The Pharmaceutical and Chemical Journal, 2019, 6(5):18-27

Available online www.tpcj.org

Research Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Formulation Development and Evaluation of Inlay Tablets of Anti-Inflammatory Drug

Santosh Kitawat[1]*, Meenakshi Bharkatiya[2], Nipun Dashora[1]

[1]Geetanjali Institute of Pharmacy, Udaipur, Rajasthan, India-313002
[2]B.N. Institute of Pharmaceutical Sciences, Udaipur, Rajasthan, India-313002
E-mail: santoshkitawat@gmail.com

Abstract Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in widespread use since the latter part of the 19th century and their popularity continues. In the present study inlay tablets of an anti-inflammatory drug was formulated and evaluated. The tablet is most widely used dosage form because of its ease of administration, compactness and ease of manufacturing. The aim of study is to formulate combination of an anti-inflammatory agent and proteolytic enzyme for oral delivery system, which helps in wound healing process. Drugs are used to treat osteoarthritis; rheumatoid arthritis, it is also used to treat acute and chronic pain and inflammation. The primary object of the present study is to formulate a robust, stable version of tablet containing an anti-inflammatory agent (Sulindac) and proteolytic enzyme (Serratiopeptidase) for the treatment on osteoarthritis and rheumatoid arthritis. Sulindac is newly invented NSAID which reduces pain and inflammation while Serratiopeptidase reduce swelling and pus formation. The combination of both agents help in wound healing process. The drug was analysed and drug sample was found to comply with all specification. In this work, tablets were prepared by using Inlay approach to provide satisfactory drug release. The prepared tablets were also evaluated for physical appearance, thickness, diameter, hardness, weight variation, friability, disintegration time and *in vitro* drug release.

Keywords Anti-inflammatory, Inlay, Serratiopeptidase, Sulindac

Introduction

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in widespread use since the latter part of the 19th century and their popularity continues. The term compressed tablet is believed to have been first used by 'John Wyeth and Brother of Philadelphinn'. During the same period molded tablets were introduced to be used as Hypodermic tablets for injections. Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer [e.g.: simplicity & economy of preparation, stability and convenience in packing, shipping, and dispensing] and the patient [e.g.: accuracy of dosage, compactness, post ability, blandness of taste and ease of administration. Although tablets are more frequently discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration [1-2]. Oral route is perhaps the most widely used route for drug delivery systems. It is well established that the active ingredient in a solid dosage form must undergo successive rate

processes, before it is available for absorption from the gastrointestinal tract. These processes are disintegration, release of the drug, and dissolution of the drug in an aqueous environment. The rate at which drug reaches the circulatory system is determined by the slowest step in the sequence of rate processes [3-4].

Sulindac is a sulfinylindene derivative prodrug whose sulfinyl moiety is converted *in vivo* to an active analgesic. Sulindac is a commonly used nonsteroidal antiinflammatory drug (NSAID) that is available by prescription only and used predominantly to treat chronic arthritis. It is a rare, but well established cause of idiosyncratic, clinically apparent drug induced liver disease. Sulindac is a nonsteroidal anti-inflammatory agent (NSAIA) of the arylalkanoic acid class that is marketed in the U. S. by Merck as Clinoril. Like other NSAIAs, it may be used in the treatment of acute or chronic inflammatory conditions. Sulindac is a prodrug, derived from sulfinylindene that is converted *in vivo* to an active sulfide compound by liver enzymes. The sulfide metabolite then undergoes enterohepatic circulation; it is excreted in the bile and then reabsorbed from the intestine. This is thought to help maintain constant blood levels with reduced gastrointestinal side effects. Some studies have shown sulindac to be relatively less irritating to the stomach than other NSAIA's except for drugs of the cyclooxygenase-2 (COX-2) inhibitor class. The exact mechanism of its NSAIA properties is unknown, but it is thought to act on enzymes COX-1 and COX-2, inhibiting prostaglandin synthesis [5].

Serratiopeptidase binds to α-2-macroglobulin in the blood in the ratio of 1:1, which helps to mask its antigenicity but retains its enzymatic activity and is slowly, transferred to site of inflammation. Serratiopeptidase hydrolyses bradykinin, histamine and serotonin responsible for oedematic status. It reduces swelling improves microcirculation and expectoration of sputum etc. Thus it can be concluded that Serratiopeptidase has antiinflammatory, anti-oedemic and fibrinolytic activity and acts rapidly on localized inflammation and when consumed in unprotected form is destroyed by acid ion the stomach. However, enteric coat of tablet enable the enzyme to pass through the stomach unchanged and absorb in the intestine [6].

Materials and Methods

Sulindac of pharmacopoeial grade was obtained as a gift sample from Wellona Pharma**,** Surat, Gujarat, India. Serratiopeptidase of analytical grade was procured from Avanscure lifesciences Pvt. Ltd. HPMC gifted by Sisco research laboratories Pvt. Ltd Mumbai. Sodium Starch glycollate, Micro Crystalline Cellulose, Magnesium Stearate, Talc gifted by S.D. Fine Chem. Ltd, Mumbai. Cros Povidone, Sodium Starch Glycolate gifted by ESSEL fine chem. Mumbai. All other chemicals were of analytical grade and used as received. Distilled water was used throughout the study and all other reagents were of analytical grade.

Manufacturing Process

1) All the excipients were weighed.
2) Drugs were weighed.
3) **Serratiopeptidase part:**

- **Step-1:-** Sifted Serratiopeptidase, DCL 11, Aerosil-200, SLS through 40# sieve and mixed in octagonal blender for 10 min.
- **Step-2:-** Sifted Magnesium stearate through 40# sieve and mixed with above blend in Octagonal blender for 2 min. LOD NMT 2.0 %.(45°C IR moisture balance).
- **Step-3**:- Compressed the lubricated blend with appropriate punch size.
- **Step-4**:- Enteric coated the tablets.

4) **Sulindac part**

- **Step-1:-** Weighed accurately Sulindac, Lactose monohydrate, MCC pH 101 and Sodium starch glycolate, pass through sieve no. 40 and mix in geometric ratio and blend for 15 minutes in Rapid Mix Granulator.
- **Step-2:-** Added binder solution hypromellose (HPMC-E5) to the above blend and granulate.
- **Step-3:-** Then, transferred the wet mass through sieve no. 12 and dried at 60ºc. Passed these dried granules in sieve no.20. After sieving, added magnesium stearate and blended for 2 min.

- **Step-4:-** Compressed Inlay tablets using Enteric coated Serratiopeptidase tablet and Sulindac lubricated blend on Tab-in Tab compression machine.

5) **Film coating part**

- **Step-1:-** Taken IPA & Water in beaker and mixed properly.
- **Step-2:-** Divided it into two parts.
- **Step-3:-** In one part added HPMC E-5 under stirring.
- **Step-4:-** In other part added PEG 6000, Titanium di-oxide, Talc, Ferric oxide red under stirring. Then, homogenized for 15 min.
- **Step-5:-** Mixed the two parts of step-3 & step-4, under stirring.
- **Step-6:-** Passed this solution through muslin cloth.

F1:-

Remark

- Rough surface observed during compression in serratiopeptidase tablet.
- Slightly sticking observed during compression.
- Enteric coated serratiopeptidase granules degrade in acidic media within 2 hr.

Recommendation:-

- Increase enteric coat on serratiopeptidase granules.
- Increase quantity of diluent.

F2:-

Remark:-

- All physical parameter found satisfactory.
- Appearance of Inlay tablet was not satisfactory.

Recommendation:-

- To improve appearance of Inlay tablet film coats the tablets.

F3:-

Remark:-

- All physical parameter found satisfactory.
- Sulindac Dissolution and Serratiopeptidase Assay were found satisfactory.

Recommendation:-

- Charge sample in stability chamber for stability study.

Recommendation:-

- To take batches by new approach (Inlay).

Table 1: Formulation of Inlay tablets of anti-inflammatory drug

S. No.	Ingredients (mg/tab)	F1	F2	F3
	Serratiopeptidase part			
1.	Serratiopeptidase	37	37	37
2.	DCL 11	30	50	50
3.	Aerosil-200	2.0	2.0	2.0
4.	Eudragit L-100	4.0	4.0	4.0
5.	Sodium Lauryl Sulphate	5.0	5.0	5.0
6.	Magnesium stearate	2.0	2.0	2.0
7.	Isopropyl alcohol	q.s	q.s	q.s
Average weight of tablet (Core)		80.0	100.0	100.0
Enteric coat				
8.	Hypromellose phthalate-55	8.0	12.3	10.3
9.	Dibutylphthalate	0.8	0.85	0.8

10.	Titanium dioxide	0.5	0.45	0.45
11.	Purified talc	0.5	0.45	0.45
12.	Ferric oxide red	0.2	0.2	0.2
13.	Iso propyl alcohol	q.s.	q.s.	q.s.
14.	Methylene chloride	q.s.	q.s.	q.s.
Average weight of tablet		90.0	114.25	112.0
(Enteric coated)				
S. No.	**Ingredients (mg/tab)**	F1	F2	F3
	Sulindac part			
1.	Sulindac	400.0	400.0	400.0
2.	Lactose monohydrate	44.0	12.50	12.50
3.	MCC P^H 101	54.2	54.7	52.50
4.	Ac-di-sol	40	--	--
5.	Sodium starch glycolate	--	40	40
6.	HPMC E-5	32	27	25.50
7.	Colloidal silicon dioxide	7.30	0.8	7.30
8.	Magnesium stearate	3.0	2.5	2.5
9.	Purified water	q.s.	q.s.	q.s.
	Avg wt of sulindac part	580.5	537.5	540.3
Average weight of Inlay tablet (Core)		670.5	651.75	652.3
Film coat				
10.	Hydroxy propyl methyl cellulose 5cps	--	--	9.750
11.	Dibutyl phthalate	--	--	0.975
12.	Purified talc	--	--	0.975
13.	Titanium dioxide	--	--	1.000
14.	Ferric oxide red	--	--	0.300
15.	Iso propyl alcohol	--	--	q.s.
16.	Purified water	--	--	q.s.
Avg wt of Inlay tablet (Coated)		--	--	665.3

Evaluation of tablets [7-11]:

The prepared tablets were evaluated for weight variation, thickness, hardness, friability and disintegration time. The average weight of the prepared tablet was found 80.5mg to 665.3 mg. The thickness of the tablet was found 6.00 mm to 6.23 mm. The hardness of the prepared tablet varied from 123 N to 127 N. The friability of all the formulation was found to be less than 0.5%. The disintegration time of Sulindac tablets was varied from 5 min. to 6min. for core tablets and 7 to 8 min for coated tablets and Serratiopeptidase tablets does not disintegrate within 2 hours.

Average weight:

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective. Not more than 2 tablets deviate from the percentage given below from the average weight. The acceptable weight variation is ±5%.

Thickness:

The thickness of the tablet was measured by using digital vernier scale. Thickness was expressed in mm.

Hardness (tablet breaking force)

Tablets must be able to withstand the rigors of handling and transportation experienced in the manufacturing plant, in the drug distribution system, and in the field at the hands of the end users. Manufacturing processes such as coating packaging and printing can involve considerable stresses, which the tablet must be withstand. For these reasons, the mechanical strength of tablets is of considerable importance and is routinely measured.

Early measuring devices were typically hand operated. For example, the Monsanto hardness tester was based on compressing tablets between two jaws via a spring gauge and screw. In the Pfizer hardness tester, the breaking load was applied through the action of a small hydraulic pump that was first operated manually but was later motorized. Modern testers employ mechanical drivers, strain gauge-based load cells for force measurements, and electronic signal processing, and therefore are preffered. Hardness of the tablet was measured by using Schleuniger Pharmatron hardness tester. Hardness was expressed in N.

***In Vivo* disintegration test**

The test was carried out on 6 tablets using the apparatus specified in I.P.-2007 distilled water at 37˚C ± 2˚C was used as a disintegration media and the time taken for complete disintegration of tablet with no palable mass remaining in the apparatus was measured.

Friability

For tablets with a unit weight equal to or less than 650 mg, take a sample of whole tablets a sample of corresponding as near as possible to 6.5 gm. For tablets with a unit weight of more than 650 mg, take 10 whole tablets. The tablets should be carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh.

If obviously cracked, cleaved, or broken tablets are present in the tablet sample after tumbling, the sample fails the test. If tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about 10˚ with the horizontal and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

***In vitro* dissolution profile**

Determine percent dissolution using U.V. spectrophotometer.
Dissolution parameters of Sulindac tablets
Media: phosphate buffer pH 6.8
Apparatus: USP type- II, Paddle
Speed: 75 rpm
Volume: 900 ml
Temperature: 37.0˚C ± 0.5˚C
Time points: 5 min.

Media Preparation

27.2 gm of potassium dihydrogen phosphate and 8 gm of sodium hydroxide dissolve in 1000ml of distilled water. Adjust pH 6.8 with NaOH.

Sample Preparation:

In vitro release of Sulindac from tablets was monitored by placing 1 tablet in each dissolution vessel containing 900 ml of phosphate buffer solution pH 6.8 as dissolution medium maintained at 37.0˚c ± 0.5˚ c and run the instrument at 75 rpm. Aliquots were withdrawn in 5 minute time intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable dilutions, were assayed spectrophotometrically at 274nm.

Table 2: IPQC Parameter of Tablets

Formulation	Weight (mg)	Hardness (N)	Thickness (mm)
F1	665.3	123	6.10
F2	665.2	127	6.00
F3	665.3	124	6.23

***In vitro* drug release profile**

In vitro drug release experiments were performed at 37.0±0.5˚c in USP type II dissolution test apparatus in phosphate buffer 6.8 pH at 75 rpm. The data obtained *in vitro* drug release study are tabulated and represented graphically as:

(a) cumulative % drug release v/s time(zero order release kinetics)
(b) log % drug retained v/s time(first order release kinetics)
(c) cumulative % drug release v/s square root of time (Higuchi model)
(d) log mt/ma*1000 v/s log time (korsemeyer peppas model)

The results showed that the maximum drug release was found in formulation F3.

The order of drug release was found to be: F3>F2>F1

The release data obtained were subjected for the kinetic treatment to know the type and order of release. From the *in vitro* drug release profile it is evident that kinetics of drug release is first order for all the prepared tablets as the plot between log percent drugs retain versus time shows good linearity. The coefficient of determination of R^2 values and the values obtained from n are near or in the range of 1 for Higuchi and Korsemeyer plots, thus results indicating the drug release from the tablets followed diffusion controlled mechanism.

Table 3: *In vitro* release data of tablets-zero order release

Time (min.)	F1	F2	F3
5	10.80	10.89	10.34
10	12.39	12.44	16.61
15	23.96	28.45	28.19
20	50.14	60.12	60.45
25	70.14	72.18	80.15
30	82.54	85.51	86.76
35	90.20	90.56	91.46
40	94.40	94.65	96.14
45	97.00	98.30	98.87

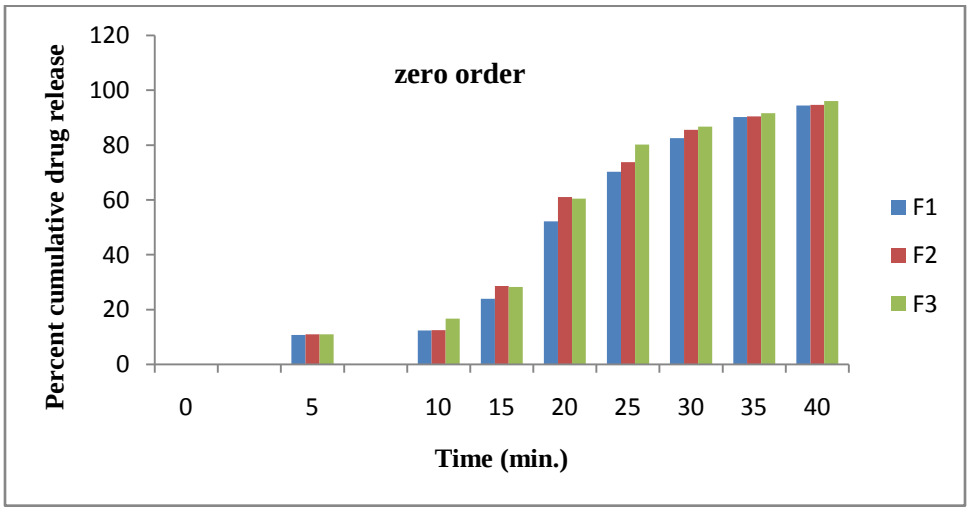

Figure 1: In vitro release profile of tablets-zero order release

Table 4: *In vitro* release data of tablets-first order release

Time (min.)	F1	F2	F3
5	1.93	1.94	1.95
10	1.93	1.94	1.93
15	1.88	1.85	1.85
20	1.60	1.45	1.49
30	1.26	1.15	1.14
35	0.99	0.95	0.94
40	0.76	0.75	0.69
45	0.45	0.1	0.08

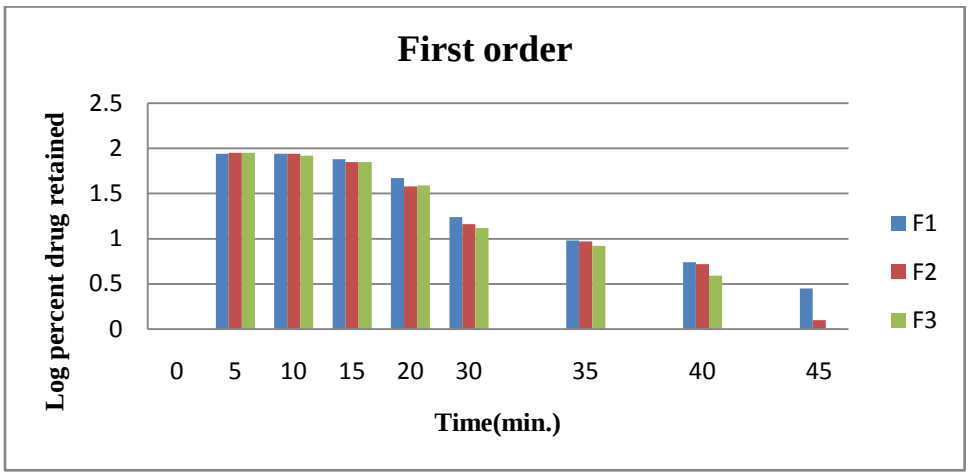

Figure 2: In vitro release profile of tablets-first order release

Table 5: *In vitro* release data of tablets-Higuchi plot

Time (min.)	F1	F2	F3
5	10.86	10.55	10.46
10	11.53	12.42	16.74
15	24.86	28.53	29.39
20	53.24	60.12	60.55
25	70.24	74.79	80.15
30	83.44	86.41	85.76
35	94.36	91.46	92.66
40	94.52	92.66	95.04
45	95.47	98.42	98.87

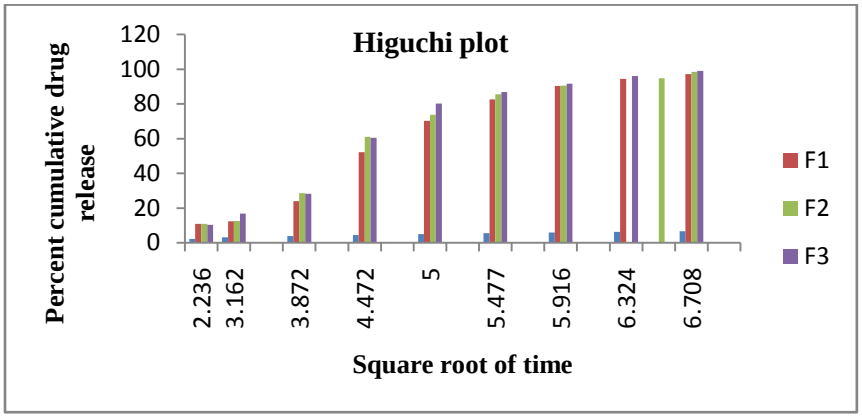

Figure 3: In vitro release profile of tablets-Higuchi Release

Table 6: *In vitro* release data of tablets-korsemeyer peppas plot

Time (min.)	F1	F2	F3
5	2.06	2.04	2.02
10	2.09	2.12	2.20
15	2.29	2.36	2.40
20	2.62	2.89	2.88
25	2.85	2.78	2.89
30	2.90	2.89	2.90
35	2.94	2.93	2.97
40	2.98	2.99	2.99
45	3.0	3.0	3.1

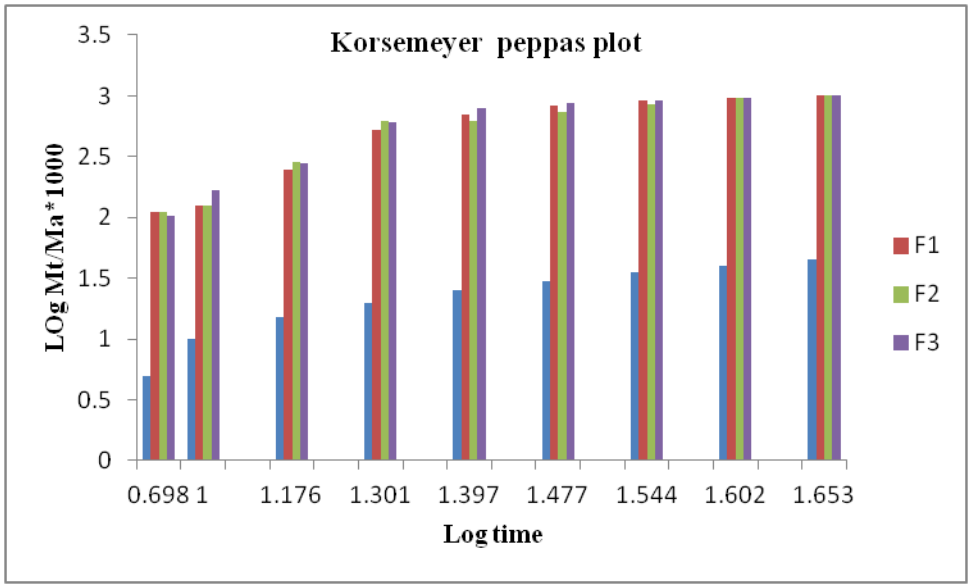

Figure 4: In vitro release profile of tablets-Korsemeyer- Peppas Release

Table 7: Fit of various kinetic models for tablets

Formulations	Zero order		First order	
	K(mg.min^{1})	R^2	K(min.^{1})	R^2
F1	2.47	0.950	0.090	0.957
F2	2.48	0.938	0.098	0.944
F3	2.49	0.932	0.108	0.939

Table 8: Fit of various kinetic models for tablets

Formulations	Higuchi model		Korsemeyer model	
	K(mg.min $^{1/2)}$	R^2	N	R^2
F1	23.13	0.945	1.193	0.930
F2	23.04	0.943	1.185	0.923
F3	23.06	0.939	1.145	0.950

Stability Studies

The stability studies were performed on the formulation F3. The formulation was stored at accelerated (40°C ± 2°C/75% RH ± 5% RH) conditions in stability chamber for 1 month. After the stability period tablets were tested for the appearance, disintegration time, hardness, friability, thickness and dissolution test.

When the tablets were kept at accelerated storage conditions all the formulation showed no significant variation in all the parameter under the test period.

After the stability study in F3 batch no changes were found in appearance, thickness, hardness, friability and disintegration time. The changes found in formulation in assay and dissolution is tabulated below:

Assay for batch F3 before stability study and after stability studies

Table 9: Assay profile for stability study (Sulindac)

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

Table 10: 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
Maximum	197.0	155.3
Minimum	225.4	168.4

The dissolution profiles before and after stability of the batch no. F3 are summarized.

Table 11: *In-vitro* dissolution profile for stability study (Sulindac)

S. No.	% Drug released		
	Time (min.)	Before stability	After stability
1.	5	10.31	9.91
2.	10	16.71	15.87
3.	15	28.29	27.90
4.	20	60.48	60.21
5.	25	80.14	78.93
6.	30	86.76	87.01
7.	35	91.66	90.79
8.	40	96.04	95.95
9.	45	98.97	98.02

There were not any significant changes found in assay, *In-vitro* dissolution studies, hardness, thickness, disintegration time, appearance.

Conclusion

In the present study inlay tablets of an anti-inflammatory drug was formulated and evaluated. The tablet is most widely used dosage form because of its ease of administration, compactness and ease of manufacturing. The aim of study is to formulate combination of an Anti-inflammatory agent and Proteolytic enzyme for oral delivery system, it helps wound healing process. Drugs are used to treat Osteoarthritis; Rheumatoid arthritis, it is also used to treat acute and chronic pain and inflammation. The primary object of the present study is to formulate a robust, stable, version of tablet containing an Anti-inflammatory agent (Sulindac) & and Proteolytic enzyme (Serratiopeptidase) for the treatment on Osteoarthritis; Rheumatoid arthritis. Sulindac is newly invented NSAID's it reduce pain and inflammation while Serratiopeptidase reduce swelling & pus formation the combination of both agent helps wound healing process. Combination of Sulindac & Serratiopeptidase not available in market so we have to develop it as market need. The drug was analysed. The drug sample was found to comply with all specification. The prepared tablets are also evaluated for physical appearance, thickness, diameter, hardness, and weight variation, friability, disintegration time, and *in vitro* drug release. The tablets are prepared by inlay approach provide satisfactory drug release. The release of drug followed first order kinetics.

From the above experimental findings it can be concluded that:

The maximum drug release was found in formulation F3> F2> F1. From the above discussion the conclusion was that the formulation prepared with inlay approach shows better disintegration time and drug release.

Acknowledgements

The authors thank Wellona Pharma**,** Surat, Gujarat, India, Avanscure life sciences Pvt. Ltd., Sisco research laboratories Pvt. Ltd Mumbai, S.D. Fine Chem. Ltd, Mumbai, ESSEL fine chem. Mumbai for providing gift samples for the present work.

References

[1]. Kottke KM, Rudnic ME. Tablet dosge form. In: Banker GS, Rhodes CT, editors. Modern Pharmaceutics, 4th ed. New York: Marcel Dekker, Inc.; 2002. p. 280

[2]. Rudnic ME, Joseph D. Oral solid dosage form. In: Gennaro AR, editor. Remington: the science and practice of pharmacy. 20th ed. Philadelphia: Lippincott Williams & Wilkins; 2000. vol. 1 p. 858-62.

[3]. Martin A, Swarbrick J, Cammarta A. Physical pharmacy, physical chemical principles in the pharmaceutical sciences. 4th ed. Philadelphia: Lea and Febiger, 1993; 324–512.

[4]. Shargel L, Yu ABC. Applied biopharmaceutics and pharmacokinetics. 3rd ed. New York: Prentice-Hall International, 1993; 136–7.

[5]. https://pubchem.ncbi.nlm.nih.gov.

[6]. Panagariya, A., Sharma, A.K., A preliminary trial of serratiopeptidase in patients with carpal tunnel syndrome. J Assoc Physicians India, 1999; 47(12): 1170-1172.

[7]. Loyd VJ. Popovich NG. Ansel H.C., pharmaceutical dosage form and drug delivery system, lippincott Williams and wilkins 2007.3 ed. p.234-8.

[8]. Indian pharmacopeia published by the Indian pharmacopeia commission, Ghaziabad 1996. p.2:736.

[9]. United States of Pharmacopoeia, Rockville.MD, 27th, USP Convention, Inc 2004. p.2125.

[10]. Shirsand SB, Suresh S, Para MS, Swamy PV, Kumar DN. Plantago ovata mucilage in the design of Fast disintegrating tablets. Indian J Pharm Sci. 2009; 71:41–5.

[11]. Mundada AS, Meshram DR, Mishra M, Bhalekar MR, Avari JG. Formulation and evaluation of bitterless rapidly disintegrating tablet of Famotidine using ion exchange resins. Int J Pharm Excipients. 2008; 7:23–5.