Formulation, Evaluation, and Characterization of an Inlay tablet containing Zolmitriptan as a Floating sustained release and Naproxen as an immediate release for treating Migraine.

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Abstract –

Zolmitriptan is a selective serotonin receptor agonist, and Naproxen is an NSAID extensively used for the treatment of Migraine. The inlay tablet is a kind of compression-coated tablet. Rather than the core tablet being fully covered in the coating, the top face of the inlay tablet is completely exposed, which means that only the smallest subcaste of the coating is deposited in the die, and the core is deposited on top of it. It contains low-dose API as sustained release and high-dose API as immediate release. The inlay tablets were formulated to reduce the frequency of administration. Inlay tablets were prepared by wet granulation. The formulation F6 was considered to be better among the trials conducted. The formulated Inlay tablet is the best combination of medicines because both follow different mechanisms of Migraine, giving a synergistic effect. By lowering the frequency of dose administration, the Inlay tablet was created to increase patient acceptance and compliance.

Keywords –

Inlay Tablet, Zolmitriptan, Naproxen, Floating drug delivery system, Migraine.

Introduction -

Pharmaceutical tablets are a unit solid dosage form that are flat or biconvex. According to the Indian Pharmacopoeia, they're made by compressing a medicine or combination of Medicinals, with or without diluents. (1) A tablet is a solid, compressed dosage form that contains medicines, either with or without excipients. The number of medicines and the route of administration determine their shape, size, and weight. (2)

Inlay tablet

The inlay tablet is a kind of compression-coated tablet. The top face of the inlay tablet is completely exposed, meaning that only the smallest layer of the coating is deposited in the die, and the core is placed on top of it, rather than the core tablet being entirely enclosed in the coating. It's a dosage form that contains a low-dose active component as immediate release and a high-dose, high-solubility active component as modified release. 110 to 115000 is the weight rate of the immediate release and modified release active constituents, and the weight of the modified release high-dose, high-solubility active component per unit ranges from 500 mg to 1500 mg, while the weight of the immediate release active component is over 50 mg (3).

Preparation of inlay tablet (4):

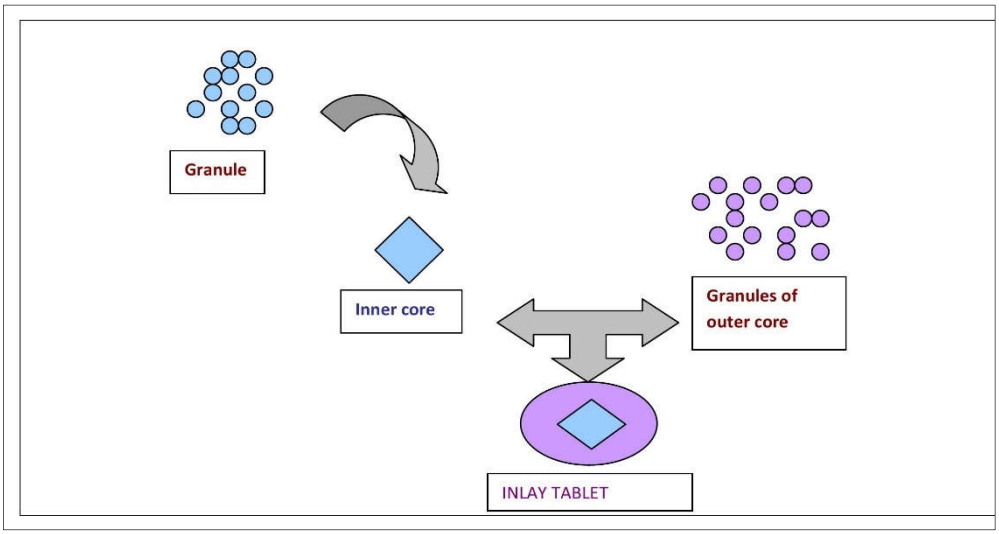


Fig. 1: Preparation of Inlay tablet

Floating drug delivery system

A floating drug delivery device, Floating drug delivery system (FDDS), or hydrodynamically controlled systems are low-density systems that have sufficient

buoyancy to float above the contents of the stomach and stay buoyant there without slowing down the stomach's rate of emptying. As the body floats on the contents of the stomach, the medication is gradually removed from the system at the appropriate pace. The residual system in the stomach is emptied when the drug has been released. Consequently, GRT is increased, and fluctuations in plasma drug concentration are better controlled. However, the buoyancy retention principle requires a minimal degree of floating force (F) in addition to the minimal stomach content required for its correct use (5).

Classification of floating drug delivery systems

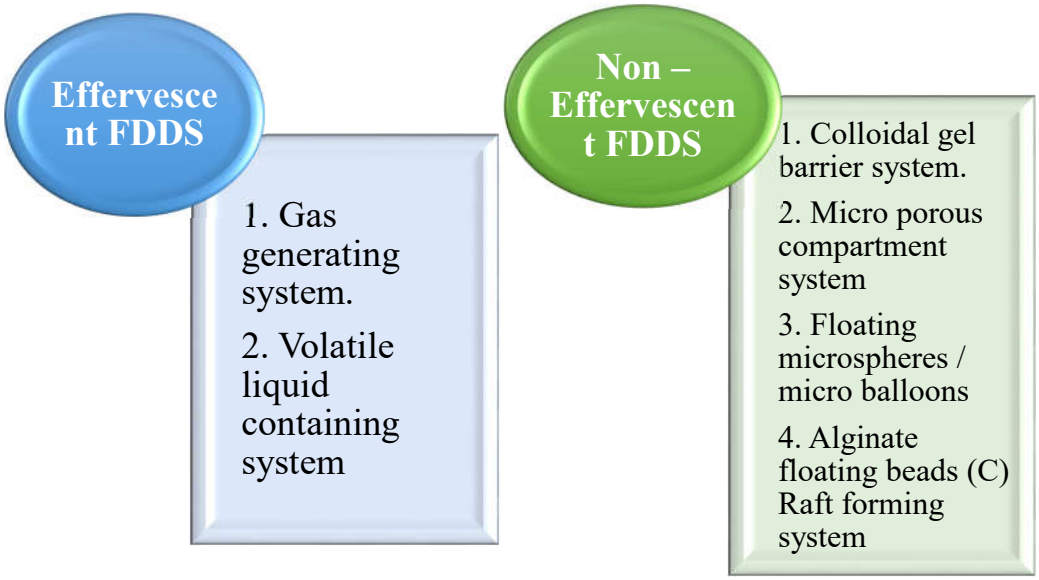


Fig.2: Classification of floating drug delivery system

Migraine

The symptoms of migraine, a common episodic neurological illness with a complex pathophysiology, include recurrent episodes of a unilateral, usually throbbing headache that is frequently severe, along with other related symptoms like nausea, phonophobia, and photophobia. Temporary neurological symptoms, usually visual but sometimes involving other senses and speech, precede headache in one-third of patients [migraine with aura (MA)] (6) According to psychophysical and neurophysiological studies Psychophysical and neurophysiological investigations have shown that migraineurs have hypersensitivity to sensory stimuli and abnormal processing of sensory information in the interval between episodes, as evidenced by higher amplitudes and lower habituation of evoked and event-related potentials (7,8). The neurophysiological correlate of migraine aura is cortical spreading

depression (CSD), and it is well accepted that migraine headaches rely on the Trigeminovascular pain pathway being activated and sensitized (9-12). The mechanisms of the start and propagation of CSD are still unknown, but it can be generated in animals by focal stimulation of the cerebral cortex. A wave of severe neuronal and glial depolarization that spreads gradually (2–6 mm min−1) is its defining feature (13).

Migraine Treatment

Nonsteroidal anti-inflammatory drugs (NSAIDs):

Aspirin (900–1000 mg), acetaminophen (1000 mg), diclofenac (65 mg), naproxen (275-825 mg) or ibuprofen (400–600 mg). Patients with mild-to-moderate episodes who do not experience nausea or vomiting are typically prescribed this class of medication. It is advised to move to a different medication class if an NSAID proves unsuccessful (14).

Triptans:

Triptans are first-line therapies that work particularly well for allodynia sufferers. Among the options are: Sumatriptan, Zolmitriptan, Almotriptan, Rizatriptan, and Eletriptan.

Materials :

Zolmitriptan was received as a gift sample from Cipla Pvt Ltd, Mumbai. Naproxen was purchased from Chempure Pvt Ltd, Mumbai.

Pre- Formulation Study

Melting Point

The melting point of both drugs was obtained using capillary method

Organoleptic Properties

This includes using descriptive terminology to note the new drug's color, odor, and taste.

Solubility

The solubility of Zolmitriptan and Naproxen was determined in various solvents.

Drug- Excipients compatibility studies: Differential scanning calorimetry (DSC) studies

A DSC study was carried out to check the compatibility of ingredients (excipients used in formulation) with the API of the formulation. D.S.C. of APIs and mixtures was taken for identification.

UV Spectroscopy Analysis: The absorbance maxima, as specified, are determined by using a UV Spectrophotometer; from the UV analysis, it was concluded that the Zolmitriptan had shown λ-max at 283 nm and Naproxen at 230 nm. Therefore, the observed lambda max of Zolmitriptan is 283 nm and has been selected for further experimental work in 0.1 N HCL. Likewise, the observed lambda max of Naproxen is 230 nm and has been selected for further experimental work in ethanol.

Pre - Pre-Compression Characteristics:

The Angle of Repose:

The funnel method was used to calculate the granules' repose angle. The following equation was used to calculate the angle of repose after the diameter of the powder cone was measured:

where, $\theta = \tan^{1} h/r$

h-height of the powder cone

r-radius of the powder cone

Bulk Density:

Both loose bulk density (LBD) and tapped bulk density (T.B.D.) were determined by using following formula.

Bulk Density = Mass/Volume

Tapped Density = Mass/Tapped Volume

Compressibility Index:

Carr's compressibility index determined the compressibility index of the granules.

Carr’s compressibility index (%) = [(Tap Density-Bulk density)/Tap density] × 100

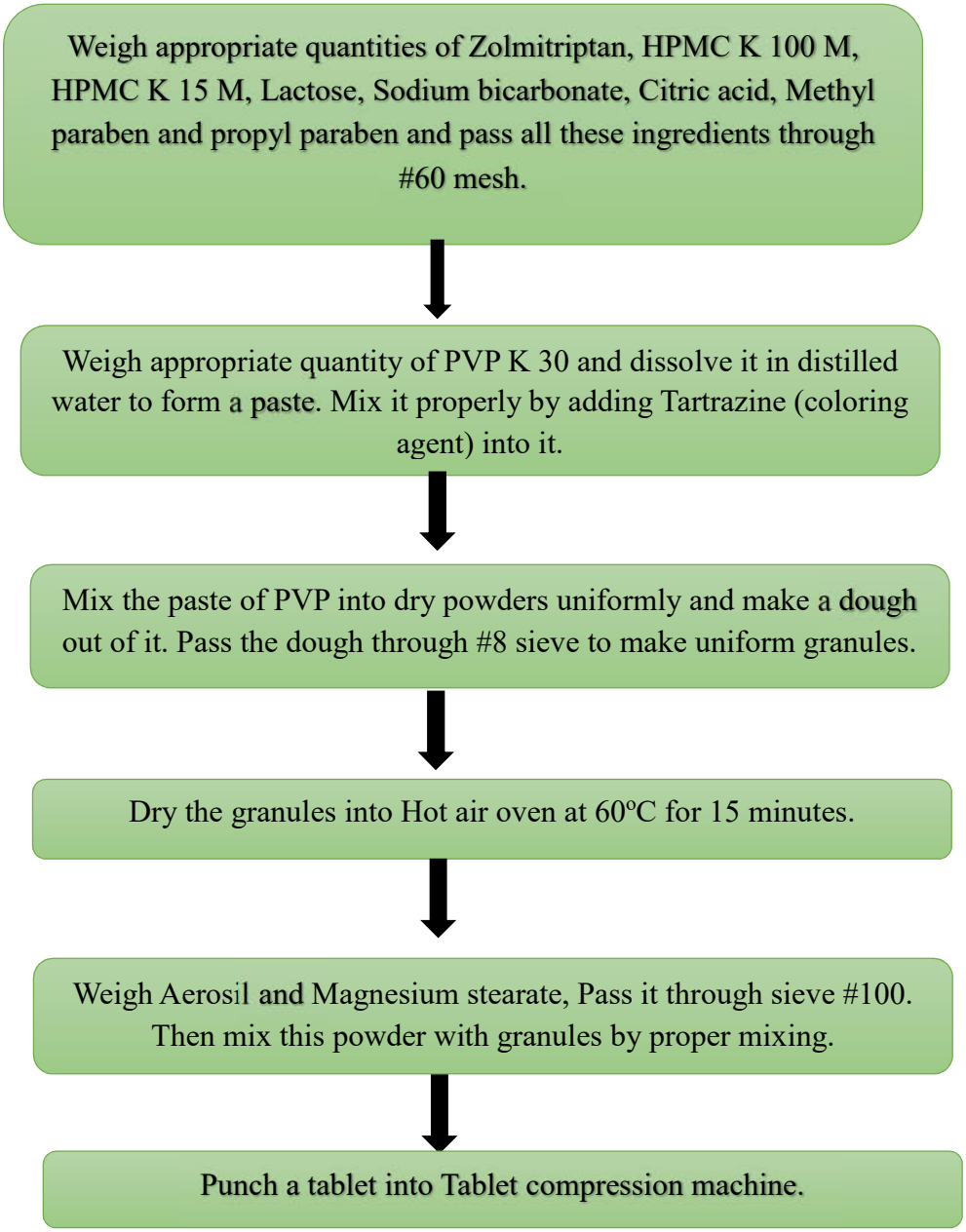
Hausner's Ratio:

Hausner's ratio determine the flowability of a powder or granular material.

Hausner's ratio = Tap density / Bulk density

Formulation of Inlay tablet: Procedure for preparation of Inlay tablet. (15)

1) **Preparation of the Inner core of Zolmitriptan as a floating tablet**


Weigh appropriate quantities of Zolmitriptan, HPMC K 100 M, HPMC K 15 M, Lactose, Sodium bicarbonate, Citric acid, Methyl paraben and propyl paraben and pass all these ingredients through #60 mesh.
Weigh appropriate quantity of PVP K 30 and dissolve it in distilled water to form a paste. Mix it properly by adding Tartrazine (coloring agent) into it.
Mix the paste of PVP into dry powders uniformly and make a dough out of it. Pass the dough through #8 sieve to make uniform granules.
Dry the granules into Hot air oven at 60ºC for 15 minutes.
Weigh Aerosil and Magnesium stearate, Pass it through sieve #100. Then mix this powder with granules by proper mixing.
Punch a tablet into Tablet compression machine.

2) Preparation of the outer core of Naproxen.

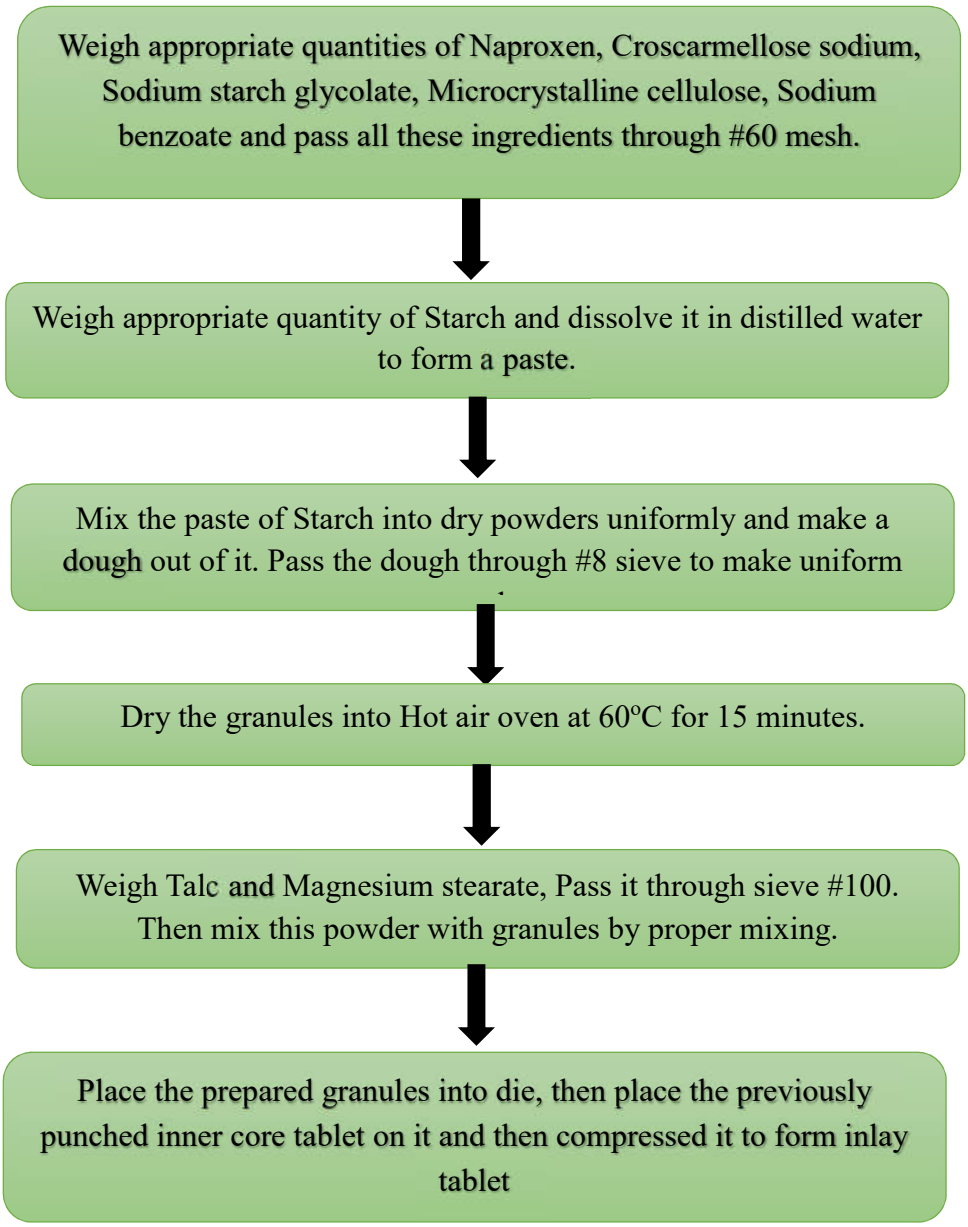


Table no. 1: Formulation table for inner core tablet

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Zolmitriptan	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
2	HPMC K 100 M	10	15	20	-	-	-	5	7.5	10
3	HPMC K 15 M	-	-	-	10	15	20	5	7.5	10
4	Lactose	55.69	50.69	45.69	55.69	50.69	45.69	55.69	50.69	45.69
5	Sodium bicarbonate	10	10	10	10	10	10	10	10	10
6	Citric acid	10	10	10	10	10	10	10	10	10
7	PVP K 30	10	10	10	10	10	10	10	10	10
8	Tartrazine	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
9	Methyl and Propyl paraben	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
10	Aerosil	1	1	1	1	1	1	1	1	1
11	Magnesium stearate	2	2	2	2	2	2	2	2	2
	Total (%)	100	100	100	100	100	100	100	100	100

Table no. 2: Formulation table for outer core table

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Naproxen	55	55	55	55	55	55	55	55	55
2	Croscarmellose sodium	10	15	20	-	-	-	5	7.5	10
3	Sodium starch glycolate	-	-	-	10	15	20	5	7.5	10
4	Microcrystalline cellulose	21.5	16.5	11.5	21.5	16.5	11.5	21.5	16.5	11.5
5	Starch	10	10	10	10	10	10	10	10	10
6	Sodium benzoate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
7	Magnesium stearate	2	2	2	2	2	2	2	2	2

8	Talc	1	1	1	1	1	1	1	1	1
	Total (%)	100	100	100	100	100	100	100	100	100

Evaluation of Post-Compression Tablet: (16)

General Appearance:

The general appearance is the physical appearance of the Tablet. It has aspects to address. General appearance would include several aspects like size, shape, odor, taste, texture, legibility, and identifying marks. The first one is patient compliance; if the Tablet is legible and good, it improves patient compliance.

Size and Shape:

The tooling used in tablet manufacturing would determine a tablet's size and shape. A micrometre is used to measure the size of the crown, and a Vernier calliper is used to measure tablet size. A sliding calliper scale is used to measure lengths of five to ten at a time on a laboratory scale.

Friability:

At 25 rpm for 4 min, 20 tablets were rotated in the Roche friabilator. The tablets were then deducted, and the loss in weight due to fracture or abrasion was recorded as percentage weight loss (% friability)

Friability (%) = Initial Weight - Final Weight

Hardness

The tablet was held in place along its oblong axis between the tester's two jaws. At this point, the number should be 0 kg/cm². The value ought to be zero kg/cm² at this stage. At this stage, the value was expressed in kilograms. The knob was rotated to apply a consistent force until the tablet broke. The Monsanto hardness tester was used to measure the tablet's hardness for each formulation.

Weight Variation Test:

A weight variation test ensures the manufactured tablets have a uniform weight. As per U.S.P., twenty tablets are weighed individually, and compendia weight is taken; the average weight is obtained by dividing compendia weight by 20 tablet weights; now, the average weight is compared with the individual weight of the Tablet.

Drug Content: **(17)**

Three tablets were weighed individually and then crushed in a mortar. The drug weight equivalent to 10 mg was taken& dilution was prepared to form a concentration up to the range of 10 ppm concentration. Finally, the absorbance of the prepared solution was checked & compared with the theoretical value.

In-Vitro Disintegration Time:

In vitro disintegration time was performed by apparatus specified in U.S.P. at 50 rpm. Phosphate buffer pH-6.8, 900 ml was used as the disintegration medium, the temperature of which was maintained at 37±2°C, and the time in seconds taken for complete disintegration of the tablet. The tablet was measured in seconds when there was no more felt mass in the device.

In vitro Drug Release Study:

The in vitro dissolution study of formulation was carried out using U.S.P. apparatus Type II in 900 ml of phosphate buffer solution (pH 6.8) at 37°C±0.5°C at a rotational speed of 50 rpm. After each 5 min starting of the test, a 5 ml sample of dissolution medium was withdrawn and analyzed spectrophotometrically at 277 nm using Shimadzu-1700 UV/ visible spectrophotometer. An equal volume of fresh dissolution medium maintains. The absorbance values were transformed to concentration using a standard calibration curve obtained experimentally.

Kinetic modelling of drug release

to determine the medication release mechanism. In vitro drug release tests were conducted on all nine Inlay tablet formulations. The following is a plot showing the outcomes of in vitro release tests in several kinetic models of release data: 1. Cumulative % of drug release vs. time (zero order rate kinetics) 2. Log cumulative % drug retained vs. time (first-order rate kinetics) 3. Log cumulative % drug release vs. square root of time (Higuchi's classical diffusion equation) 4. Log cumulative % drug release vs. log time (Pappas exponential equation) (18)

Stability Studies:

According to ICH guidelines, Stability studies were carried out. The prepared Inlay tablet was kept at three different temperatures. The first formulation was kept at room temperature, the second was held at a cold temperature, and the third was kept in the stability chamber at a

temperature of 40°C/ 75%RH for three months. At the end of 3 months, samples were withdrawn, observed for physical appearance, and investigated for % drug release.

Floating lag time and total floating time

The floating lag time can be defined as the time it takes to emerge on the surface of the dissolution medium, and Total floating time is the amount of time the tablet continuously floats on the medium's surface. The lag time was measured in a beaker with 250 ml of pH 1.2 buffer solution and kept at 37°C. The floating lag time, measured in minutes, is the time it takes for the tablet to reach the surface and float. (19)

Drug characteristics:

Organoleptic properties

Table no.3: Organoleptic properties of drug

Sr. No.	Property	Zolmitriptan	Naproxen
1	Color	White	White
2	Odor	Odorless	Odorless
3	Taste	Bitter	Bitter

Determination of melting point:

Melting Point of Zolmitriptan and Naproxen was found to be 142 °C and 153 °C respectively.

Zolmitriptan

Determination of analytical wavelength

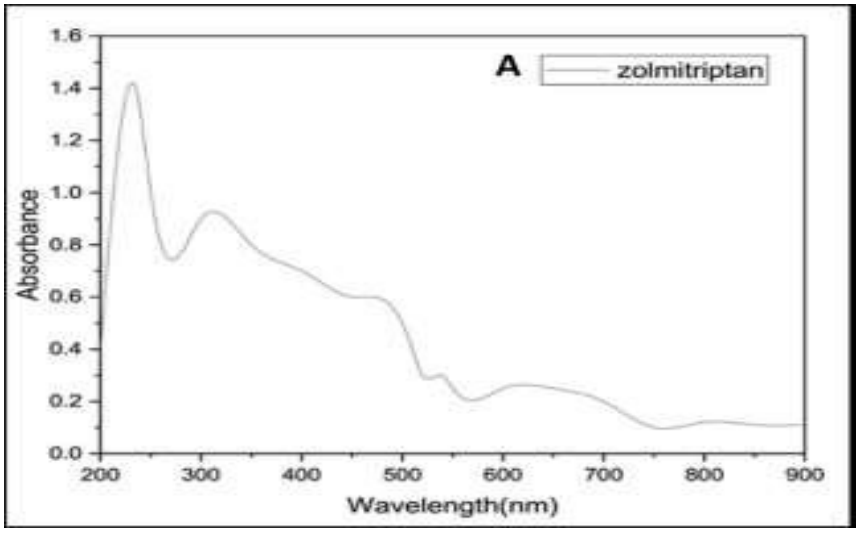


Fig. 3: Lambda max of Zolmitriptan

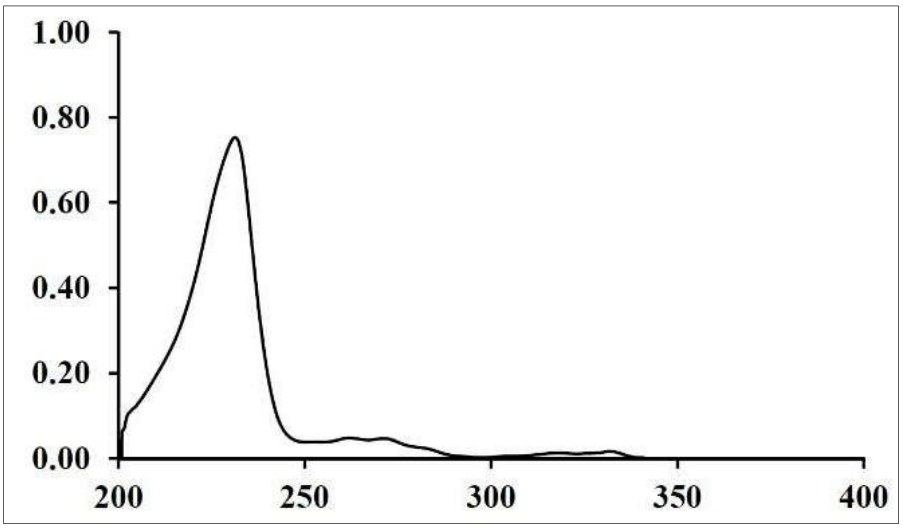


Fig. 4: Lambda max of Naproxen

Differential scanning colorimetry:

DSC thermograms of Zolmitriptan, Naproxen, and a mixture of Zolmitriptan +Naproxen +Excipients are depicted in Fig. The drug exhibited a sharp melting endotherm at 141.85°C, 158.61°C respectively.

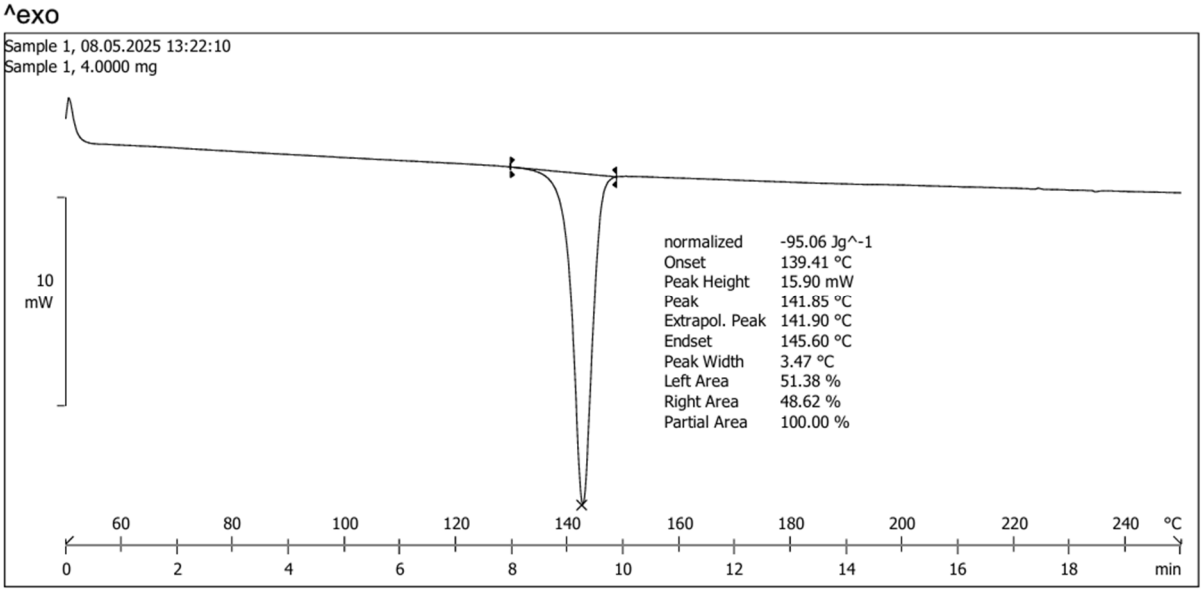


Fig. 5: DSC Thermogram of API Zolmitriptan

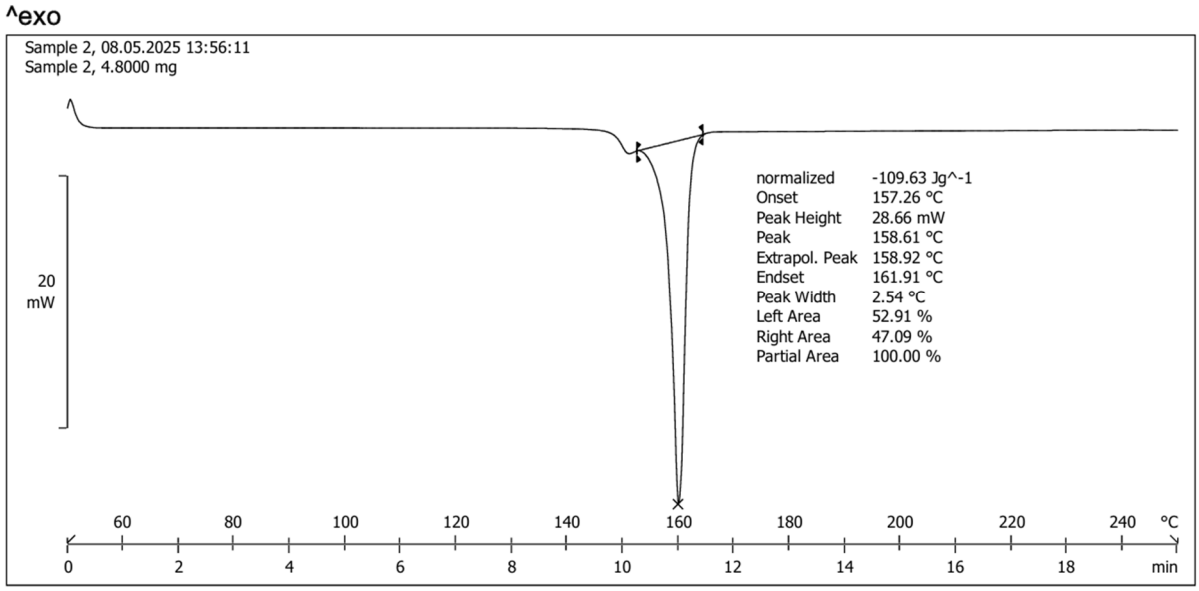


Fig.6: DSC Thermogram of API Naproxen

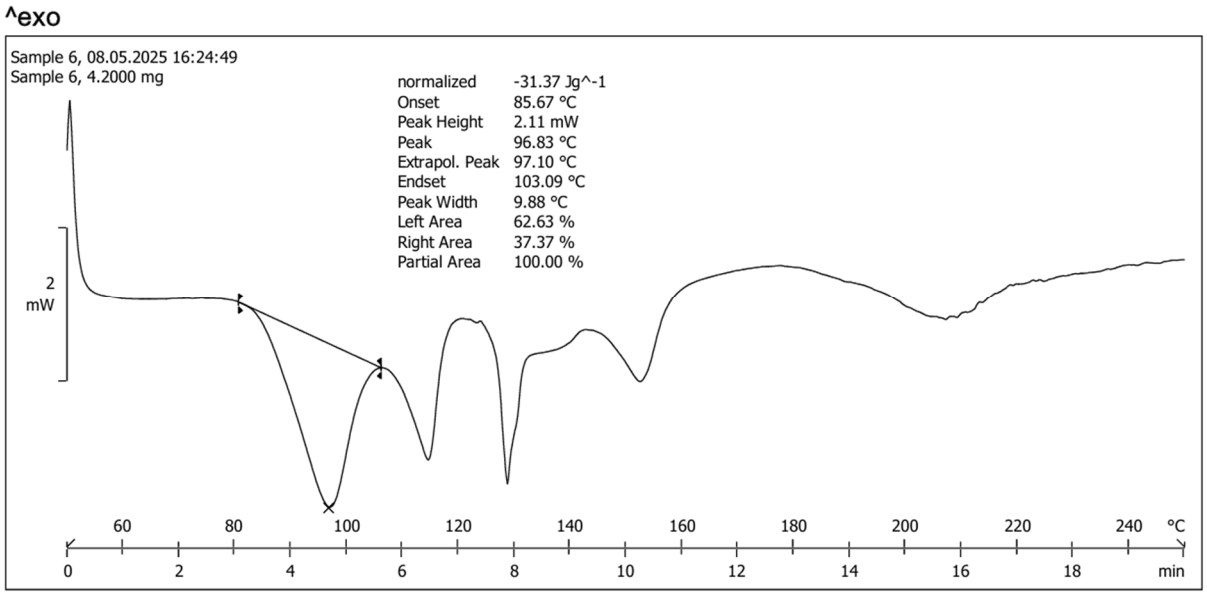


Fig. 7: DSC Thermogram of API Zolmitriptan + API Naproxen + Excipients

Precompression parameters

A) Inner core tablet

Table No. 4: Pre-Compression parameter of inner tablet

Formulation	Bulk Density (g/cc)	Tapped Density (g/cc)	Hausner's Ratio	Compressibility Index (%)	Angle of repose (degree)
SR1	0.43 ± 0.06	0.49 ± 0.03	1.17 ± 0.01	14.87 ± 0.54	30.44 ± 0.40
SR2	0.40 ± 0.01	0.50 ± 0.04	1.40 ± 0.20	16.22 ± 0.24	29.61 ± 0.37
SR3	0.41 ± 0.04	0.45 ± 0.04	1.20 ± 0.10	13.56 ± 0.29	27.59 ± 0.35
SR4	0.47 ± 0.12	0.49 ± 0.02	1.14 ± 0.53	11.75 ± 0.21	26.57 ± 0.32
SR5	0.33 ± 0.11	0.51 ± 0.08	1.16 ± 0.35	13.29 ± 0.18	30.45 ± 0.25
SR6	0.42 ± 0.07	0.44 ± 0.02	1.12 ± 0.07	12.99 ± 0.27	26.33 ± 0.07
SR7	0.57 ± 0.28	0.53 ± 0.06	1.18 ± 0.58	14.47 ± 0.37	28.43 ± 0.26
SR8	0.54 ± 0.23	0.51 ± 0.04	1.17 ± 0.02	15.77 ± 0.28	28.59 ± 0.31
SR9	0.37 ± 0.06	0.49 ± 0.02	1.18 ± 0.02	15.48 ± 0.45	29.45 ± 0.41

B) Outer core tablet

Table No. 5: Pre-Compression parameter of outer tablet

Formulation	Bulk Density (g/cc)	Tapped Density (g/cc)	Hausner's Ratio	Compressibility Index (%)	Angle of repose (degree)
IR1	0.37 ± 0.03	0.38 ± 0.01	1.33 ± 0.40	8.97 ± 0.12	27.85 ± 0.13
IR2	0.37 ± 0.05	0.41 ± 0.05	1.16 ± 0.12	8.57 ± 0.12	25.03 ± 0.89
IR3	0.35 ± 0.02	0.41 ± 0.03	1.15 ± 0.05	9.23 ± 0.23	30.26 ± 0.64
IR4	0.39 ± 0.02	0.40 ± 0.02	1.13 ± 0.14	7.47 ± 0.46	27.09 ± 1.66
IR5	0.34 ± 0.02	0.42 ± 0.05	1.15 ± 0.02	7.63 ± 0.46	25.29 ± 1.12
IR6	0.42 ± 0.05	0.45 ± 0.05	1.07 ± 0.05	7.67 ± 0.23	28.63 ± 0.41
IR7	0.35 ± 0.03	0.35 ± 0.03	1.16 ± 0.06	8.00 ± 0.52	27.10 ± 0.95
IR8	0.35 ± 0.02	0.41 ± 0.05	1.33 ± 0.49	7.90 ± 0.52	24.70 ± 1.47
IR9	0.40 ± 0.05	0.37 ± 0.06	1.19 ± 0.18	7.70 ± 0.35	29.21 ± 0.69

Post compression parameters of Inlay tablet

Table No.6: Post compression parameter/ Evaluation of Tablet

Formulation	Uniformity of Weight (mg)	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Disintegration time for IR (Sec)
F1	881.00 ± 1.73	3.16 ± 0.08	4.03 ± 0.12	0.23 ± 0.02	30.00 ± 0.58
F2	922.00 ± 3.46	3.05 ± 0.05	4.53 ± 0.29	0.28 ± 0.01	28.00 ± 0.58
F3	911.33 ± 2.31	3.21 ± 0.04	5.70 ± 0.17	0.26 ± 0.03	28.00 ± 0.29
F4	909.33 ± 1.15	3.16 ± 0.07	5.63 ± 0.23	0.25 ± 0.01	27.00 ± 0.35
F5	902.00 ± 3.46	3.25 ± 0.03	4.57 ± 0.12	0.23 ± 0.01	56.00 ± 0.81
F6	891.67 ± 2.89	3.17 ± 0.12	6.00 ± 0.17	0.23 ± 0.02	25.00 ± 1.04
F7	912.00 ± 3.46	3.07 ± 0.04	5.23 ± 0.12	0.26 ± 0.03	49.00 ± 0.69
F8	882.67 ± 4.62	3.10 ± 0.03	5.27 ± 0.29	0.24 ± 0.03	31.00 ± 1.15
F9	904.00 ± 6.93	3.04 ± 0.03	4.63 ± 0.12	0.29 ± 0.02	32.00 ± 1.04

Content uniformity

Table No. 7: Content uniformity of Zolmitriptan and Naproxen

Drug content in %	Zolmitriptan	Naproxen
F1	95.77 ± 0.66	96.84 ± 0.08
F2	97.48 ± 0.45	95.17 ± 0.56
F3	99.20 ± 0.69	97.89 ± 0.72
F4	96.75 ± 2.38	94.23 ± 1.03
F5	97.17 ± 2.75	97.56 ± 0.88
F6	98.75 ± 0.65	97.88 ± 1.11
F7	94.88 ± 1.63	95.54 ± 0.22
F8	96.84 ± 0.73	96.74 ± 0.45
F9	95.54 ± 1.33	94.29 ± 1.75

In-vitro Dissolution Studies

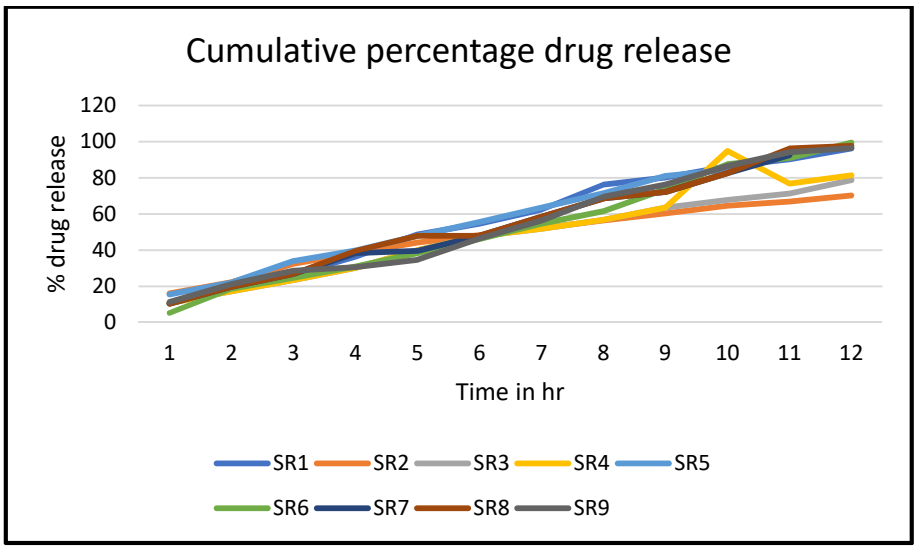


Fig. 8: Cumulative percentage drug release of Zolmitriptan

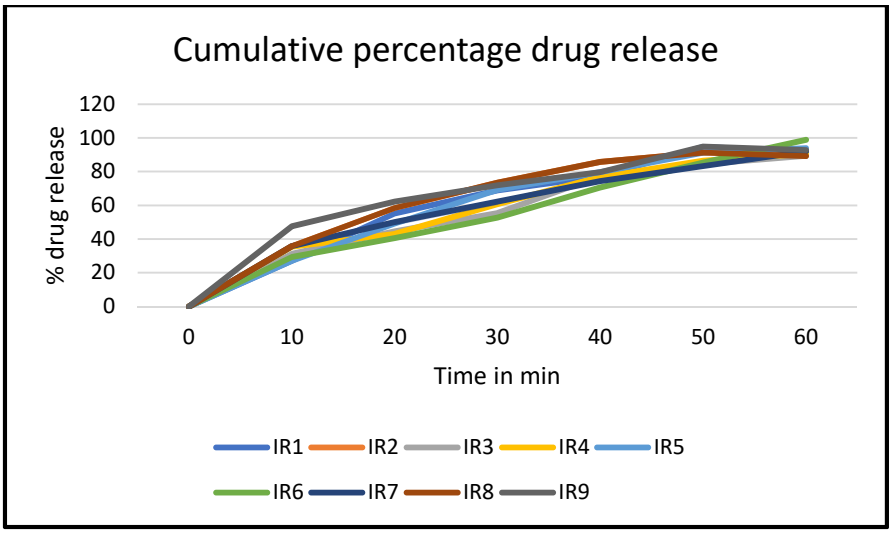


Fig. 9: Cumulative percentage drug release of Naproxen

Drug release kinetics

A) Zolmitriptan

Correlation coefficient (r) & rate constant (k) Values of Zolmitriptan inlay tablets containing HPMC K 100 M and K 15 M excipients. Kinetics studies were carried out of the optimized formulation (F6).

Table No. 8 : Drug release kinetics for Zolmitriptan

Models	Zero order	First order	Higuchi	Korsmeyers Peppas	Hixon-Crowel
R^2 value	0.9284	0.9788	0.9714	0.9222	0.9963(Best fit)

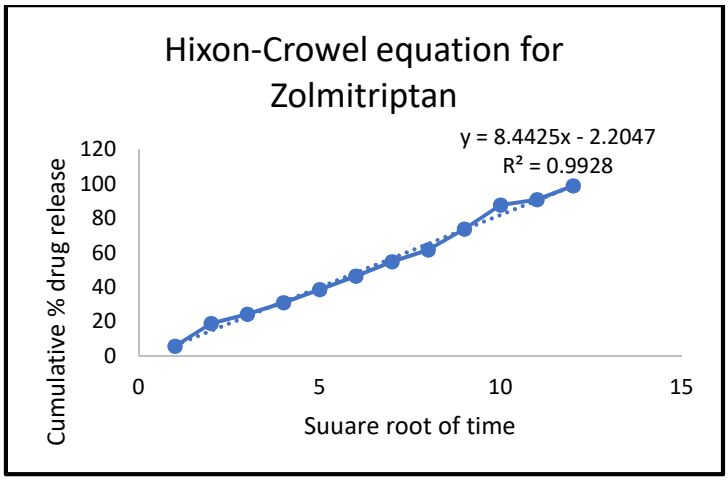


Fig. 10: Hixon-Crowel equation for Zolmitriptan

B) Naproxen:

Correlation coefficient (r) & rate constant (k) Values of Naproxen inlay tablets containing sodium starch glycolate and croscarmellose sodium. Kinetics studies were carried out on the optimized formulation (F6).

Table No. 9: Drug release kinetics for Naproxen

Models	Zero order	First order	Higuchi	Korsmeyers Peppas	Hixon-Crowel
R^2 value	0.9916	0.8771	0.7938	0.9930 (Best fit)	0.9220

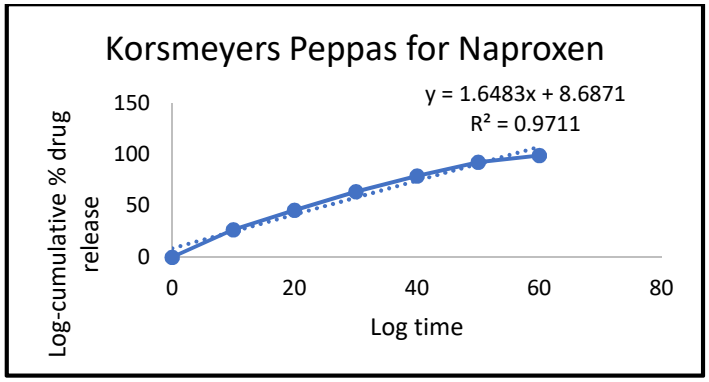


Fig: Korsmeyers Peppas equation for Naproxen

10.9 Evaluation of Floating tablet

Table No. 10: Evaluation of floating (inner core) tablet

Formulation	Floating lag time (min)	Total floating time (hrs)
F1	4	12
F2	4.5	11
F3	4	11.5
F4	5	12
F5	6	9.5
F6	3.5	12
F7	4	10.5
F8	5	11.5
F9	4.5	12

10.10 Stability study

Stability studies were carried out of the Optimized formulation (F9) at 40ºC ± 2ºC & 75%± 5% RH for 30 days as per ICH guidelines. At various time intervals (initial &30 days). The samples' drug concentration, percentage of drug release, thickness (mm), and hardness (kg/cm2) were assessed. The characteristics of the examination did not alter much.

Table No. 11: Comparison of Various Parameters for Stability Study of F6 batch

Time interval	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content of Zolmitriptan (%)	Drug content of Naproxen (%)
0 day	6.0 ± 0.17	3.17±0.1	0.23 ±0.98	98.75 ± 0.65	97.88± 1.11%
30th day	6.0 ± 0.37	3.17±0.1	0.28 ±0.76	97.71 ± 1.38	97.72 ± 0.22%
60th day	5.8 ± 0.33	3.16±0.1	0.31 ±0.56	96.80 ± 0.69	97.23 ± 0.23%
90th day	5.2 ± 0.35	3.08±0.2	0.36 ±0.88	95.13 ± 0.48	97.04 ± 0.63%

Conclusion:

A common NSAID for treating migraines is naproxen, while zolmitriptan is a selective serotonin receptor agonist. The Inlay tablet was formulated with various concentrations of polymers such as HPMC K 100 M, HPMC K 15 M, and Sodium starch glycolate, Croscarmellose sodium as a Superdisintegrant by wet granulation. The formulated blend was evaluated for pre-compression parameters, which showed good flow properties. Weight homogeneity, hardness, thickness, diameter, and friability of the prepared tablets were all found to be within acceptable bounds. The Drug content of the formulated Tablets was found to be within the Pharmacopeial limit. The Disintegration time was calculated only for immediate release layer and it was found to be 25 seconds. The Floating lag time and Total floating time of the formulations from F1- F9 was found to be in the range of 3.5 to 5 minutes and 14 to 16 hours, layer of the coating is deposited in the die, and respectively.The in-vitro dissolution studies of the formulated Inlay tablets were performed using USP type-II dissolution apparatus. From the formulated batches, the formulation F6 shows higher percentage drug release. Based on the Disintegration and in-vitro release studies of Inlay tablets, formulation F6 was optimized and selected for stability study and drug kinetics. The inlay tablets were designed to be administered less often. Inlay tablets were prepared by wet granulation. The formulation F6 was considered to be better among the trials

conducted. The formulated Inlay tablet is the best combination of drugs because both follow different mechanisms of Migraine, giving a synergistic effect. By lowering the frequency of dose administration, the Inlay tablet was created to increase patient acceptance and compliance.

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