37.
25. Wouters IM, Geldart D. Characterising Semi-Cohesive Powders using angle of repose. Particle & particle systems characterization. 1996 Aug;13(4):254-9.
26. Christopher TB, Mokhtaruddin AM, Husni MH, Abdullah MY. A simple equation to determine the breakdown of individual aggregate size fractions in the wet-sieving method. Soil and Tillage Research. 1998 May 18;45(3-4):287-97.
27. Rasti A, Pineda M, Razavi M. Assessment of soil moisture content measurement methods: Conventional laboratory oven versus halogen moisture analyzer. Journal of Soil and Water Science. 2020 Nov 26;4(1):151-60.
28. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: an innovative drug delivery system and dosage form. Int J ChemTech Res. 2010 Jan 1;2(1):576-83.
29. Yalkowsky SH, Alantary D. Estimation of melting points of organics. Journal of pharmaceutical sciences. 2018 May 1;107(5):1211-27.

30. Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: a modern formulation approach in drug delivery system. Indian journal of pharmaceutical sciences. 2009 Jul;71(4):349.
31. Shete G, Puri V, Kumar L, Bansal AK. Solid state characterization of commercial crystalline and amorphous atorvastatin calcium samples. AAPS PharmSciTech. 2010 Jun;11(2):598-609.