FORMULATION AND EVALUATION OF BILAYER TABLET OF ANTI-INFLAMMATORY DRUG

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***Abstracts*- The present work is a formulation and evaluation of bi-layer tablet of Divalproex sodium, which is used in treatment of epilepsy, bipolar disorders and used in prophylaxis of migraine, was carried out.**
The formulation known as bi-layered tablet was developed with the aim to deliver the Divalproex sodium as immediate release and extent the drug release for 18 hours for the better and extended clinical effect. Compatibility studies by FTIR indicate that no significant interactions between excipients. Both layer were prepared by wet granulation and punched separately. Six formulations (IF1-IF6) of immediate release tablets were prepared by using sodium starch glycolate and croscarmellose sodium. Nine formulations (SF1-SF9) of sustained release were prepared by using HPMC K4M and HPMC K100M in different ration and combination. All formulations were evaluated for pre- compression and post-compression parameters. Bi-layered tablets were prepared by using selected best formulations of each layer. IF6 from immediate release layer as they showed 98.62 % drug release within 20 minutes. SF8 from sustained release layer as they showed 94.29 % drug release at 18 hours and also the release pattern was within the limit of sustained release tablet. Prepared bi-layered tablet were evaluated for post-compression paramaters. Drug excipient interaction was determined by FTIR. Short term stability studies of formulated bi-layered tablet were carried out at 400C / 75% RH for 3 months. The release kinetics of immediate release layer formulations (IF1-IF6) was found to following clearly first order kinetics as the values for ' r' is (0.985 to 0.960) and values of ' n' is more than 0.89 shown that Super case II transport. The release kinetics of sustained release layer (SF1-SF8) was found to following zero order kinetics as the value for ' r' is (0.9918 to 0.9736)found to be high in comparison to first order (0.8986 to 0.7303) and Higuchi's squareroot of time (0.9794 to 0.9074). ' n' values in between 0.6634 to 0.6064 shown non-fickian release and drug. Stability studies at 40 0C / 75 % RH for 3 months for bi-layered tablet batches indicated that there are no significant loss in drug content, release profile and physical appearance. In summary, the release profiles bi-layered tablet formulations were quite promising for once a day formulation

***Key Words*: formulation and evaluation, Tablet , Anti-inflammatory.**

INTRODUCTION

Oral route is most commonly employed route of drug administration. Although different route of administration are used for the delivery of drugs, due to flexibility in dosage form design and patient compliance oral route is preferred1. The popularity of the oral route is attributed ease of administration, patient acceptance, accurate dosing, cost effective manufacturing method and generally improved shelf-life of the product.

There are several techniques of conventional drug delivery system where tablets, capsules, pills, liquids, are used as drug carrier. Among them, solid formulation do not require sterile conditions and are therefore, less expensive to manufacture.

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. Tablets are solid dosage forms containing medicinal substances with or without suitable diluents5. According to Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents

PLAN OF WORK

1. Literature survey
2. Collection of drug, polymers & other excipients
3. Formulation developments

Pre-formulation study
Determination of melting Solubility
Determination of λmax
Standardization of drug
Compatibility study

- Formulation design
- Compression and evaluation of SRL and IRL
- Selection of best formulation of SRL and IRL
- Compression of bi-layered tablet from selected formulation
- Evaluation of bi-layered tablet

MATERIALS AND METHOD

List of materials

Sl No.	Ingredients	Company Name
1.	Divalproex sodium	Gift sample from ROAQ Chemicals Pvt. Ltd. Vadodara
2.	Sodium Starch Glycolate	S.D. Fine Chem. Ltd, Mumbai
3.	Croscarmellose	S.D. Fine Chem. Ltd, Mumbai
4.	HPMC K4M	Yarrow Chem Products, Mumbai
5.	HPMC K100M	Yarrow Chem Products, Mumbai
6.	Lactose	S.D. Fine Chem. Ltd, Mumbai
7.	Micro Crystalline Cellulose	S.D. Fine Chem. Ltd, Mumbai
8.	PVP K 30	S.D. Fine Chem. Ltd, Mumbai
9.	Ponceau 4R	Indian fine chemicals, Mumbai-20
10.	Magnesium Stearate	S.D. Fine Chem. Ltd, Mumbai
11.	Talc	S.D. Fine Chem. Ltd, Mumbai

List of Equipment

Sl No.	Equipment	Model/company
1.	Fourier Transform Infrared spectrophotometer	Thermo Nicolet
2.	UV-Visible spectrophotometer	UV-1800, Shimadzu
3.	Electronic balance	Teraoke
4.	Hot air oven	Kemi
5.	Multi tablet Punching machine	LAB PRESS, CipMachinaries Ltd. Ahmedabad
6.	Roche Friabilator	PSM Industries, Bangalore
7.	Hardness tester	Monsanto hardness tester
8.	Disintegration test apparatus	DT-1500, Lab India

9.	Dissolution test apparatus	DS-800, Lab India
10.	FTIR- spectrophotometer	Tensor 27 Bruker
11.	DSC Apparatus	DSC-60, Shimadzu
12.	Stability chamber	106 Model/ LabTop, Sky Lab Instruments & Engineering Pvt.Ltd.

PRE-FORMULATION STUDIES

Pre-formulation testing is the first step in rational development of dosage forms of a drug substance. Pre-formulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the excipients that could affect drug performance and development of as efficacious, stable and safe dosage form. It provides a framework for the drug combination with pharmaceutical excipients in the dosage form.

Determination of λ 74max

Divalproex sodium was dissolved in methanol further diluted with the same and scanned for maximum absorbance in UV double beam spectrophotometer (Shimadzu 1800) in the range from 190 to 380 nm.

Solubility

The solubility of Divalproex sodium was determined in distilled water, methanol, ethanol, acetone, chloroform and pH 6.8 phosphate buffer by shake flask method. An excess amount of Divalproex sodium is added to each vial containing 10 ml of selected solvent till the saturation of the solution. The mixtures were subjected to the mechanical agitation for 48 hours in isothermal shaker at 250C ± 10C followed by filtration through watmann's filter paper. Absorbance is measured by UV-Visible Spectrophotometer. The drug content is calculated by using the standard graph.

Melting point

Melting point of the Divalproex sodium was determined by capillary method in triplicate.

Standard Curve for Divalproex sodium74

100 mg of Divalproex sodium was accurately weighted and dissolved in 100 ml of methanol to prepare first stock solution. 10 ml of above solution was taken and diluted to 100 ml with the same solvent to prepare II stock solution. The aliquot amount of II stock solution was further

diluted to get 5, 10, 15, 20, 25 and 30 of drug per ml of the final solution. Then the absorbance

was measured in a UV spectrophotometer at 210 nm against methanol blank.

Compatibility studies

The compatibility studies of the drug with polymers are studies using FT-IR spectroscopy.

- FT-IR Spectroscopy

FT-IR spectroscopy was carried out to check the compatibility between drug and excipients. Infrared spectroscopy was conducted using s thermo Nicolet FTIR and the spectrum was recorded in the region of 4000 to 400 cm-1. The sample (drug and drug-excipient mixture in 1:1 ratio) in KBr (200-400mg) was compressed in to discs by applying a pressure of 5 tons for 5 min in hydraulic press. The interaction between drug-excipients was observed from IR-spectral studies by observing any shift in peaks of drug in the spectrum of physical mixture of drug- excipients.

- DSC Analysis for formulation

Thermal properties of the pure drug and the physical mixture of drug and excipients were analyzed by Different Scanning Calorimeter -60, Shimadzu limited Japan. The samples were heated in a thermetically sealed aluminium pans. Heat runs for each sample were set from 25 to 3500C at a heating rate of 100C/min, using nitrogen as blanket gas.

Formulation Design

Calculation of dose

The total dose of Divalproex sodium for once daily formulation was calculated by the following equation, using available pharmacological data.

Dt = Dose (1+0.693xt/t1/2)

Where, Dt = Total dose of drug,

Dose = Dose of immediate release part.

t = time in hr during which the sustained release is desired (18 hrs) t1/2 = half life of the drug (9 hrs)

Therefore,

Dt = 125(1+0.693x18/9), Dt ≈ 298.25

Therefore maintenance dose = 298.25-125 = 173.25 mg.

Hence, the formulation should release 125 mg drug within 1 hour and 173.25 mg drug in 18 hours.

A) Formulation of Immediate release layer.

Formulation of immediate release layer (IRL)

Sl. No.	Ingredients	IF1	IF2	IF3	IF4	IF5	IF6
1	Divalproex sodium	125	125	125	125	125	125
2	Lactose	82	79.5	82	79.5	82	79.5
3	Croscarmellose sodium	10	12.5	–	–	5	6.25
4	Sodium starch glycolate	–	–	10	12.5	5	6.25
5	Microcrystalline cellulose	25	25	25	25	25	25
6	Ponceau 4R	0.02	0.02	0.02	0.02	0.02	0.02
7	Magnesium stearate	3	3	3	3	3	3
8	Talc	5	5	5	5	5	5
9	Total	250	250	250	250	250	250

B) Formulation of sustained released layer.

Formulation of sustained release layer (SRL)

Sl. No.	Ingredients	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9
1	Divalproex sodium	173.25	173.25	173.25	173.25	173.25	173.25	173.25	173.25	173.25
2	Lactose	52.75	45.25	37.75	52.75	45.25	37.75	52.75	45.25	37.75
3	HPMC K4M	45	52.5	60	–	–	–	22.5	26.25	30
4	HPMC K100M	–	–	–	45	52.5	60	22.5	26.25	30
5	Microcrystalline cellulose	20	20	20	20	20	20	20	20	20
6	Magnesium stearate	3	3	3	3	3	3	3	3	3
7	Talc	6	6	6	6	6	6	6	6	6
8	Total	300	300	300	300	300	300	300	300	300

Preparation of IRL

IRL of Divalproex sodium (DS) was prepared by wet granulation by using different Superdisintegrants such as SSG and Croscarmellose sodium. PVP K30 solution with containing coloring agent was used as binding solution. As DS was oily in characteristics, MCC was used as adsorbent. Manufacturing steps-

- Pass all the ingredients though sieve #80.
- Mix Divalproex sodium with MCC geometrically and then mix with lactose. Add Superdisintegrants and mix for 10 to 15 min in mortar and pestle.
- Make wet mass using binding agent PVP K 30 solution containing color.
- Pass the cohesive mass through sieve # 16 to get uniform granules.
- Dry the granules at 500C for 15 min in hot air oven.
- Lubricate the granules with lubricating agent and compressed into 250 mg each tablet weight by adjusting hardness. The formulations are shown on table no 13.

Preparation of SRL

Accurately weighed Divalproex sodium and polymer and others ingredients were taken in mortar and pestle and mixed well. The powder were mixed with sufficient quantity for PVP K30 solution until wet mass formed. The cohesive mass obtained was passed though sieve # 16 and the granules were dried in a hot air oven at 500C for 20 min. The dried granules again passed through sieve # 22 to break the large lumps. Then granules were mixed with talc and magnesium stearate and compressed into 300 mg each tablet by adjusting hardness. The formulations.

Preparation of bi-layered tablet

By the study of disintegration and drug release profile of IRL and SRL, best formulations of each layer were chosen and bi-layered tablet were prepared by double compression in single rotatory tableting machine.

Evaluation of Pre-formulation Parameters:

Angle of Repose:

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel greely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using equation.

$\theta = \tan^{-1}$

Where, θ = the angle of repose

h = height of the heap of the powder r = radius of the heap of the powder

ANGLE OF REPOSE

Sl.No	Angle of Repose(θ)	Type of flow
1	< 25	Excellent
2	25-30	Good
3	30-40	Passable
4	> 40	Very poor

Determination of bulk density and tapped density:

A quantity of 2 g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using following formulas.

Carr' s index:

It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by

$$\text{Carr's index \%} = \frac{\text{Tapped density}}{\text{Tapped density}} \times 100$$

% COMPRESSIBILITY INDEX

Sl.No	% Compressibility index	Property
1	5-12	Free flowing
2	12-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	> 40	Extremely poor

Hausner' s ratio:

Hausner's ratio is a indirect index of ease of powder flow. Hausner's ratio was measured by the ratio of tapped density to bulk density.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

HAUSNER'S RATIO

Sl.No.	Hausner' s ratio	Property
1.	0-1.2	Free flowing
2.	1.2-1.6	Cohesive flowing

Evaluation of prepared formulations

Evaluation of Divalproex sodium IRL, SRL and bi-layered tablet

The tablets prepared were evaluated for the following parameters:

Weight variation
Hardness
Friability
Drug content
Dissolution Studies
Stability Studies
Weight Variation Test:

To study weight variation, 20 tablets of each formulation were weighted using electronic balance and the test was performed according to the official method

IP standards of Uniformity of weight

S.N.	Avg. Wt of Tablet (mg)	% of Deviation
1	≤80 mg	10
2	> 80 mg – 250 mg	7.5
3	≥250 mg	5

Hardness:

The resistance of tablets to shipping or breakage under condition of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in the terms of kg/cm2 . 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

Friability:

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. 10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded.

Percentage friability was calculated by using the formula.

$$\% \text{ Friability} = \frac{Weight\ initial - Weight\ final}{Weight\ initial} \times 100$$

Tablet thickness:

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation. Vernier caliper consists of metric and imperial scales. The main matric scale is read first then

read " hundredths of mm" of imperial scale (count the number of division until the lines concedes with the main metric scale. The imperial scale number is multiply with 0.02. Then that number obtained from imperial scale added with main metric scale to get final measurement.

dissolution studies of immediate release layer:

The in-vitro dissolution studies were performed using USP-II (paddle) dissolution apparatus at 100 rpm. Phosphate buffer pH 6.8 dissolution media is maintained at 37± 0.500C. A 5 ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. The withdrawn samples were diluted with pH 6.8, filtered and analyzed on UV spectrophotometer at 210 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

dissolution studies of sustained release layer:

The in vitro release of sustained release layer was carried out for 18 hours using

USP type-II apparatus (DT-1200) at 100 rpm for the first 45 minute in 900 ml 0.1N HCL maintaining at 37 ±0.50C and then at phosphate buffer pH 6.8 in 900ml for another 18 hour. A 5 ml was withdrawn at different time intervals and replaced with an equal volume of fresh medium. The samples were suitably diluted with blank dissolution medium, filtered and analyzed on UV spectrophotometer at 210nm.

Drug Content for IRF, SRF and Bi-layered tablet:

Ten tablets were weight and average weight is calculated. All tablets were crushed and powder equivalent to 100 mg drug was dissolved in pH 6.8 phosphate buffer and the volume was made up to 100 ml with pH 6.8 phosphate buffer. The solution was kept in sonicator for 1 hr. From the stock solution, 1ml solution was taken in 10 ml volumetric flask and the volume was made with pH6.8 phosphate buffer. Solution was filtered and absorbance was measured

Spectrophotometrically at 210 nm against pH6.8 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

Mathematical modeling of drug release profile:

The cumulative amount of Divalproex sodium release from the formulated tablets at different time intervals were fitted to Zero order kinetics, first order kinetics, higuchi model and korsmeyer-peppas model to characterize mechanism of drug release.

1. Zero-order Kinetic model – Cumulative %drug release versus Time.

2. First-order Kenetic medel – Log cumulative % drug remaining versus Time.
3. Higuchi's model – cumulative percent drug released versus square root of time.
4. Nordmeyer equation / peppa' s medel- Log cumulative percent drug released versus log time.

Zero order kinetic

It describes the system in which the release rate is independent of its concentration

. Qt=Q0 + K0t

Where, Qt = amount of drug dissolved in time t

Q0 = initial amount of drug in the solution

K0 = zero order release constant

If the zero order drug release kinetic is obeyed, a plot of Qt versus t will give straight line with a slope of K0 and an intercept at Q0.

First Order Kinetic

It describes the drug release from the system in which the release rate is concentration dependent.

Log Qt = logQ0 + K1t/2.303

Where Qt = amount of drug dissolved in time

Q0 = initial amount of drug in the solution

K1 = first order release constant

If the release pattern of drug follows first order kinetics, then a plot of log (Q0 – Qt) versus t will be straight line with a slope of K1 /2.303 and an intercept at t= 0 of logQ0. Higuchi' s Model

It describes the fraction of drug release from a matrix is proportional to square root of

time. Mt / M∞ = KHt1/2

Where,

Mt and M∞ are cumulative amount of drug release at time t and infinite

time, and KH = Higuchi dissolution constant reflection formulation characteeistics.

If the Higuchi model of drug release is obeyed, then a plot of Mt /M∞ versus t1/2 will be

straight line with slope of KH.

The power law describes the fractional drug release is exponentially related to the release rime and adequately describes the release of drug from slabs, cylinders and spheres, as expressed in following equation.

Mt / M∞ = K tn

Log (Mt / M∞) = log K + n log t

Table 19: Mechanism of Drug Release as per Korsmeyer Equation/ Peppa' s Model

Sl. No	' n' value	Drug release
1	0.45	Fickian release
2	0.45 <n> 0.89	Non-Fickian release
3	0.89	Case II transport
4	Higher than 0.89	Super case II transport

Stability Studies

The optimized formulation was subjected for two month stability study according to standard guidelines. The selected formulations were packed in aluminum foils, which were in wide mouth bottles closed tightly. They were stored at 400C / 75% RH for 3 months and evaluated periodically.

RESULTS

Determination of λmax

The λmax of Divalproex sodium was found to be 210 nm in methanol and phosphate buffer pH 6.8.

5.1 Standard curve of Divalproex sodium.

The absorbance was measured in a UV spectrophotometer at 210 nm against methanol.

Spectrophotometric data of Divalproex Sodium

S.no.	Conc. (µg/ml)	Absorbance			Mean ±SD
		Trial 1	Trial 2	Trial 3	
1	0	0.000	0.000	0.000	0.000±0.000
2	5	0.050	0.043	0.046	0.046±0.004
3	10	0.097	0.095	0.098	0.097±0.002
4	15	0.143	0.144	0.146	0.144±0.002
5	20	0.185	0.188	0.187	0.187±0.002

6	25	0.240	0.237	0.237	0.238±0.002

Drug solubility studies

The solubility studies of drug were done by using various media like distilled water, methanol, and chloroform and phosphate buffer pH 6.8. The data for solubility studies in those media The result shows maximum solubility in chloroform.

Solubility of Divalproex sodium

Solvent s	Solubility (mg/ml)
Distilled water	7.35
Methanol	48.4 5
Chloroform	55.2 4
Phosphate buffer pH 6.8	29.7 3

Result showed that Divalproex sodium is more soluble in chloroform in compare to other solvents.

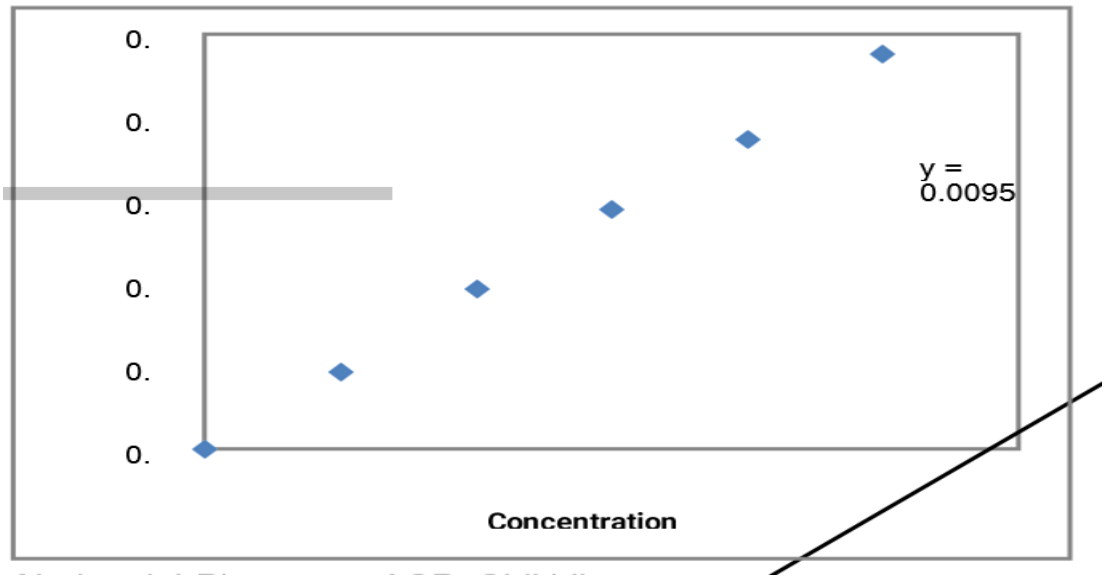
Melting Point

Melting point of drug was determined by capillary method. The result is found to be 219-2230C.

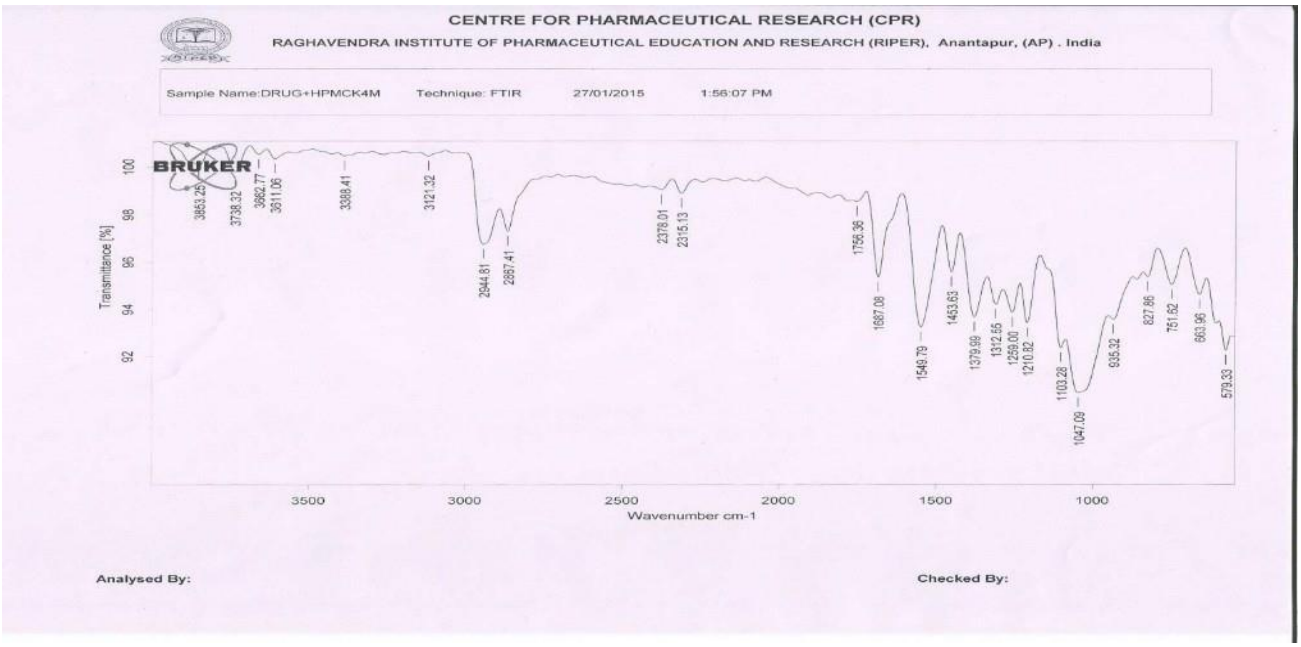
FT-IR spectrum

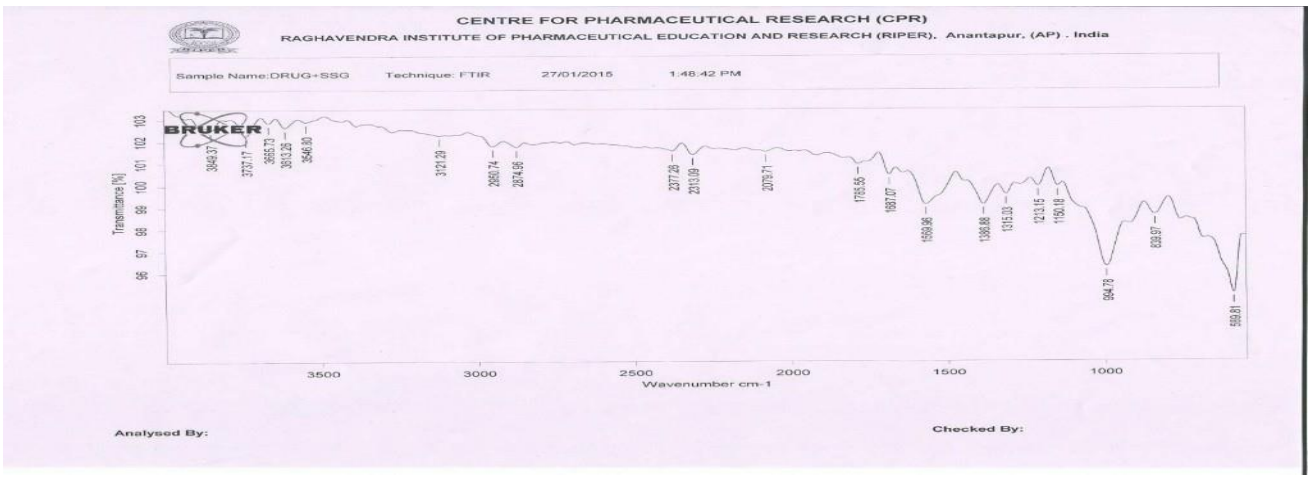
FT-IR spectrum of pure drug Divalproex sodium and combination of drug with polymers were obtained. All the characteristic peaks of Divalproex sodium were present in spectrum of drug and polymer mixture, indicating compatibility between drug and polymers. The entire FT-IR spectrum and was tabulated.

FTIR figure of Drug and Drug with excipients

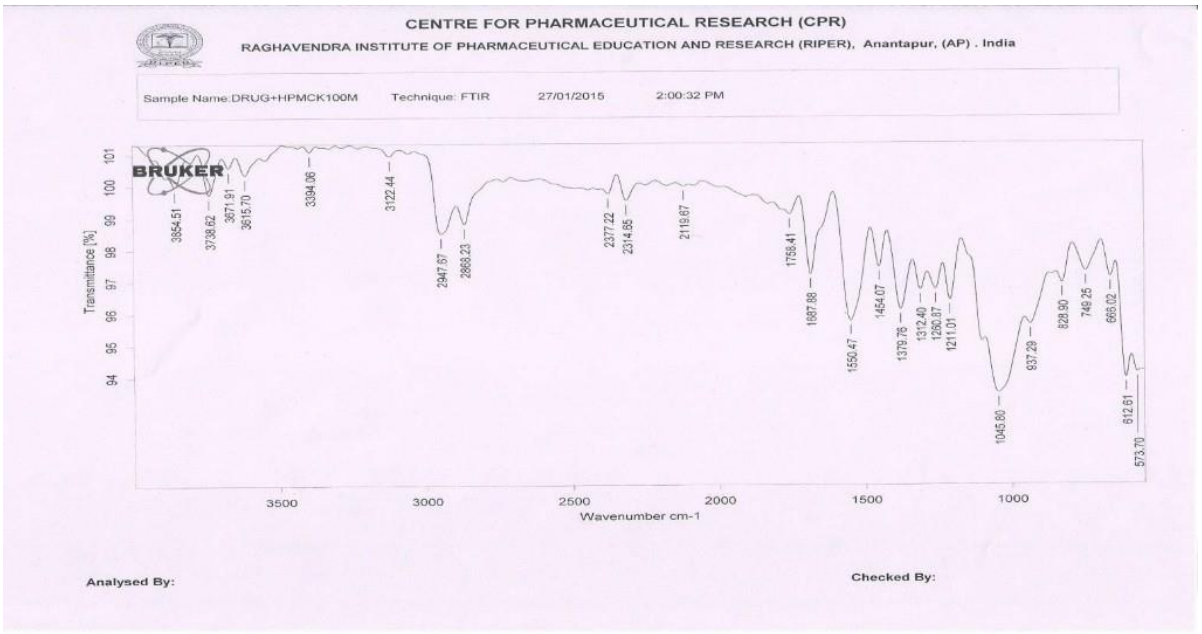


FTIR of Divalproex sodium + Corscarmellose sodium

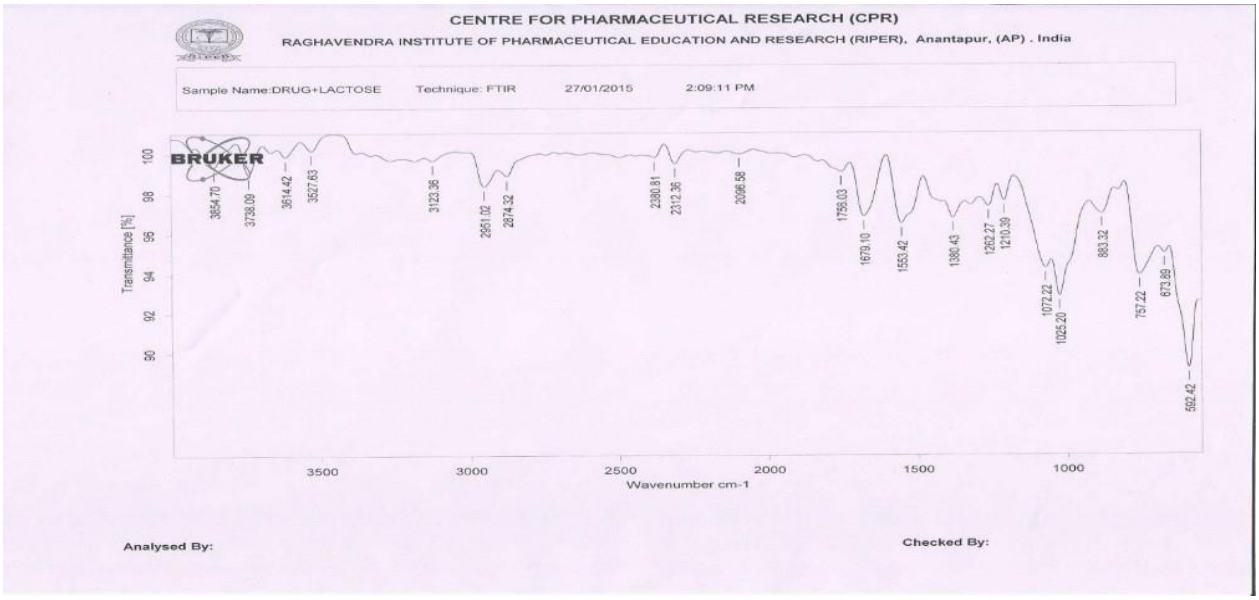




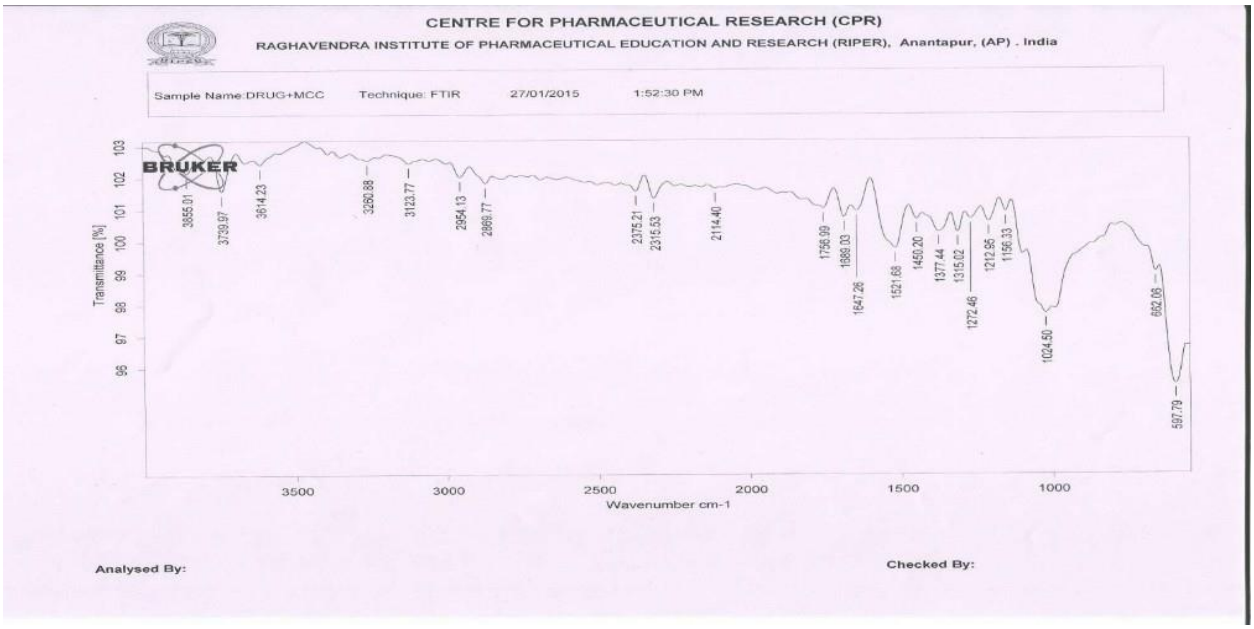
FTIR of Divalproex sodium + HPMC K4M



FTIR of Divalproex sodium + HPMC K100M



FTIR of Divalproex sodium + Lactose



FTIR of Divalproex sodium + Microcrystalline Cellulose (MCC)

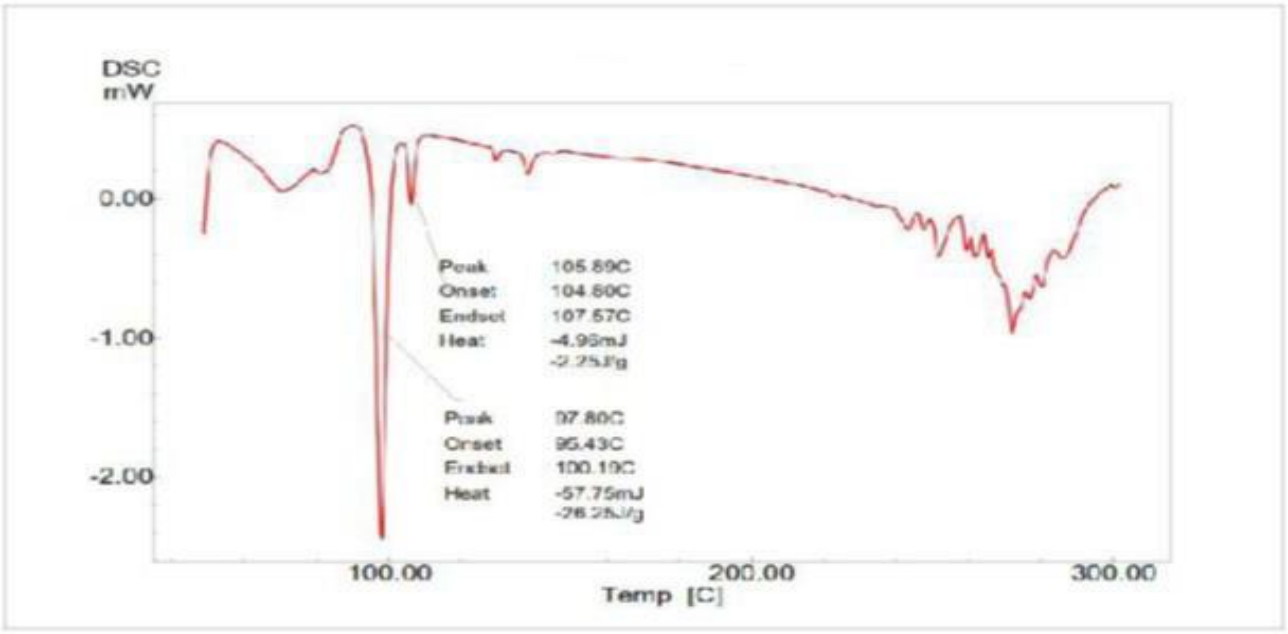
Compatibility study of drug and excipients using FTIR

Functional group	Wave number (cm^{-1})							
	Standard peaks	Pure drug	SSG	Croscarmel ose	HPMC K4M	HPMC K100M	lactose	MCC
Aliphatic C-H stretch	3300-2500	2919.4	2950.74	2950.80	2944.81	2947.67	2951.02	2954.13
C-H bend	1470-1450	1455	1386.88	1372.74	1453.63	1454.07	1380.43	1450.20
C-H stretch	1300-1000	1211	1213.15	1210.95	1210.28	1211.01	1210.39	1212.95

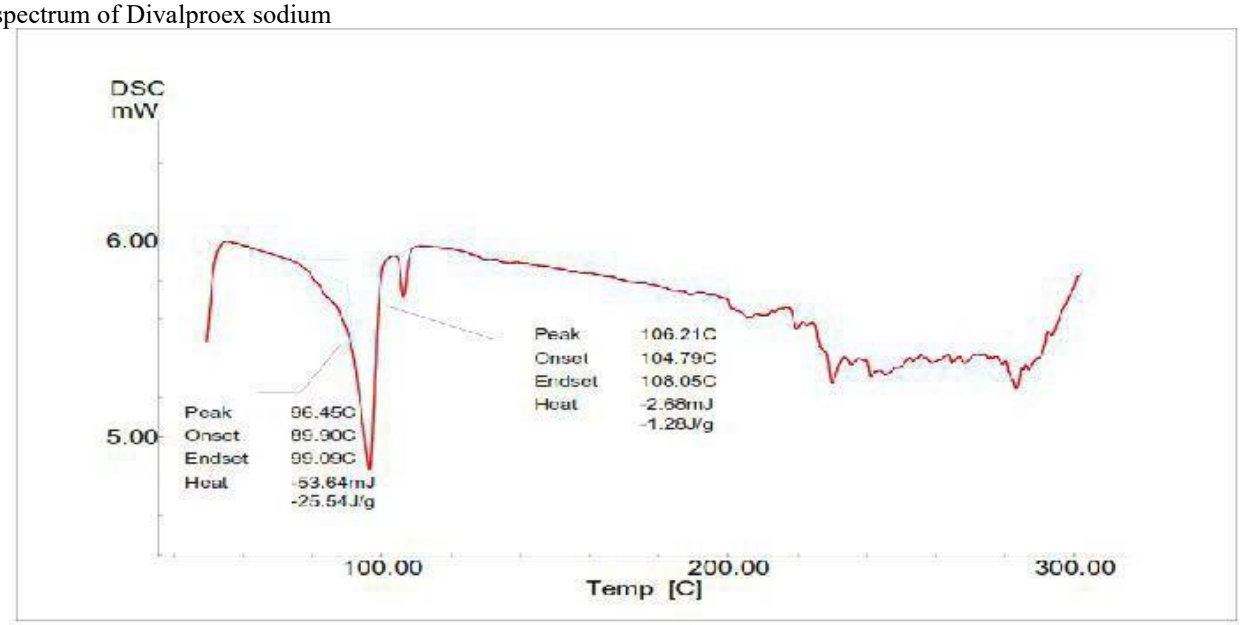
Carboxylic acid	3100-3300	3119.41	3121.29	3277.37	3121.32	3122.44	3123.36	3123.77
O-H bend		1059.94	994.78	1040.53	1047.09	1045.80	1025.20	1024.50

DSC Study

DSC Analysis



DSC spectrum of Divalproex sodium



EVALUATION OF PRE-COMPRESSION PARAMETERS

Pre-compression parameters for IRL and SRL

Formulation	Bulk Density Mean ± SD	Tapped Density Mean ± SD	Car's Index Mean ± SD	Haunsers Index Mean ± SD	Angle of Repose Mean ± SD
IF1	0.557±0.002	0.637± 0.005	12.610± 0.217	1.145± 0.030	16.596± 0.356
IF2	0.556±0.005	0.655± 0.004	15.084± 0.226	1.174± 0.020	18.360± 0.275

IF3	0.523±0.004	0.626± 0.003	15.773± 0.109	1.164± 0.022	19.421± 0.173
IF4	0.585±0.003	0.684± 0.003	13.899± 0.177	1.163± 0.013	20.147± 0.156
IF5	0.612±0.010	0.682± 0.007	11.767± 0.206	1.133± 0.009	17.913± 0.039
IF6	0.666±0.004	0.755± 0.006	11.148± 0.157	1.142± 0.025	17.101± 0.077
SF1	0.592±0.005	0.694± 0.003	13.779± 0.206	1.154± 0.009	19.604± 0.279
SF2	0.591±0.008	0.699± 0.002	14.494± 0.328	1.169± 0.017	18.480± 0.063
SF3	0.605±0.004	0.681± 0.003	11.223± 0.186	1.133± 0.009	18.201± 0.088
SF4	0.623±0.005	0.703± 0.002	11.531± 0.127	1.132± 0.010	22.548± 0.280
SF5	0.596±0.004	0.710± 0.004	16.144± 0.249	1.200± 0.028	18.331± 0.077
SF6	0.591±0.004	0.727± 0.002	18.716± 0.397	1.256± 0.029	18.168± 0.104
SF7	0.615±0.003	0.728± 0.004	14.825± 0.673	1.174± 0.028	18.467± 0.091
SF8	0.512±0.001	0.623± 0.002	17.564± 0.436	1.243± 0.024	19.347± 0.072
SF9	0.620±0.002	0.693± 0.001	10.754± 0.181	1.124± 0.017	17.396± 0.021

POST-COMPRESSION EVALUATION PARAMETERS:

Post-compression parameters for IRL and SRL

Batch code	Weight variation Mean ± SD	Hardness (kg/cm2) Mean ± SD	Friability (%) Mean ± SD	Thickness Mean ± SD	Drug content(%) Mean ± SD	disintegration time (sec) Mean ± SD
IF1	249.9±1.57	5.95±0.05	0.74±0.09	2.87±0.04	98.12± 1.19	120.33± 1.52
IF2	250.3±1.60	4.18±0.10	0.58±0.04	2.91±0.10	97.65± 1.82	91.66±2.08
IF3	250.9±1.60	6.35±0.03	0.56±0.06	2.90±0.07	98.65± 1.28	73.33±2.51
IF4	251.55±1.99	6.17±0.07	0.65±0.05	2.87±0.03	99.61± 0.94	48.33±3.05
IF5	251.45±2.52	4.14±0.04	0.63±0.03	2.92±0.06	99.43± 1.32	59.33±2.08
IF6	250.05±1.81	4.53±0.11	0.69±0.04	2.89±0.09	99.51± 1.81	37.33±1.52
SF1	302.6±1.41	5.38±0.10	0.32±0.06	3.34±0.09	99.38± 1.19	
SF2	302.9±2.29	4.33±0.02	0.35±0.02	3.30±0.14	98.61± 1.03	
SF3	302.5±1.59	6.14±0.04	0.43±0.03	3.31±0.03	97.43± 1.28	
SF4	301.75±1.14	6.23±0.06	0.36±0.02	3.28±0.05	98.57± 0.85	
SF5	300.65±1.37	5.14±0.03	0.41±0.06	3.30±0.06	98.43± 1.27	
SF6	302.30±1.31	4.52±0.02	0.48±0.03	3.33±0.03	97.63± 0.61	
SF7	303.20±1.46	6.74±0.04	0.42±0.06	3.28±0.08	99.47± 1.04	
SF8	301.25±1.55	6.16±0.02	0.37±0.04	3.30±0.04	99.51± 1.20	

SF9	302.42±1.04	6.56±0.03	0.31±0.03	3.32±0.07	98.49± 0.93	

Post-compression parameters for bi-layered tablet

Formulation	Weight variation Mean ± SD	Hardness Mean ± SD	Friability Mean ± SD	Thickness Mean ± SD	Drug content (%) Mean ± SD
BTF	550.75±0.46	7.05±0.15	0.38±0.01	6.28±0.14	99.23±0.53

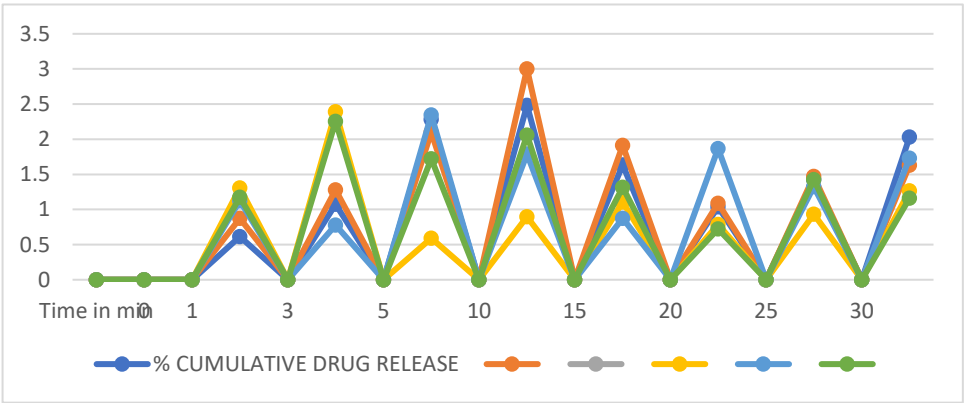
In-vitro dissolution study

In-vitro dissolution study of IRL

Time in min	% CUMULATIVE DRUG RELEASE					
	IF1	IF2	IF3	IF4	IF5	IF6
0	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
1	17.056± 0.612	21.226± 0.872	20.847±0.450	26.532± 1.306	30.323± 1.125	36.008± 1.174
3	31.805± 1.075	31.908± 1.280	33.738±2.620	54.965± 2.391	56.561± 0.778	60.653± 2.255
5	53.454± 2.280	56.489± 2.100	56.488±1.288	68.244± 0.593	64.455± 2.346	68.247± 1.723
10	64.837± 2.481	68.251± 3.001	68.250±1.176	81.525± 0.896	77.735± 1.791	83.424± 2.060
15	71.106± 1.634	78.121± 1.913	74.141±1.523	89.829± 1.107	81.543± 0.873	92.918± 1.314
20	80.408± 1.038	83.445± 1.088	82.685±0.582	94.829± 0.788	87.246± 1.865	98.624± 0.722
25	86.676± 1.427	92.366± 1.472	90.280±1.281	97.497± 0.931	92.376± 1.325	98.827± 1.427
30	91.047± 2.031	94.842± 1.632	93.135±0.852	98.075± 1.265	96.743± 1.731	99.404± 1.162

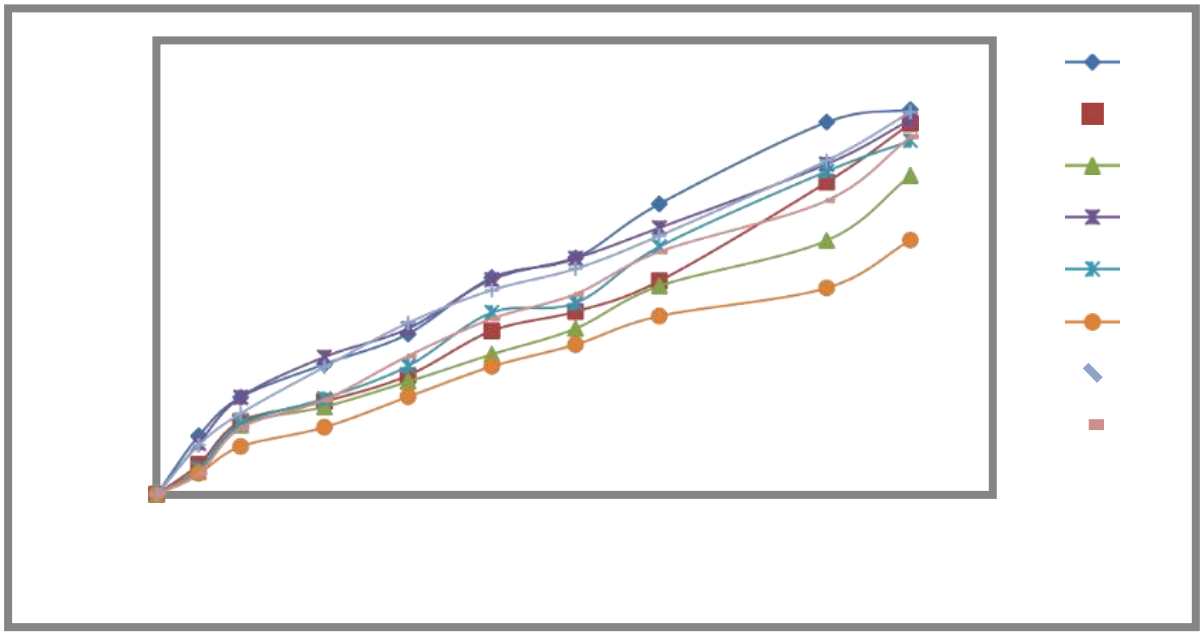
Release profile of immediate release layer

In-vitro dissolution study of SRL



Time in min	% CUMULATIVE DRUG RELEASE							
	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8
0	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000

60	15.408±1.222	7.905±1.234	6.017±1.508	13.469±1.222	6.741±1.281	5.558±1.591	13.006±1.994	5.391±0.882
120	25.634±1.764	19.263±1.532	18.231±1.281	25.637±0.732	18.521±1.421	12.635±0.751	21.351±1.317	17.527±1.114
240	34.323±2.715	24.502±1.083	23.091±1.547	33.235±1.164	25.279±1.003	17.697±1.151	33.589±1.503	24.917±1.426
360	42.342±0.632	31.362±1.321	29.735±0.941	38.852±1.521	33.852±1.835	25.742±1.427	45.247±0.941	36.518±0.831
480	57.151±1.196	43.141±1.974	36.936±1.251	56.674±2.061	47.993±0.539	33.733±2.378	53.869±1.510	46.331±0.891
600	62.342±0.412	48.234±0.826	43.752±1.423	62.316±1.839	50.491±0.694	39.513±1.114	59.523±1.163	52.852±0.792
720	76.620±1.642	56.263±2.227	54.964±2.137	70.315±2.001	65.327±1.779	47.031±1.480	68.215±0.906	64.017±0.710
960	98.183±0.352	82.430±1.267	66.957±1.402	87.123±0.645	86.182±0.467	54.439±2.565	88.053±0.676	77.498±0.918
1080	101.512±1.093	97.816±0.630	84.113±1.317	98.822±1.325	97.692±0.844	67.057±1.191	100.859±2.165	94.298±0.560



Release profile of sustained release layer Dissolution study of Bi-layered

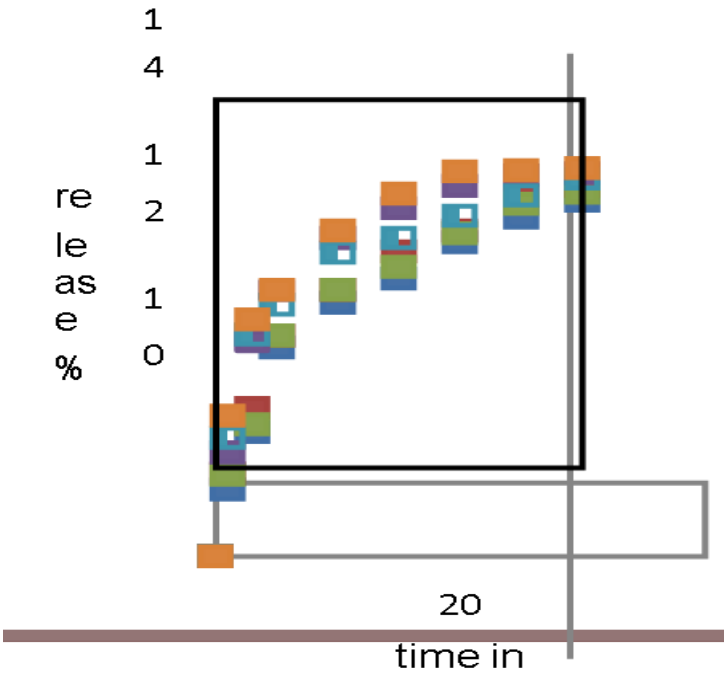
Kinetic Release

I. For immediate release tablets

Kinetic release for IRL

FORMULATION CODE	KINETIC MODELS				
	Zero Order R2	First Order R2	Higuchi R2	Korsmeyer n	R2
IF1	0.8362	0.9816	0.9689	0.8915	0.6657
IF2	0.8228	0.9844	0.9677	0.8694	0.6263
IF3	0.8231	0.9819	0.9643	0.8711	0.6336
IF4	0.7068	0.9850	0.9059	0.8424	0.5642
IF5	0.7101	0.9606	0.9055	0.804	0.5134

IF6	0.6835	0.9792	0.8945	0.803	0.5129



Zero order Kinetics for IRL

Kinetic Release
For immediate release tablets
Kinetic release for IRL

FORMULATION CODE	KINETIC MODELS				
	Zero Order R2	First Order R2	Higuchi R2	Korsmeyer n	R2
IF1	0.8362	0.9816	0.9689	0.8915	0.6657
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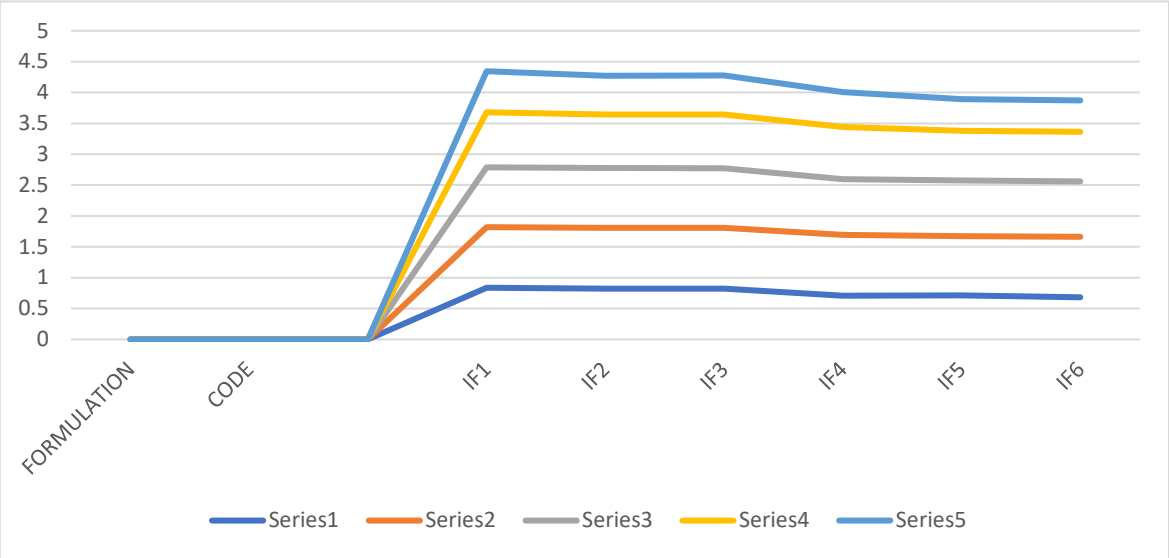
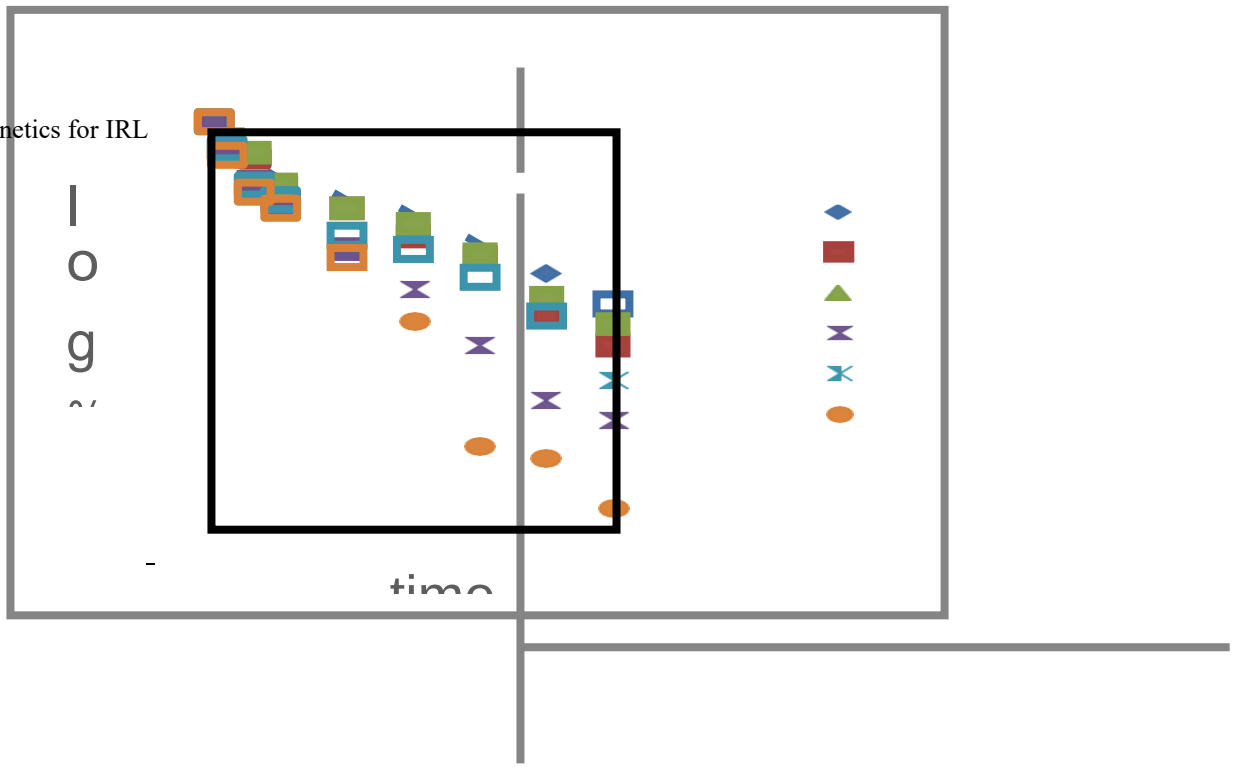
IF4	0.7068	0.9850	0.9059	0.8424	0.5642
IF5	0.7101	0.9606	0.9055	0.804	0.5134
IF6	0.6835	0.9792	0.8945	0.8034	0.5129



Zero order Kinetics for IRL

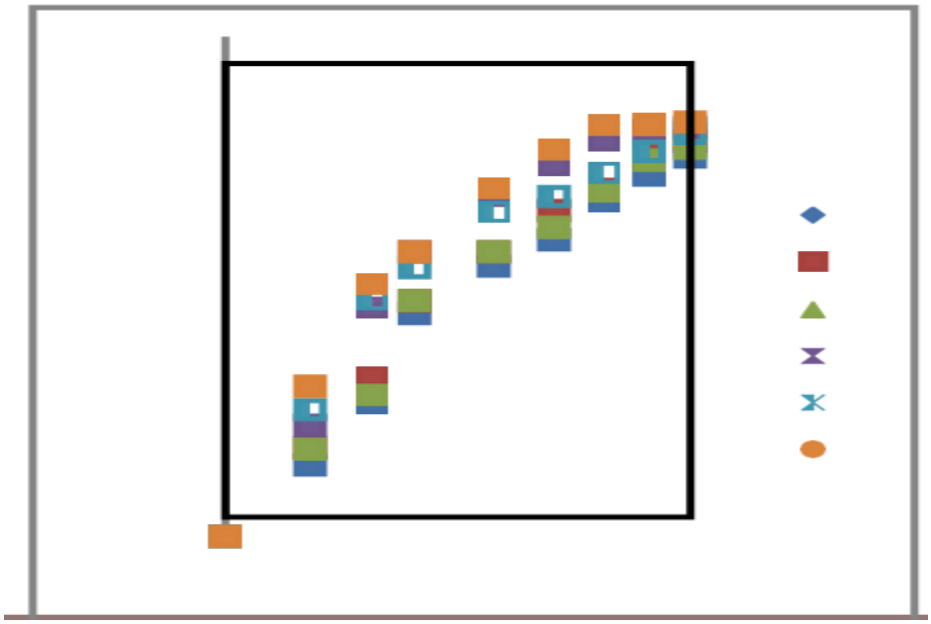
Zero order Kinetics for IRL

First order Kinetics for IRL

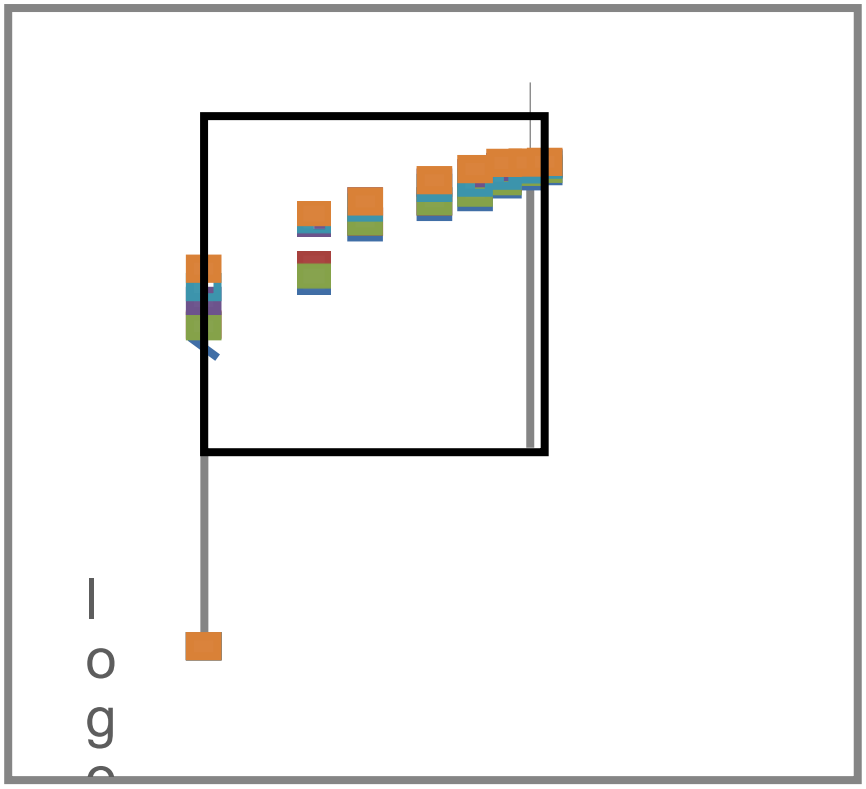


First order kinetics for IRL

Higuchi release kinetics for IRL



Korsemeyer-peppas release Kinetics of IRL



Korsemeyer-peppas release Kinetics for IRL

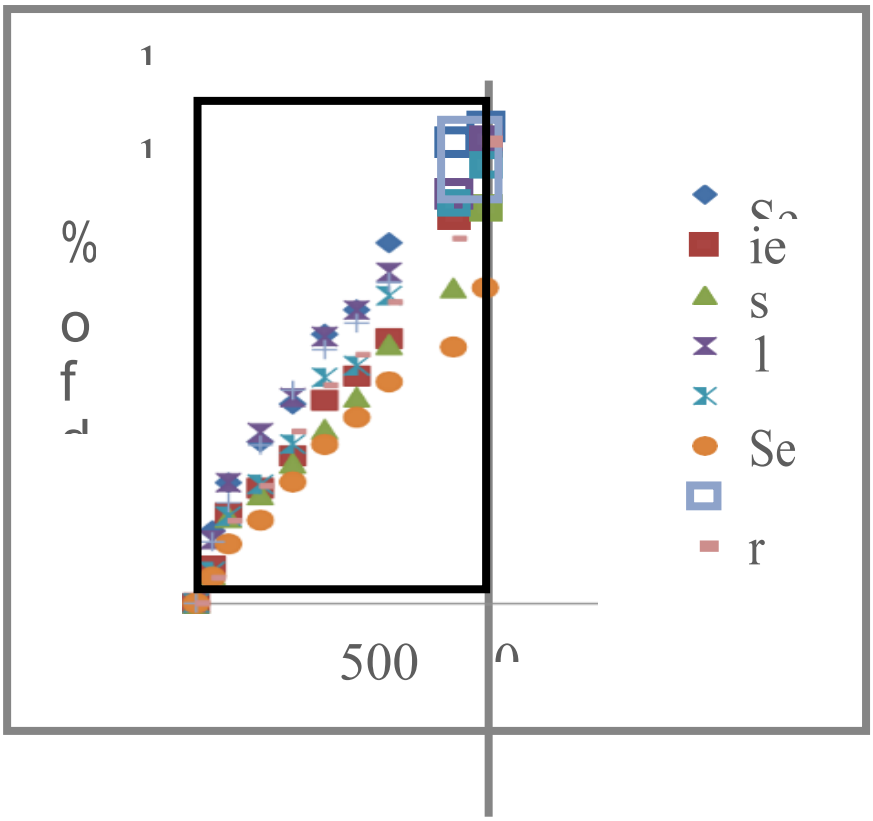
For sustained release layer

Kinetic release for SRL

FORMULATION CODE	KINETIC MODELS			
	Zero order R2	First order R2	Higuchi R2	Korsmeyer n R2

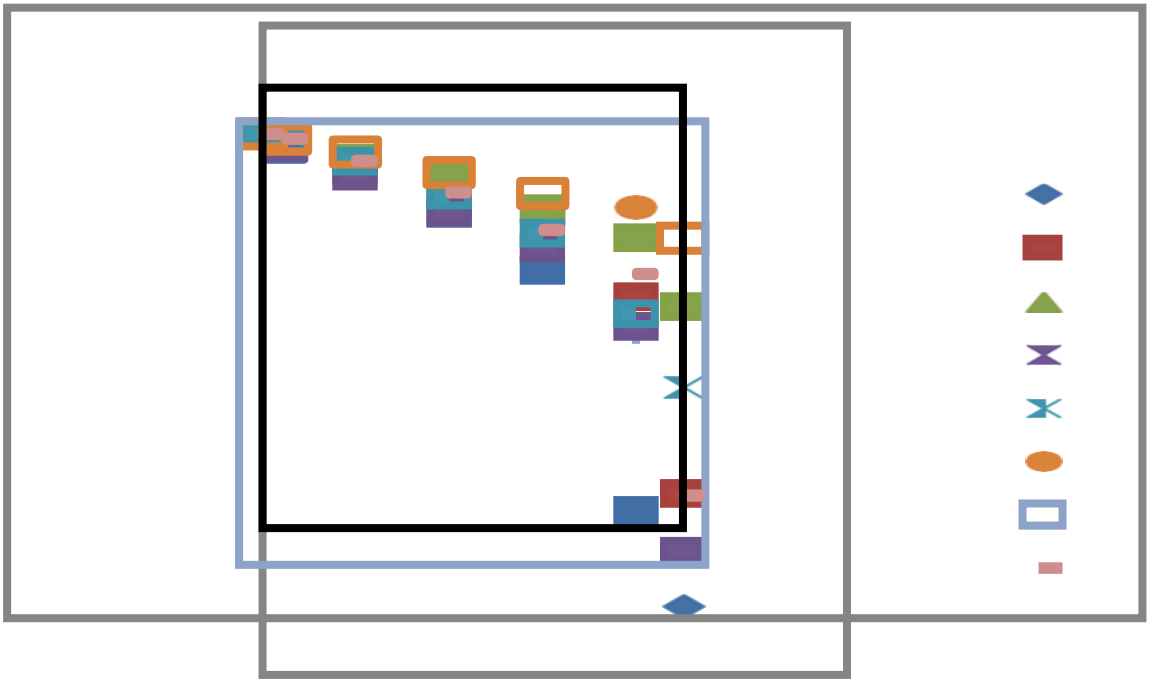
SF1	0.9821	0.8296	0.9653	0.6549	0.9975
SF2	0.9838	0.7303	0.9074	0.6426	0.9794
SF3	0.9838	0.8986	0.9297	0.6296	0.9699
SF4	0.9736	0.7718	0.9794	0.6510	0.9983
SF5	0.9918	0.8975	0.9404	0.6571	0.9736
SF6	0.9847	0.8975	0.9518	0.6064	0.9692
SF7	0.9827	0.7693	0.9685	0.6528	0.9987
SF8	0.9873	0.7926	0.9427	0.6634	0.9602

Zero order kinetics for SRL



zero order kinetics for SRL

First order kinetics for SRL



First order kinetics for SRL

Stability Studies:

Stability data

Stability period	400C / 75% RH				
	Hardness Mean ± SD	% Friability Mean ± SD	% Drug content Mean ±SD	Drug release	
				IRL (30 min)	SRL (1080 min)
Initial	7.05±0.67	0.36±0.01	99.23±0.532	99.413	95.823
1 month	7.08±0.49	0.43±0.03	99.35±0.751	99.581	95.421
2 month	6.41±0.49	0.56±0.06	98.96±0.792	99.142	94.736
3 month	5.33±0.60	0.73±0.03	96.94±0.921	98.728	94.381

The bi-layered tablets were subjected to short term stability study, storing the formulation at 400C / 75% RH for 3 months. The data for stability studies revealed that no considerable differences in physical parameters, drug content and in vitro drug release rate were observed.

CONCLUSION

In the present work bi-layered tablet of Divalproex sodium were prepared by wet granulation method, using superdisintegrants such as sodium starch glycolate and croscarmellose for immediate release layer and polymer like HPMC K4M and HPMC K100M for sustained release layer.

Best formulations of each layer were selected for bi-layered tablet and bi-layered tablet were prepared. Bi-layered tablet of Divalproex sodium were subjected to hardness, weight variation, friability, drug content uniformity, drug release and drug polymer interaction.

The above studies lids to following conclusions:

FTIR and DSC studies indicated that the drug is compatible with all the excipients. Both immediate and sustained release layer were prepared by wet granulation method and punched separately. The prepared tablets of both layers were evaluated for post compression parameters.

According to the dissolution profile date one formulation of each layer were selected for bi-layered tablet. IF6 from immediate release formulations as they showed

98.62 % drug release within 20 minute. SF8 from sustained release formulation as they showed 94.29 % drug release within 18 hours.

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