FORMULATION AND *IN-VITRO* EVALUATION OF BILAYER TABLET CONTAINING ZOLMITRIPTAN AND NAPROXEN

Chitra Bhagvantrao Hangargekar[*1], Shivanad Malkappa Patil[2]

[*1] K.T. Patil College of Pharmacy, Osmanabad, Maharashtra- 413501, India
[2]Department of Pharmaceutical sciences, Shree Dev Bhoomi Institute of education, Science and technology, Dehradun, Uttarakhand-248007, India

Corresponding Author
Chitra Bhagvantrao Hangargekar
K.T. Patil College of Pharmacy,
Osmanabad, Maharashtra- 413501,
Email: chitra223753@gmail.com
Phone no: +91 8975094851

ABSTRACT

Migraine is a chronic neurological disorder and characterized by splitting headaches. A combination of Zolmitriptan (ZT) and Naproxen sodium (NS) was found to be effective. Time to reach C_{max} and biological half-lives of both the drugs are different and hence optimum levels of both the drugs cannot be maintained simultaneously in the blood when these drugs are administered orally in the form of conventional tablets. Therefore, the objective of present investigation was formulation development and in vitro evaluation of a bi layer tablet dosage form containing ZT and NS in a fixed dose combination as immediate release layer and a delayed release layer containing ZT to maintain optimum plasma levels of both drugs at a time and for a prolonged period. Formulation variables for immediate release layer include Crospovidone, Croscarmellose sodium and Sodium starch glycolate as super disintegrants. Carboxy Methyl Ethyl cellulose was used as delayed release polymer. Each layer was optimized individually and best compositions were selected. Using direct compression method bi layer tablets were prepared and evaluated. The cumulative percent drug release versus time plots of ZT from bi layer tablets indicate the pattern of drug release. The rate of drug release followed first order kinetics. Differential Scanning Calorimetry and Fourier infrared spectroscopic studies revealed the absence of incompatibility between drugs and excipients.

Keywords: Zolmitriptan, Naproxen sodium, Crospovidone, Croscarmellose sodium, Carboxy Methyl Ethyl cellulose

INTRODUCTION

The development of sustained or controlled drug delivery systems has got momentum over the past decade due to immense focus on the marketing of new drug molecules as the combination of these new drug molecules has increased to counter multiple diseases that require different dosage regimens [1, 2]. Bilayer tablet has patient compliance and is beneficial for either sequential release of two drugs in combination or sustained and immediate release of the same drug one as initial and other as a maintenance dose [3–5].

Bilayer tablets are appropriate for the sequential release of two drugs to be given combined. It separates the two mismatching drugs. The sustained-release tablets whose one layer provides instant drug release as the initial loading dose while the second layer contains the sustained dose. Bilayer tablet is an advanced technology that helps in overcoming the limitations of a single-layered tablet. It delivers both the main and the sustaining dose of one same or two different drugs and promoting patient compliance and convenience [6-8].

It can be used as an extension of conventional technology. Possible use of single entity feed granules. Improved patient convenience as a reduced number of daily doses is needed than the normal delivery system resulting in better drug regimen efficiency. It is responsible for the maintenance of physical and chemical stability and the separation of incompatible components. The other advantages including the retaining of the potency and ensuring the accuracy of the dose, it has a great microbial and chemical stability as compared to other oral dosages and offers the least content uniformity and high precision. Bilayer tablet stops the direct contact of two drugs; however, it increases the efficacy of two drugs through combination. They can be designed in a way to modify its release, wherein one layer can be modified as immediate-release while the other layer can be modified as an extended-release. It is inexpensive and is suitable for large scale production [9, 10].

Zolmitriptan is a selective 5-hydroxytryptamine 1B/1D receptor agonist with a weak affinity for the 5-HT 1A receptor subtypes. Its action on 5-HT 1B/1D receptors causes vasoconstriction in intracranial blood vessels; as well it can inhibit the release of pro-inflammatory neuropeptides from trigeminal perivascular nerve endings. It crosses the blood-brain-barrier as evidenced by the presence of radioactive [3H]-zolmitriptan labels within the cells of the trigeminal nucleus caudalis and nucleus tractus solitaries. [11]

Naproxen is a nonselective COX inhibitor. As an NSAID, naproxen appears to exert its anti-inflammatory action by reducing the production of inflammatory mediators called prostaglandins. It is metabolized by the liver to inactive metabolites. Naproxen works by reversibly inhibiting both the COX-1 and COX-2enzymes as a non-selective coxib. [12, 13] This results in the inhibition of prostaglandin synthesis. Prostaglandins act as signaling molecules in the body, inducing inflammation. Thus, by inhibiting COX-1/2, naproxen induces an anti-inflammatory effect.

The objective of present investigation was formulation development and in vitro evaluation of a bi layer tablet dosage form containing ZT and NS in a fixed dose combination as immediate

release layer and a delayed release layer containing ZT to maintain optimum plasma levels of both drugs at a time and for a prolonged period.

MATERIALS AND METHODS

Materials: Naproxen and Zolmitriptan were obtained as gift samples from Alembic pharmaceuticals Ltd., Gujarat. Carboxy Methyl Ethyl cellulose(Colorcon Asia Pvt Ltd., Goa), icrocrystalline cellulose, Crospovidone, Croscarmellose sodium, Sodium starch glycolate, Mannitol, Lactose Monohydrate, Dibasic Calcium Phosphate, Carboxy Methyl Ethyl cellulose, Microcrystalline Cellulose, Magnesium stearate, Carboxy Methyl Ethyl cellulose (Geocon products, Mumbai),and all other chemicals used were ofanalytical grade.

Methods

Characterizations of immediate release (IR) and sustain release (SR) granules:

Both IR and SR granules were evaluated for various pre-compression parameters. LOD was measured only for Zolmitriptan granules as Naproxen tablets were prepared by dry granulation technique. Angle of repose was measured by fixed funnel method. Bulk and tapped densities were determined by tapped density apparatus from which compressibility index and Hausner's ratio values were calculated according to the USP guideline.

Evaluation of drug-excipient compatibility study in stability chamber:

Compatibility studies of both Zolmitriptan and Naproxen with probable excipients to be used were conducted through both individual and binary mixture of APIs and excipients as well as both formulation blends were prepared and packaged in glass vials and sealed with rubber stopper and Low Density Polyethylene (LDPE) plug. These samples were incubated at room condition (25 °C ±2 °C & 60% ±5% RH), accelerated condition (40 °C ±2 °C & 75% ±5 % RH) and dry heat condition, 50 °C for one month. The LDPE plugs were punctured for samples of accelerated condition (40 °C ±2 °C & 75% ±5% RH) .

Drug-excipient compatibility studies by FTIR and DSC:

The compatibility of drugs with their respective excipients was studied by FTIR spectroscopy. The scanning was performed 20 times for both Zolmitriptan and Naproxen with resolution of 1 cm-1 over the region of 4000–400 cm-1. The scans were evaluated for the presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction. DSC is a reliable method to screen drug excipients compatibility and provides maximum information about possible interactions. A sharp endothermic peak at any temperature indicates the melting point of drug. In formulation mixer, sharp endothermic peak at any temperature indicating the stability of the formulation up to that temperature

Evaluation of polymorphic change by X-RD:

Degree of crystalline is one of the factors influencing the solubility and dissolution rate of a drug substance. Hence, crystalline nature of a substance and extent of its conversion to amorphous form was studied by X-Ray Diffractometry (X-RD).

Formulation development of immediate release Zolmitriptan tablets:

Table 1: Formulation design of Zolmitriptan immediate release tablets

S. No	Ingredients	F1	F2	F3	F4	F5	F6
1	Zolmitriptan	5	5	5	5	5	5
2	Microcrystalline cellulose	34	36	34	36	34	31
3	Mannitol	51	46	51	56	51	48
4	Crospovidone	2	5	--	--	--	--
5	Croscarmellose sodium	--	--	2	5	--	--
6	Sodium starch glycolate	--	--	--	--	2	8
7	Aerosil	2	2	2	2	2	2
8	Aspartame	4	4	4	4	4	4
9	Magnesium stearate	2	2	2	2	2	2
10	Strawberry flavor	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	Average weight (mg)	100 mg	100	100 mg	100	100 mg	100 mg

Table 2: Formulation for the optimized preparation of Naproxen (250 mg) extended release tablets

S. No	INGREDIENTS	C1	C2	C3	C4	C5	C6
1	Naproxen	250	250	250	250	250	250
2	Dibasic Calcium Phosphate	91.5	119	94.2	88.2	84.4	67.2
3	Lactose Monohydrate	111.5	102.2	72.8	79.6	74.6	69.6
4	Carboxy Methyl Ethyl cellulose	18.00	19.20	54.00	53.20	62.4	84.20
5	IPA +water	qs	qs	qs	qs	qs	qs
6	Microcrystalline Cellulose	5.00	5.00	5.00	5.00	5.00	5.00
7	Magnesium stearate	5.00	5.00	5.00	5.00	5.00	5.00
8	Carboxy Methyl Ethyl cellulose	7.00	7.00	7.00	7.00	7.00	7.00
9	Opadry	12.00	12.00	12.00	12.00	12.00	12.00
10	IPA +water	qs	qs	qs	qs	qs	qs
	Total (mg)	500.00	500.00	500.00	500.00	500.00	500.00

Preparation of Zolmitriptan and Naproxen bilayer tablets:

For preparing bilayer tablets, the dissolution test was conducted for both layers of immediate release and sustain release separately with the aim of selecting the best formulations. Based on dissolution behavior, formulations were selected for bilayer tablet preparation. Sustain release Naproxen layer was placed in the die cavity and punched with low compression force. Then the immediate release zolmitriptan layer was placed in the die cavity and allowed for punching with optimum hardness of 6-8kg/cm2 to form bilayer tablets. Compression was made by using 8 mm punches. The total weight of each bilayer tablet was adjusted to 600mg, containing 5 mg of zolmitriptan in immediate release layer and 250 mg of Naproxen in sustain release layer which was tabulated in Table 3. Prepared bilayer tablets were evaluated for various post-compression parameters and in vitro dissolution studies

Table 3: Formulation of Zolmitriptan and Naproxen bilayer tablets

API/ excipients	**Amount (mg)**
Zolmitriptan	5
Naproxen	250
Microcrystalline cellulose	36
Mannitol	46
Crospovidone	5
Aerosil	2
Aspartame	4
Magnesium stearate	2
Strawberry flavor	Q.S
Dibasic Calcium Phosphate	94.2
Lactose Monohydrate	72.8
Carboxy Methyl Ethyl cellulose	54.00
IPA +water	qs
Microcrystalline Cellulose	5.00
Magnesium stearate	5.00
Carboxy Methyl Ethyl cellulose	7.00
Opadry	12.00
IPA +water	Qs
Total weight	600mg

Evaluation of pre formulation parameters: [14, 15]

All the formulations were evaluated for flow properties independently at both pre-granulation and pre-compression stages. The fixed funnel method was employed to measure the angle of repose. Bulk and tapped densities were determined by tapped density apparatus from which compressibility index and Hausner's ratio values were calculated.

Evaluation of Multi-layered tablets: [14, 15]

Weight Variation

Ten tablets were selected at random and weighed individually. Average weight was calculated and standard deviation was computed.

Hardness

Hardness is termed as the tablet crushing strength and it is the force required to break a tablet diametrically. Hardness of tablets was measured by selecting 5 tablets randomly and the hardness of each tablet was measured with Pfizer hardness tester. It is usually measured in terms of kg/cm2.

Friability

Ten tablets were weighed and placed in the friabilator, which was then operated for 25 revolutions per minute. After 4 minutes, the tablets were dusted and reweighed. The percentage friability was determined using the formula,

Percentage friability = [Initial weight - Final weight/Initial weight] × 100

Disintegration Time

The disintegration time of the tablets was determined as per Indian pharmacopoeia. The test was carried out using tablet disintegration apparatus. Distilled water was used as a disintegrating media at 35-39 °C. The time required to obtain complete disintegration of all the tablets was noted.

Drug Content

Ten tablets were crushed in a mortar and following procedure carried out.

Drug Content for Zolmitriptan

Preparations equivalent to 10 mg was weighed accurately and transferred to 100ml volumetric flask and dissolved in 0.1N HCl. The volume was made up to the mark with 0.1N HCl. Absorbance of the resulting solution was measured at 285 nm using appropriate blank solution. The drug content was estimated using calibration curve.

Drug Content for Naproxen

Preparations equivalent to 20mg was weighed accurately and transferred to 100ml volumetric flask and dissolved in 7.4 phosphate buffer. The volume was made upto the mark with 7.4 phosphate buffer. Absorbance of the resulting solution was measured at 332 nm using appropriate blank solution. The drug content was estimated using calibration curve.

In-vitro Dissolution Studies

In vitro dissolution studies were conducted using Dissolution test apparatus DS 800 (Lab India, Mumbai). The dissolution specifications for all types of tablets tested were given in the table 5. For dissolution of Multi-layered tablets, 0.1N HCl was used as dissolution medium for the first 30min and 7.4 P^H phosphate buffers for the remaining time. Samples of 5mL were withdrawn at predetermined time intervals and replaced with 5mL of fresh dissolution medium. The collected samples were diluted with dissolution fluid, wherever necessary, and were analyzed for Zolmitriptan at 206nm and Naproxen at 332nm by using Double beam UV Visible Spectrophotometer SL 164 (Elico, Hyderabad).

RESULTS AND DISCUSSION

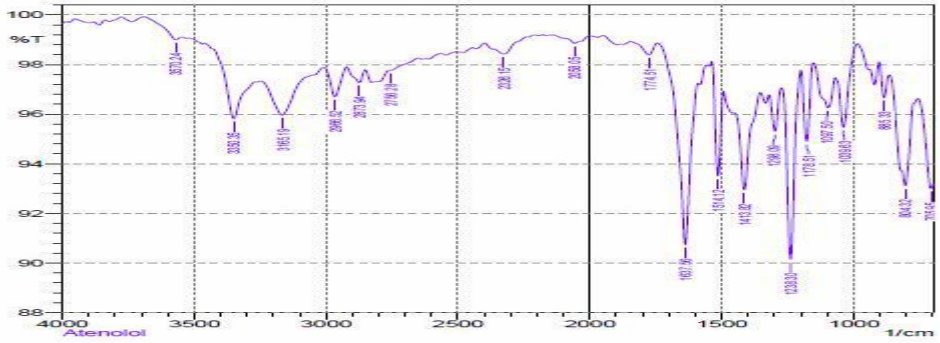

Figure 1: FTIR spectrum of zolmitriptan pure drug

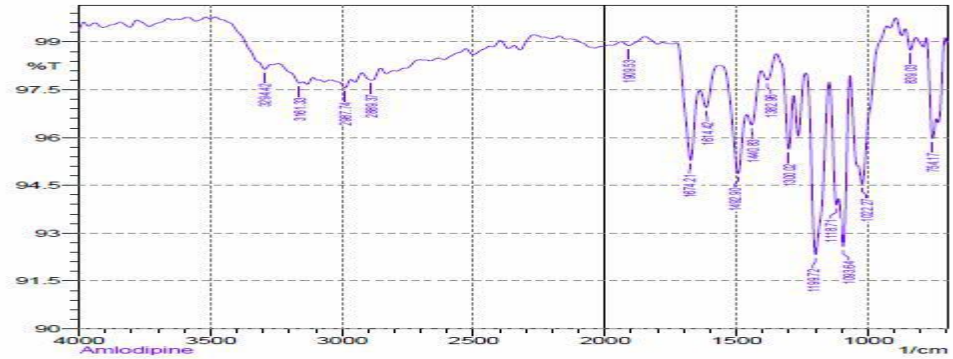

Figure 2: FTIR spectrum Naproxen pure drug

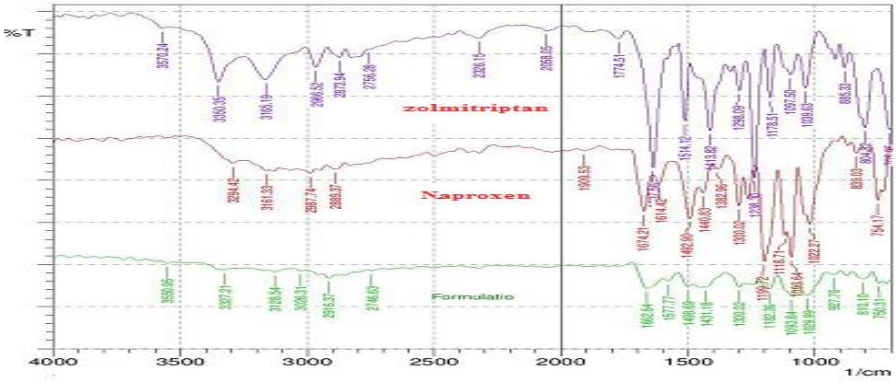

Figure 3: FTIR spectrum of Zolmitriptan and Naproxen with optimized formulation

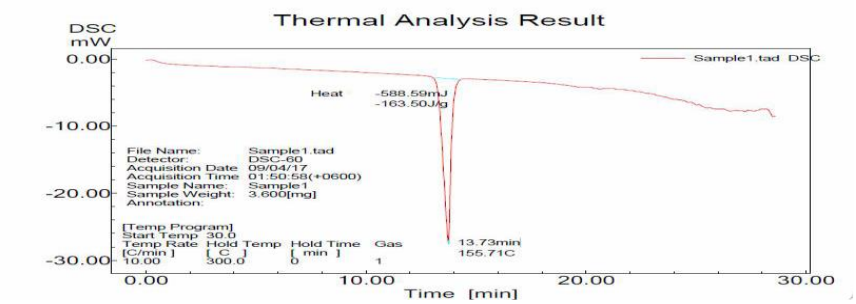

Figure 4: DSC thermogram of pure Zolmitriptan

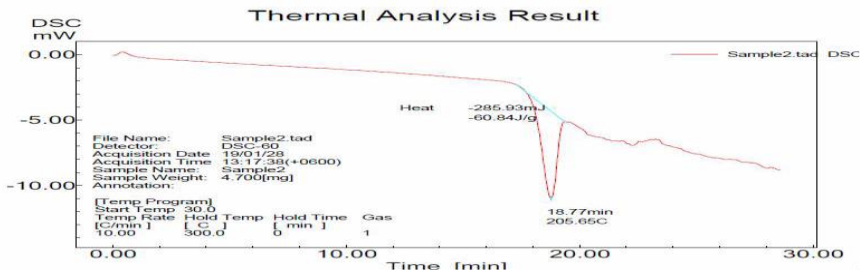

Figure 5: DSC thermogram of pure Naproxen

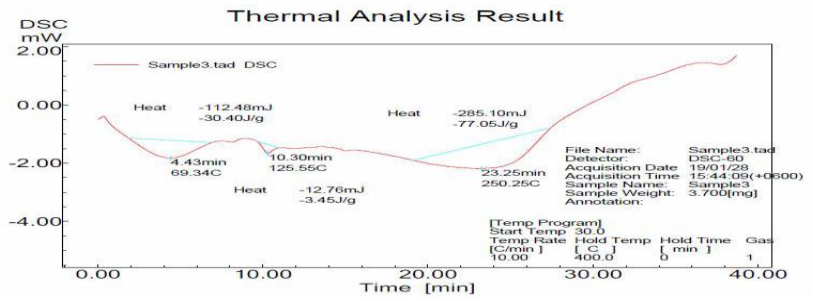

Figure 6: DSC thermogram of optimized formulation mixer

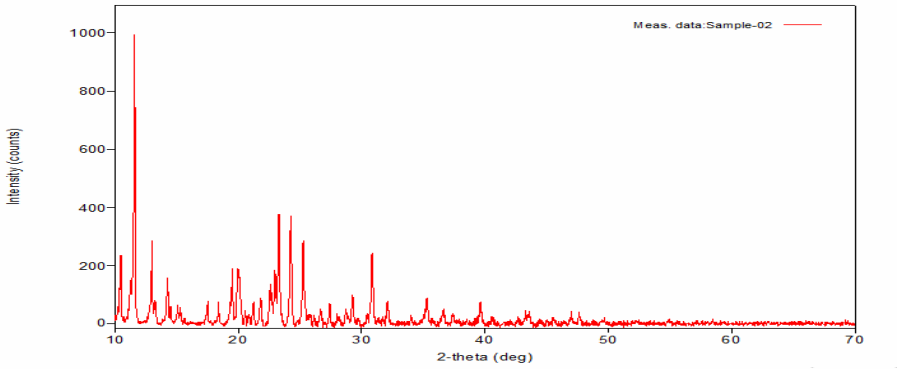

Figure 7: X-RD of Zolmitriptan

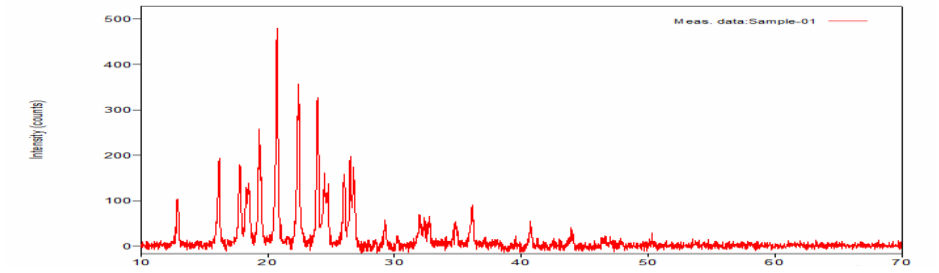

Figure 8: X-RD of pure Naproxen

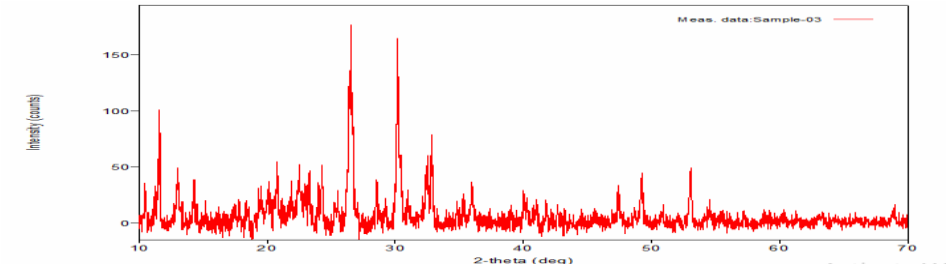

Figure 9: X-RD of crushed tablet

Drug-drug and drug-excipient compatibility studies

Compatibility studies by physical observation in stability chamber:

The drug-drug and drug-excipient samples were collected from stability chamber after one month. Any change in physical appearance and odor was investigated. In all individuals and combinations at room condition (25 °C ±2 °C & 60% ±5% RH) were complies with specification while most of the combination showed sensitivity (e.g. discoloration, bad odor and lump formation) at accelerated open condition (40 °C ±2 °C & 75% ±5% RH), while only Zolmitriptan: Povidone K-30 and Naproxen: Magnesium stearate (1:1) at 50°Cshowed lump formation with bad odor generation.

Compatibility studies by FTIR:

Same peaks were observed in drug product crushed powder which indicated that there were no polymorphic changes in the drug substance during the preparation of tablets with excipients. Furthermore, the absence of shifts inthe wave numbers of the FTIR peaks of the solid dispersions compared to the physical mixture indicates the lack of significant interaction between the drugs and excipients at the molecular level are shown in **figure 1-3**.

Compatibility studies by DSC:

Sharp endothermic peak was observed at 155.71 0C and205.65 ^{0}C indicating the melting point of Zolmitriptan and Naproxen respectively. In formulation mixer the peak was found at 69.35 ^{0}C indicating that the formulation was stable up to 69^{0}C. All are shown in **figure** 4-6.

Table 4: Evaluation of pre compression parameters of immediate release tablets Zolmitriptan

S. No	Parameters	F1	F2	F3	F4	F5	F6
1	Bulk density (g/ml)	0.390	0.401	0.387	0.490	0.511	0.495
2	Tapped density g/ml)	0.450	0.476	0.458	0.581	0.603	0.574
3	Carr's index(%)	13.3	15.7	15.5	14.43	15.04	13.76
4	Hausner's ratio	1.15	1.18	1.18	1.17	1.17	1.16
5	Angle of repose	26.7	29.4	28.7	27.3	28.5	27.9

Table 5: Evaluation of pre compression parameters of sustained release tablets Naproxen

S. No	Parameters	C1	C2	C3	C4	C5	C6
1	Bulk density (g/ml)	0.733± 0.05	0.718± 0.05	0.596± 0.03	0.680 0.05	0.707± 0.06	0.710± 0.03
2	Tapped density (g/ml)	0.799	0.650	0.797	0.798	0.778	0.700
3	Carr's index(%)	9.5	8.41	9.03	10.34	8.05	9.19
4	Hausner's ratio	1.13	1.14	1.15	1.18	1.17	1.16
5	Angle of repose (^{0})*	25.62	34.8	25.43	26.1	26.96	24.06

Pre-compression parameters

The Pre-compression parameters Zolmitriptan and Naproxen were evaluated for their bulk density, tapped density, compressibility index and Hausner's ratio, and angle of repose, as shown in **Table 4and 5**. The bulk densities were found to be in the range of 0.387 to 0.733± 0.05gm/ml. The angle of repose varied from 24.06 to 34.8. The low values of angle of repose indicate the free flowing nature ofthe poeder. The tapped densities ranged 0.45 to 0.799 gm/ml and the Carr's indexes were in the range of 9.05 to 13.53. Hausner's ratio was found in the range of 1.12 to 1.18was found.

Table 6: Evaluation of post compression parameters of immediate release tablets Zolmitriptan

Sr. No	Parameters	F1	F2	F3	F4	F5	F6
1	Weight variation (mg)	150± 0.5	150± 0.6	151± 0.5	150± 0.5	150± 0.5	149± 0.2
2	Thickness (mm)	3.53± 0.08	3.49± 0.04	3.51± 0.04	3.53± 0.02	3.76± 0.03	3.63± 0.02

3	**Friability (%)**	0.60	0.48	0.64	0.57	0.62	0.51
4	**Hardness (Kg/cm)**	3.3± 0.2	3.6± 0.2	3.1± 0.4	3.4± 0.2	3.6± 0.4	3.3± 0.3
5	**Disintegration time (sec)**	26± 1.15	17± 2.1	32± 1.16	23± 2.15	41± 2.27	30± 1.19
6	**Dispersion time(sec)**	33± 2.18	22± 1.15	38± 2.47	28± 1.21	49± 3.25	38± 1.90
7	**Content uniformity (%)**	96.1± 0.8	99.1± 1.3	93.2 ±1.6	97.4± 2.1	94.3± 2.4	96.1± 1.31
8	**Water absorption ratio**	13.1± 1.7	12.4± 1.8	13.1 ±0.8	14.3± 1.7	13.9± 1.7	15.1± 0.6
9	**Assay(% w/w)**	98.1	99.3	97.3	98.1	96.9	97.1
10	**Wetting time**	42.1± 1.61	37.3± 1.37	47.1± 1.01	39.1± 1.62	59.1± 1.89	52.7± 1.09

Table 7: Evaluation of post compression parameters of sustained release tablets Naproxen

S. no.	**Parameters**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**
1	**Hardness(kg/cm^2)**	7.5	7.7	7.4	6.2	6.1	5.5
2	**Thickness (mm)**	5.60	5.72	5.54	5.73	5.71	5.62
3	**Friability(%)**	0.15	0.260	0.28	0.30	0.34	0.17
4	**Weight variation(mg)**	599±5	597±2	592±5	596±5	598±5	595±5
5	**Content uniformity (%)**	97.5	96.8	96.5	98.3	95.7	97.4

Post-compression parameters

The bilayer tablets of Zolmitriptan and Naproxen were prepared by wet granulation method. The prepared tablets were evaluated for their weight variation, hardness, friability and drug content uniformity, and the results are presented in **Table 6 and7.** The values were found to be within the prescribed limits varied between 0.09 ± 0.024 to 1.4 ± 0.02 %. Hardness was in the range of 3.1±0.4 to 7.4 kg/cm2. Friability was found to be less than 1% in all the batches which indicates the ability of the prepared tablets to withstand shock during the time of transportation and handling. Drug content was uniform within the prepared batches and ranged between 93.2±1.6 to 96.84 ± 0.16%.

***In vitro* Dissolution study:**

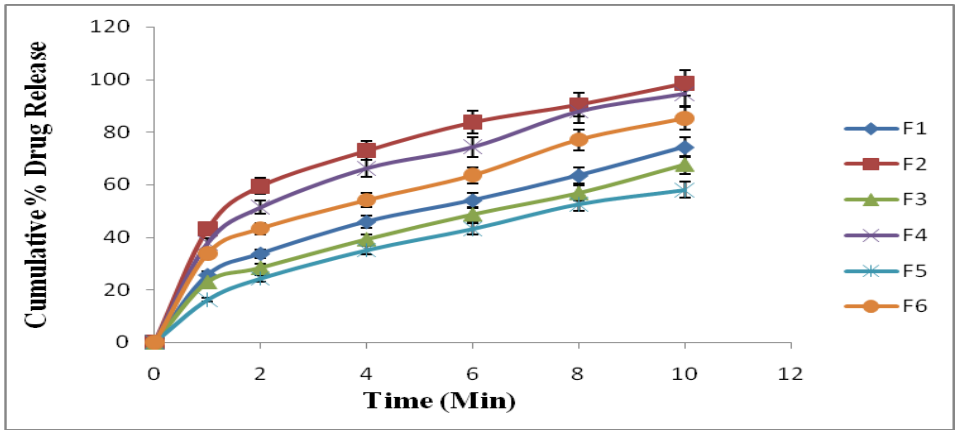

Figure 10: *In vitro* Dissolution of formulation No. F1 – F6 (Zolmitriptan)

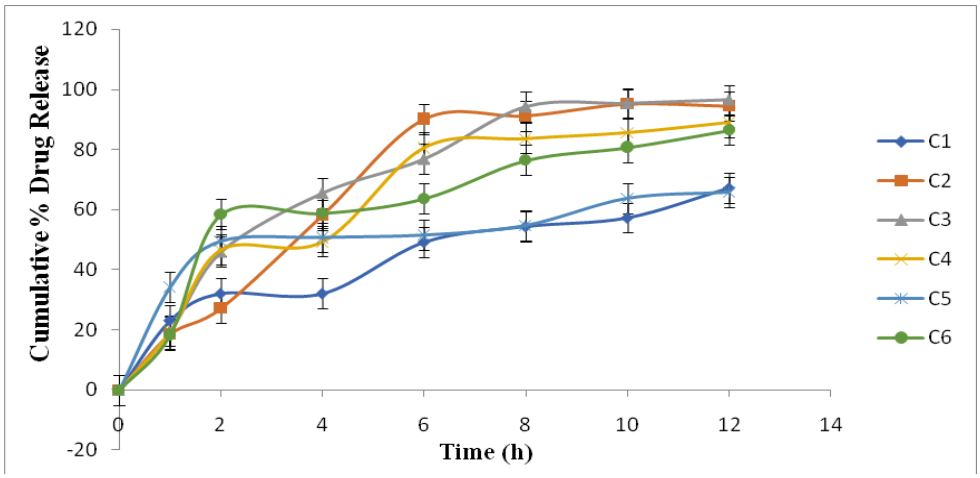

Figure 11: *In vitro* Dissolution of formulation No. C1 – C6 (Naproxen)

In vitro dissolution studies were conducted using Dissolution test apparatus DS 800 (Lab India, Mumbai). The dissolution specifications for all types of tablets tested were given in the table 5. For dissolution of Multi-layered tablets, 0.1N HCl was used as dissolution medium for the first 30min and 7.4 P^H phosphate buffers for the remaining time. From the results, drug release of Zolmitriptan immediate release layer was found to be 98.64±2.34% in 30 minutes and that of the Naproxen sustain release layer was 96.47±0.05% at the end of 12 hours and values are represented in the **Figure 10 & 11**.

Table 8: Release profiles of Zolmitriptan (F2) and Naproxen (C3) from bilayer tablets in various models.

Drug	Zero order		First order		Higuchi		Korsmeyar-Peppas		Hixson-Croswel	
	K_0	R^2	K_1	R^2	H_h	R^2	n	R^2	K_{HC}	R^2
F2	111.3	0.62	-2.6	0.94	120.4	0.88	0.35	0.84	3.87	0.81
C3	4.2	0.86	-0.07	0.99	22.72	0.95	0.73	0.97	0.15	0.97

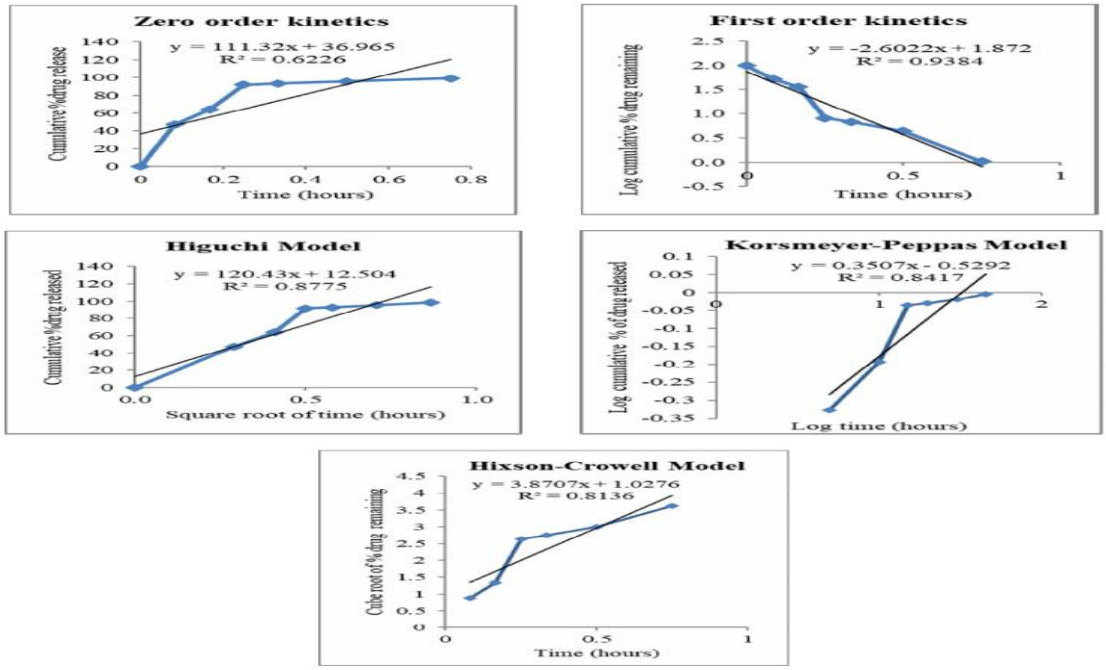

Figure 12: Drug release kinetics of Zolmitriptan (immediate release) layer in bilayer tablet

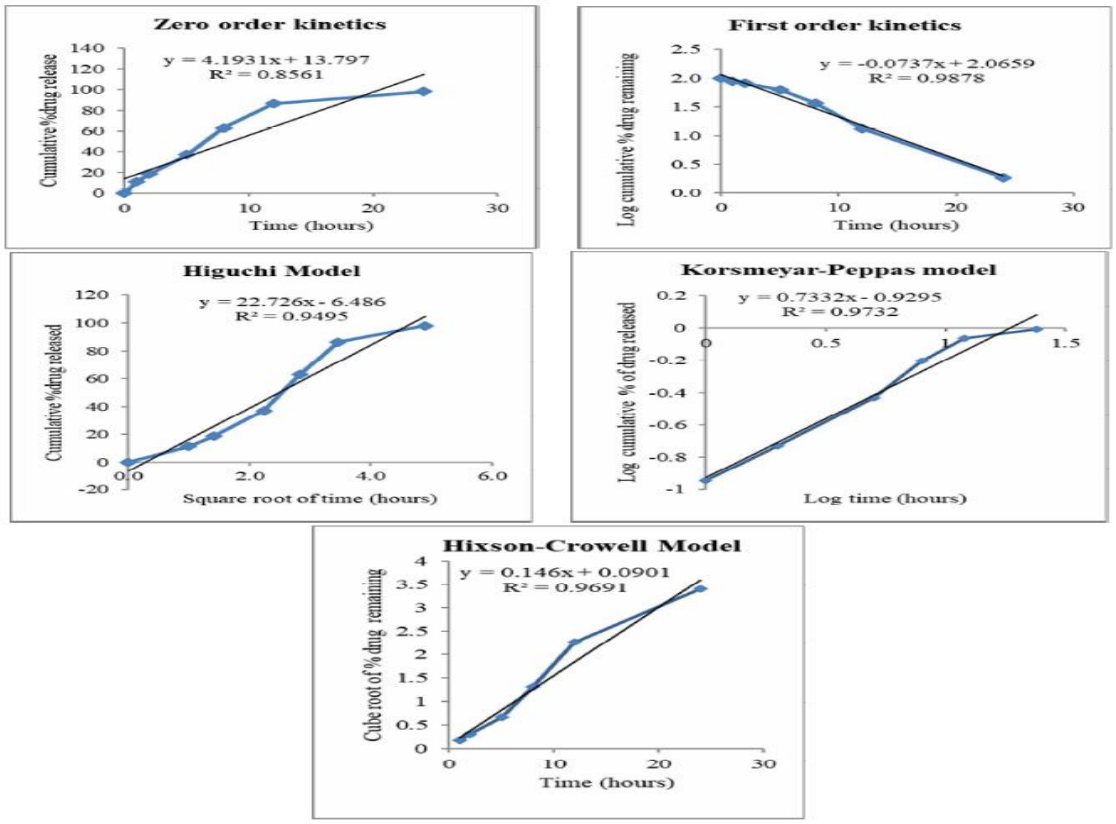

Figure 13: Drug release kinetics of Naproxen (sustained release) layer in bilayer table

Release kinetics

The data suggested that the release kinetics of the drugs Zolmitriptan and Naproxen follows first order drug release, as the values of regression coefficient obtained were highest for first order drug release profiles (R^2=0.94 and 0.99).

CONCLUSION

The present study demonstrated the successful formulation and evaluation of an anti-migraine and NSAIDS in a single dosage form as bilayer tablet. In the bilayer tablet, immediate release layer of Zolmitriptan was prepared by direct compression method using various super disintegrants in which optimized formula (F2) contains Crospovidone as super disintegrant and sustain release layer of Naproxen was prepared by wet granulation method using different release retarding agents in which optimized formula (C3) contains combination of Lactose Monohydrate and Carboxy Methyl Ethyl cellulose s release retardants. The drug excipient compatibility studies carried out using FTIR revealed that there was no interaction found between drugs and excipients. All the pre- and postcompression studies revealed that the results were found to be within the official limits. *In vitro* release studies reveal that Zolmitriptan immediate release layer in bilayer tablet was found to be 98.64±2.34% within 30 minutes and Naproxen sustained release layer was 96.47±0.05% at the end of 12 hrs. Release kinetics showed good linearity by best fitting in to first order kinetics and stability studies showed no changes after exposing to accelerated conditions for a period of 3 months with respect to physical characteristics and *in vitro* drug release studies.

From the above study, it can be concluded that the prepared bilayer tablets achieve the objective of the research work in treating the Migraine and arthritis with the sequential release of two drugs. As these tablets are supposed to be given twice a day which reduces the dosage frequency and are cost effective, it can be best alternative to conventional dosage forms having more frequency of administration.

REFERENCES

1. P. Mishra, P.K. Sharma, R. Malviya, A review on Bi-layer tablets-An emerging trend, J. Drug Deliv. Therapeut. 4 (4) (2014) 110–114.
2. S.S. Kale, V.S. Saste, P.L. Ughade, D.T. Baviskar, Bilayer tablet, Int. J. Pharmaceut. Sci. Rev. Res. 9 (1) (2011) 25–30.
3. D. Arun, N. VenuGopal, L. Shekar, A review of novel approach in bilayer tablet technology, Int. J. Pharam. Biol. Chem. Sci. 1 (1) (2012) 1–8.
4. M.A. Bhuiyan, I. Dewan, bilayer tablet technology: An Overview, 2014.
5. M.U. Din, S.M. Din, T.P. Shukla, An overview on bilayered tablet technology, Am.-Eurasian J. Sci. Res. 9 (1) (2014), 06-15.
6. J.A. Avbunudiogba, O.E. Cash-Torunarigha, I. Onah, Effect of humidity on the physical properties of aspirin tablets produced by melt granulation and slugging methods, J. Pharm. Biol. Sci. 7 (5) (2013) 20–25.

7. S.V. Rao, B. Priyanka, K. Padmalatha, Bilayer tablet technology: a novel approach, GSC Bio. Pharm. Sciences 7 (2) (2019), 022-028.
8. J.R. Robinson, V.H. Lee, Controlled Drug Delivery: Fundamentals andApplications/, in: Joseph R. Robinson, HL Lee Vincent (Eds.), Dekker, New York,1987.
9. L. Liu, X. Xu, Preparation of bilayer-core osmotic pump tablet by coating the indented core tablet, Int. J. Pharaam. 352 (1–2) (2008) 225–230.
10. A. Siswanto, A. Fudholi, A.K. Nugroho, S. Martono, In vitro release modeling of aspirin floating tablets using DDSolver, Indones. J. Pharm. 26 (2) (2015) 94.
11. Emma J. Seaber; Richard W. Peck; Deborah A. Smith; John Allanson; Nanco R. Hefting; Jan J. van Lier; Frans A.E. Sollie; Johan Wemer; Jan H.G. Jonkman (1998). "The absolute bioavailability and effect of food on the pharmacokinetics of zolmitriptan in healthy volunteers". British Journal of Clinical Pharmacology (abstract). 46 (5): 433–439.
12. Duggan KC, Walters MJ, Musee J, Harp JM, Kiefer JR, Oates JA, et al. (November 2010). "Molecular basis for cyclooxygenase inhibition by the non-steroidal anti-inflammatory drug naproxen". The Journal of Biological Chemistry. 285 (45): 34950–9.
13. Hinz B, Cheremina O, Besz D, Zlotnick S, Brune K (April 2008). "Impact of naproxen sodium at over-the-counter doses on cyclooxygenase isoforms in human volunteers". International Journal of Clinical Pharmacology and Therapeutics. 46 (4): 180–6.
14. CVS Subrahmanyam: Textbook of Physical Pharmaceutics. Vallabh Prakashan, Second Edition 2010.
15. Patrick J. Sinko: Martin's Physical Pharmacy and Pharmaceutical Sciences. Lippincott Williams & Wilkins, Fifth Edition; 337 – 432, 533 – 583.