DESIGN AND EVALUATION OF BILAYERED TABLET CONTAINING DIVALPROEX SODIUM

Mr. Panthalarasa S

Master of Pharmacy, Department of Pharmaceutics, JKKMMRF's Annai JKK Sampoorani ammal College of Pharmacy, B. Komarapalayam, Namakkal District, Tamil Nadu-638183

***Corresponding author:**

Dr S Chandra M Pharm,Ph.D

Professor and Head, Department of Pharmaceutics, JKKMMRF's Annai JKK Sampoorani ammal College of Pharmacy, B. Komarapalayam, Namakkal District, Tamil Nadu-638183.

ABSTRACT:

The objective of the study is to design and evaluate bi-layered tablet of Divalproex sodium containing immediate release layer and sustained release layer. Divalproex sodium is considered as the most important antiepileptic drug and widely used for treatment of epilepsy and bi-polar disorders and prophylaxis of migraine. The FTIR study revealed that there was no interaction between drug and polymer and combination can be safely prepared. Both layers were prepared by wet granulation technique as poor flow property exhibited by pure drug. The immediate release layer was formulated by using sodium starch glycolate, croscarmellose sodium as super disintegrants and evaluated for physical parameters, disintegration time and in vitro drug release. The optimized immediate release layer (IF6) with highest in vitro release of 98.11 was selected for bi-layered tablet formulation. HPMC K4M and HPMC K100M polymer used to retard the drug release from sustained release layer in different proportion and combination and evaluated for physical parameter along with in vitro drug release studies. The optimized sustained release layer (SF8) which extends the Divalproex sodium release more than 18 hrs was selected. In vitro drug release studies were performed using USP type II apparatus (paddle method) in 900 ml of phosphate buffer pH 6.8 at 100 rpm. Finally Bi-layered tablets were prepared by double compression of selected sustained release layer and immediate release layer of Divalproex sodium. The tablets were evaluated for hardness, thickness, weight variation, friability, drug content uniformity and in vitro drug release. All the physical parameters were in acceptable limit of pharmacopeial specification. The stability studies, shown the bi-layer tablet was stable at 400C / 75% RH for a period of 3 months.

Keywords: Bi-layered tablet, epilepsy, wet granulation, Divalproex sodium, immediate release, sustained release.

INTRODUCITON

Pharmaceutical dosage form

Drugs are rarely delivered as pure chemical entities but are approximately usually provided as prepared formulations i.e. dosage form. After converting them into an appropriate dose formulation, they are delivered in several dosage forms.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 preferred[1]. 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[2].Depending on the method/route of administration, dosage forms come in several types. These include many kinds of liquid, solid, and semisolid dosage forms. Common dosage forms include pill, tablet, or capsule, drink or syrup, among them, solid formulation do not require sterile conditions and are therefore, less expensive to manufacture[3].There are several techniques of conventional drug delivery system where tablets, capsules, pills, liquids, are used as drug carrier.The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing[4]. Tablets are solid dosage forms containing medicinal substances with or without suitable diluents[5]. 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[6]. They are varying in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is most popular dosage form and 70% of the total medicines are dispensed in the form of tablet[7].

Immediate Release Drug Delivery System

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments[8]. For immediate release formulation, super disintegrants play key component. Super disintegrants are used to improve the efficacy of solid dosage form. This achieved by various mechanisms, swelling, porosity and capillary action, heat of wetting, particle repulsion forces, deformation recovery, enzymatic reaction by which the tablets are broken into small particles[9].

Sustained Release Drug Delivery System

Sustained release systems include any drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled release system. If it is unsuccessful of this day nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged released system[10].

Table 1: Classification of polymers used in sustained release drug delivery systems (SRDDS)[11]

S.No	Polymer characteristics	Material
1.	Insoluble, inert	Polyethylene, Polyvinylchloride, Ethyl cellulose, Methyl acrylates-methacrylate co-polymer.
2.	Insoluble, erodible	Carnauba wax, Stearyl alcohol, Stearic acid, Polyethylene glycol, Castor oil, Monostearate Triglycerides.
3.	Hydrophilic	Methylcellulose, Hydroxyethyl cellulose, HPMC, Sodium CMC, Sodium alginate, Galactomannose, Carboxypolymethylene.

Bi-layered tablet

In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). Bilayer tablets have some key advantages compared to conventional monolayer tablets. For instance, such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. In addition, bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with pre-determined release profiles by combining layers with various release patterns, or by combining slow-release with immediate-release layers [12].

MATERIALS AND EQUIPMENTS

Materials

Divalproexsodium,Sodium,Starch,Glycolate,Croscarmellose,HPMC,K4M,HPMC,K10M,Lactose,Micro Crystalline,Cellulose,PVP K 30,Ponceau 4R,Magnesium Stearate,Talc

Instruments

Fourier Transform Infrared spectrophotometer, UV-Visible spectrophotometer, Electronic balance, Hot air oven, Multi tablet Punching machine, Roche Friabilator, Hardness tester, Disintegration test apparatus, Dissolution test apparatus, FTIR- spectrophotometer, DSC Apparatus, Stability chamber

PRE FORMULATION STUDIES

Pre-formulation testing is the first step in rational development of dosage forms of a drugs 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 performanceand development of as efficacious, table and safe dosage form. It provides a framework for the drug combination with pharmaceutical excipients in the dosage form.

Determination of λ max[13]

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 from190 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 ofthe solution. The mixtures were subjected to the mechanical agitation for 48 hours in isothermal shaker at $25^0C \pm 1^0C$ 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[14]

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

Standard Curve for Divalproex sodium[13]

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

Compatibility studies

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

FT-IR Spectroscopy[15]

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 minin hydraulic press. The interaction between drug-excipients was observed from IR-spectralstudies by observing any shift in peaks of drug in the spectrum of physical mixture of drug- excipients.

DSC Analysis for formulation[16]

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 350^0C at a heating rate of 10^0C/min, using nitrogen as blanket gas.

FORMULATION AND DEVELOPMENT

Calculation of dose[17]

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.

Formulation of Immediate release layer:

Table 2: 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	Sodium starch glycolate	10	12.5	-	-	5	6.25
3	Croscarmellose sodium	-	-	10	12.5	5	6.25
4	Lactose	82	79.5	82	79.5	82	79.5
5	Microcrystalline cellulose	25	25	25	25	25	25
6	Magnesium stearate	3	3	3	3	3	3
7	Talc	5	5	5	5	5	5
8	Ponceau 4R	0.02	0.02	0.02	0.02	0.02	0.02
9	Total	250	250	250	250	250	250

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 asadsorbent. 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 50^0C for 15 min in hot air oven.
- Lubricate the granules with lubricating agent and compressed into 250 mg each tabletweight by adjusting hardness. The formulations are shown on table no2.

Formulation of sustained release layer:

Table 3: 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	HPMC K100M	45	52.5	60	-	-	-	22.5	26.25	30
3	HPMC K4M	-	-	-	45	52.5	60	22.5	26.25	30
4	Lactose	52.75	45.25	37.75	52.75	45.25	37.75	52.75	45.25	37.75
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 SRL

Accurately weighed Divalproex sodium and polymer and others ingredients were taken in mortarand 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 50^0C 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 were shown on table no3.

Preparation of bi-layered tablet

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

EVALUATION PARAMETERS

Evaluation Of Pre-Formulation Parameters

Angle of Repose:[18]

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 toflow through the funnel greely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using equation.

$\theta = \tan^{-1}(h / r)$

Where, θ = the angle of repose

h = height of the heap of the powder

r = radius of the heap of the powder

Table 4: 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:[19]

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.

$$Db = \frac{w}{Bulk\ volume\ of\ the\ powder}$$

$$Dt = \frac{w}{Tapped\ volume\ of\ the\ powder}$$

Carr's index:[20]

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

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

Table 5: % 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:[21]

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

$$\text{Hausner's ratio} = \frac{}{k}$$

Table 6: 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

Weight Variation Test:[22]

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

Table 7: 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:[23]

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 checkedby using Monsanto hardness tester. The hardness was measured in the terms of kg/cm^2 .5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

Friability:[24]

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 tabletswere 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.

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

Tablet thickness:[24]

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 the read "hundredths of mm" of imperial scale (count the number of division until the lines concedeswith 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.

***In-vitro* dissolution studies of immediate release layer:**[25]

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±0.50^{0}C. A5 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.

***In vitro* dissolution studies of sustained release layer**[26]

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 ±0.5^{0}C 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:[26]

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 wasmade 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:[26]

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. Korsmeyer 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.

$$Q_t = Q_0 + K_0 t$$

\Where, Q_t = amount of drug dissolved in time t

Q_0 = initial amount of drug in the solution

K_0 = zero order release constant

If the zero order drug release kinetic is obeyed, a plot of Q_t versus t will give straight linewith a slope of K_0 and an intercept at Q_0.

First Order Kinetic

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

$$\text{Log } Qt = \log Q0 + K1t/2.303$$

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.

$$M_t / M\infty = K_H t^{1/2}$$

Where,M_t and $M\infty$ are cumulative amount of drug release at time t and infinite time, and K_H = Higuchi dissolution constant reflection formulation characteristics.

If the Higuchi model of drug release is obeyed, then a plot of M_t /$M\infty$ versus $t^{1/2}$ will be straight line with slope of K_H.

Korsmeyer-Peppas Model

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.

$$M_t / M\infty = K\, t^n$$

$$\text{Log } (M_t / M\infty) = \log K + n \log t$$

Table 8: 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[26, 27]

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 mouthbottles closed tightly. They were stored at 40^0C / 75% RH for 3 months and evaluated periodically.

RESULTS

determination of $\lambda_{max=}$

The λ_{max} of Divalproex sodium was found to be 210 nm in methanol and phosphate buffer pH 6.8

Standard curve of Divalproex sodium.

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

Table 9: 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	0.049	0.045	0.045	0.047±0.004
3	10	0.095	0.096	0.097	0.097±0.003
4	15	0.142	0.143	0.147	0.145±0.002
5	20	0.184	0.186	0.188	0.187±0.003
6	25	0.241	0.238	0.239	0.239±0.002

Drug solubility studies

The solubility studies of drug were done by using various media like distilled water, methanol, chloroform and phosphate buffer pH 6.8. The data for solubility studies in those mediaare shown in table 5. The result shows maximum solubility in chloroform.

Table 10: Solubility of Divalproex sodium

Solvents	**Solubility (mg/ml)**
Distilled water	7.37
Methanol	48.46
Chloroform	55.23
Phosphate buffer pH 6.8	29.75

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

Melting Point

Melting point of drug was determined by capillary method. The result is found to be **219-223^{0}C.**

FT-IR spectrum

FT-IR spectrum of pure drug Divalproex sodium and combination of drug with polymerswere obtained as shown in figures 6-12. 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 in table 11.

FTIR figure of Drug and Drug with excipients

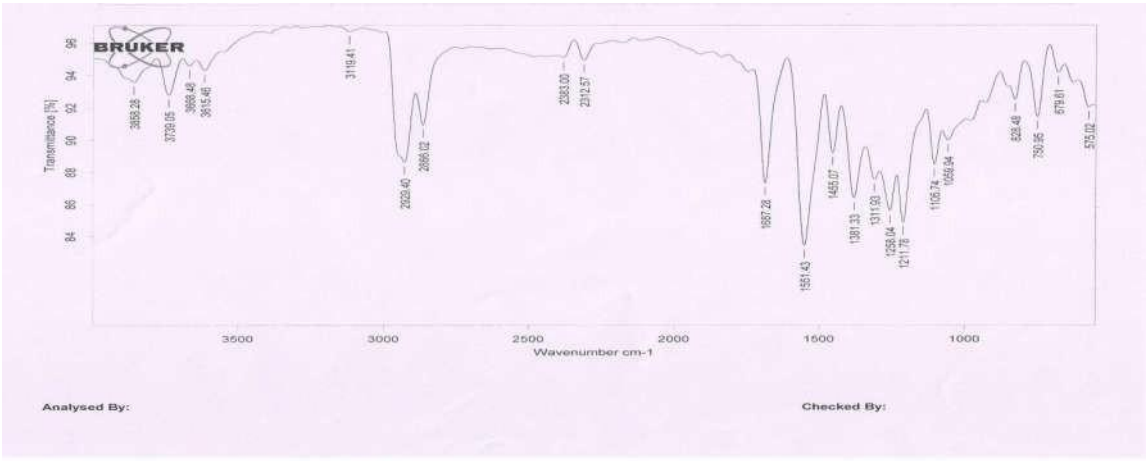

Figure 1: FTIR of Drug Divalproex sodium

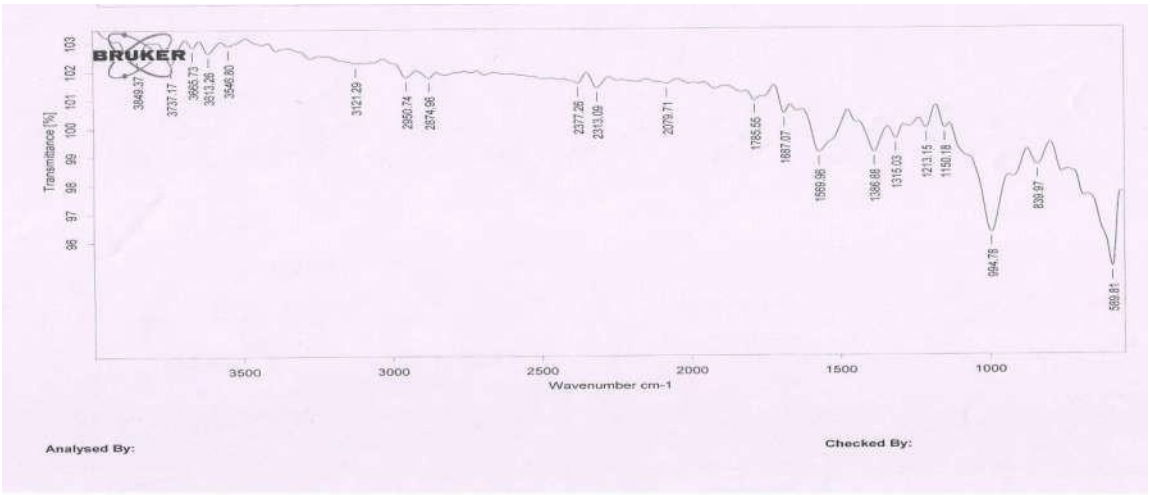

Figure 2: FTIR of Divalproex sodium + Sodium Starch Glycolate (SSG)

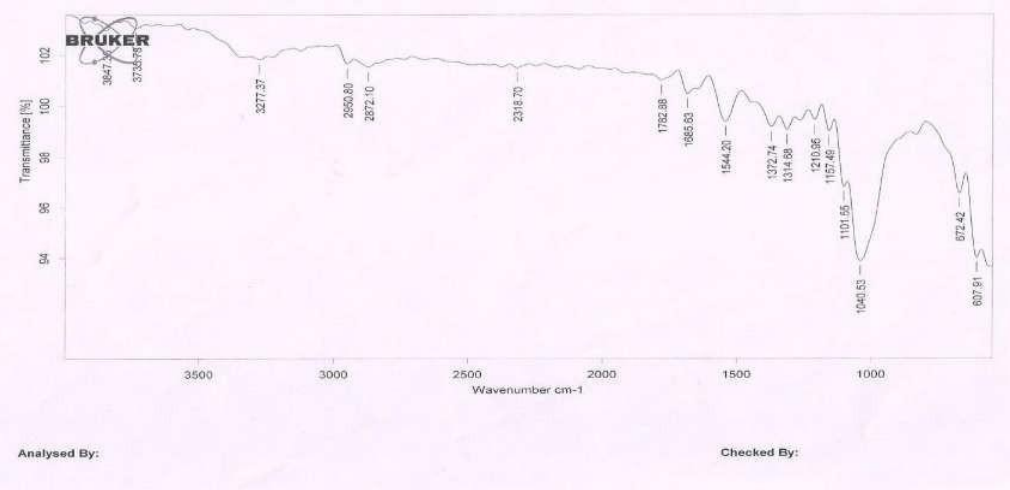

Figure 3: FTIR of Divalproex sodium + Corscarmellose sodium

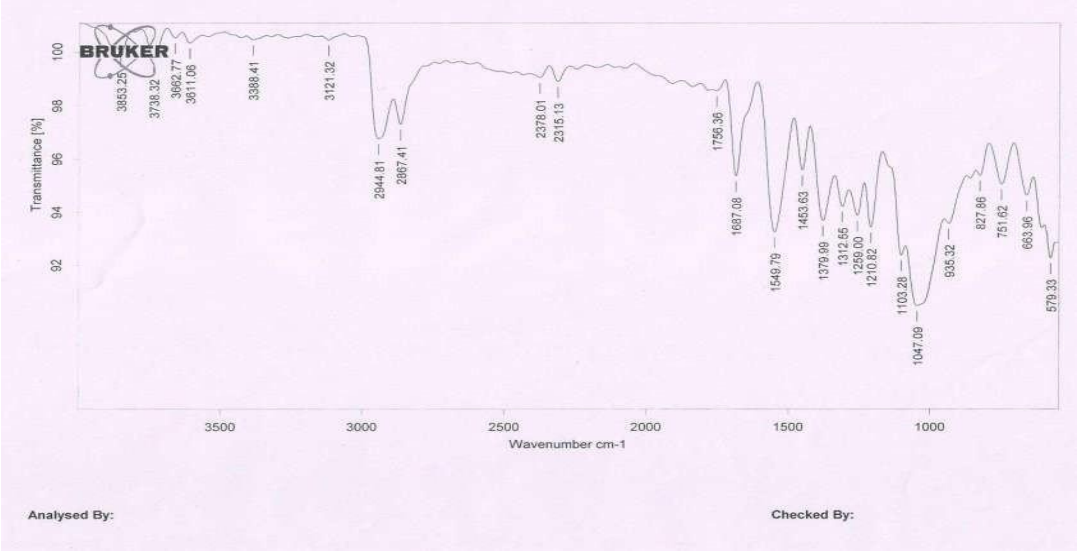

Figure 4: FTIR of Divalproex sodium + HPMC K4M

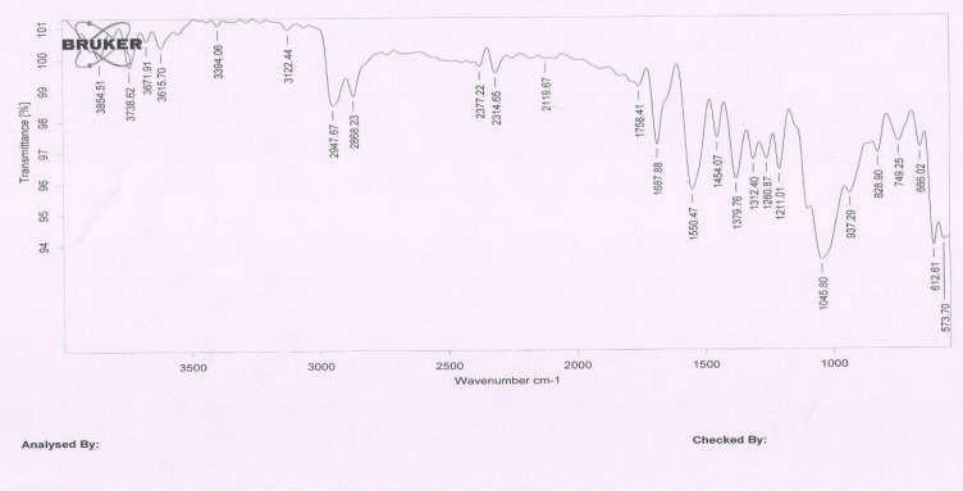

Figure 5: FTIR of Divalproex sodium + HPMC K100M

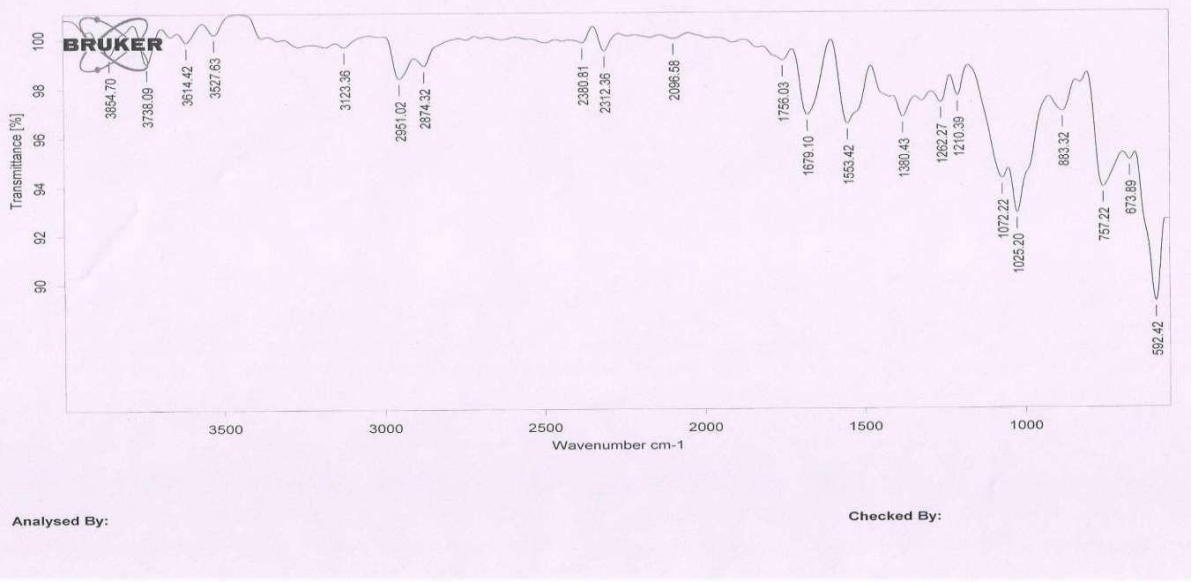

Figure 6: FTIR of Divalproex sodium + Lactose

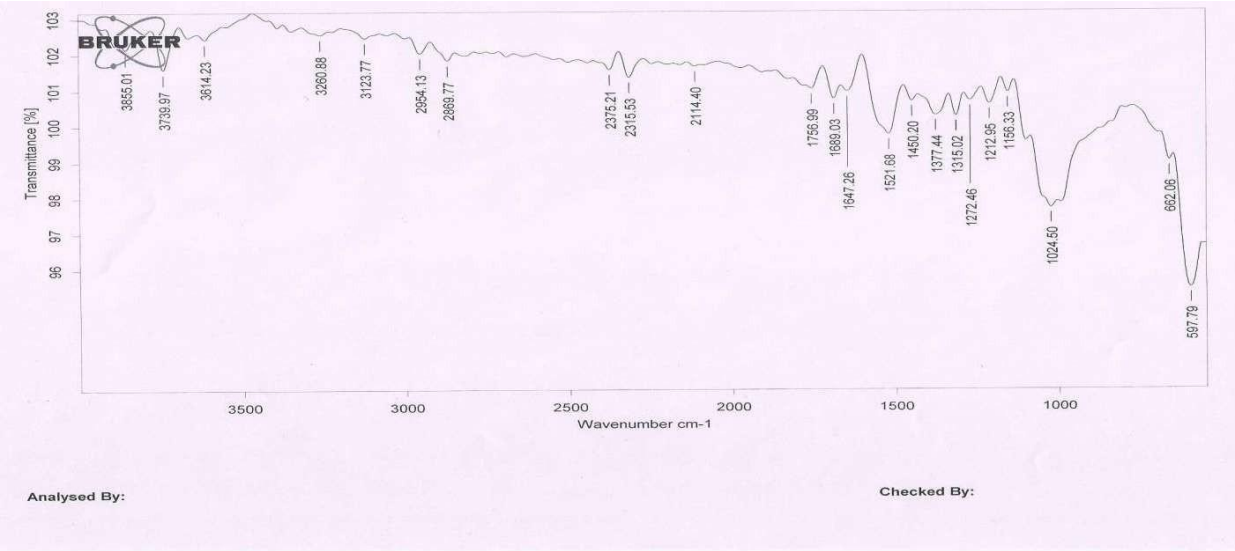

Figure 7: FTIR of Divalproex sodium + Microcrystalline Cellulose (MCC)

Table 11: Compatibility study of drug and excipients using FTIR

Functional group	Wave number (cm^{-1})							
	Standard peaks	Pure drug	SSG	Croscarmellose	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

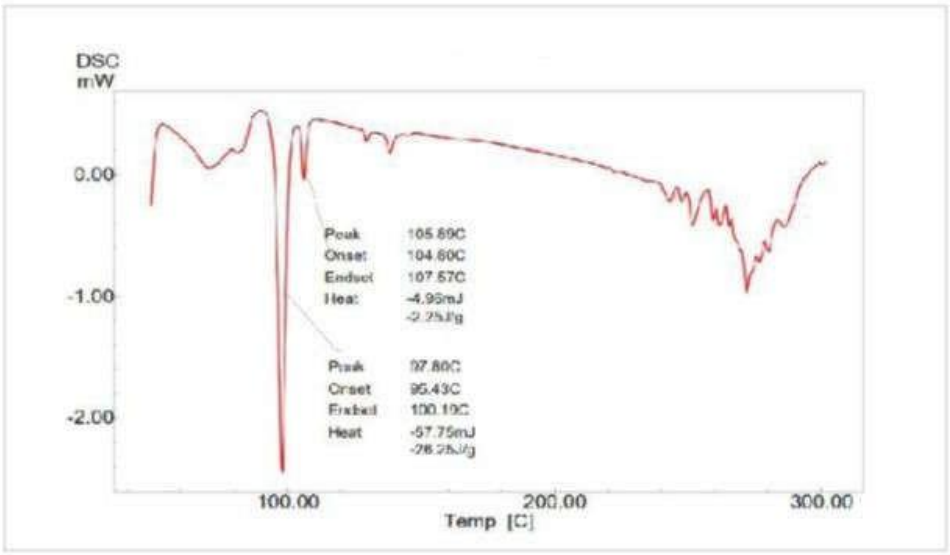

Figure 8: DSC spectrum of Divalproex sodium

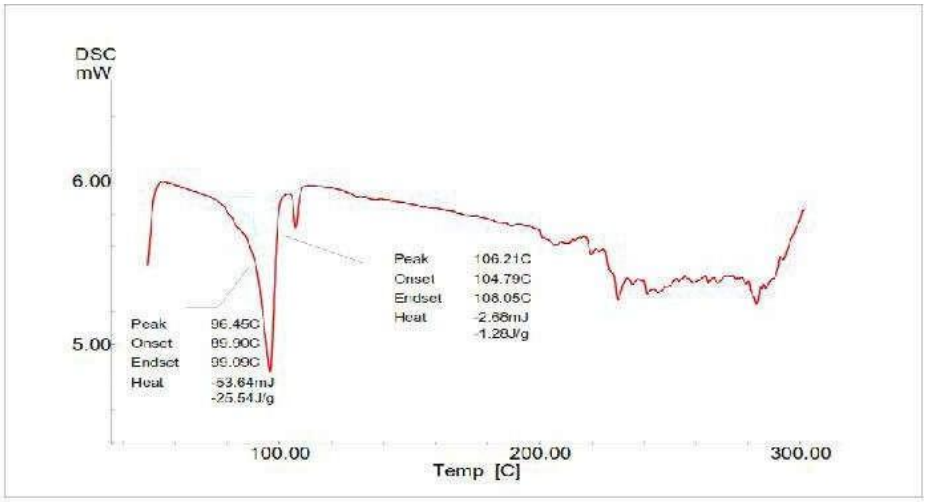

Figure 9: DSC spectrum of Formulation

EVALUATION OF PRE-COMPRESSION PARAMETERS

Table 12: 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	0.522±0.005	0.623±0.004	15.771±0.110	1.163±0.021	19.420±0.175
IF2	0.587±0.002	0.685±0.002	13.897±0.172	1.162±0.014	20.145±0.155
IF3	0.556±0.003	0.638±0.004	12.612±0.216	1.144±0.032	16.594±0.357
IF4	0.556±0.002	0.655±0.001	15.084±0.223	1.174±0.022	18.360±0.285
IF5	0.610±0.012	0.683±0.006	11.766±0.216	1.134±0.005	17.915±0.035
IF6	0.665±0.008	0.756±0.002	11.147±0.165	1.143±0.015	17.105±0.072
SF1	0.624±0.006	0.702±0.004	11.533±0.126	1.133±0.012	22.550±0.270
SF2	0.595±0.005	0.712±0.005	16.143±0.245	1.202±0.021	18.330±0.080
SF3	0.592±0.002	0.728±0.002	18.717±0.395	1.257±0.026	18.169±0.105
SF4	0.593±0.003	0.695±0.002	13.778±0.208	1.155±0.008	19.606±0.275
SF5	0.590±0.009	0.698±0.008	14.495±0.325	1.167±0.020	18.485±0.060
SF6	0.606±0.002	0.682±0.005	11.222±0.188	1.132±0.019	18.203±0.078
SF7	0.615±0.003	0.728±0.004	14.825±0.673	1.174±0.028	18.467±0.091
SF8	0.513±0.002	0.624±0.004	17.562±0.431	1.242±0.026	19.345±0.075
SF9	0.622±0.003	0.692±0.002	10.755±0.182	1.125±0.015	17.394±0.031

POST-COMPRESSION EVALUATION PARAMETERS:

Table 13: Post-compression parameters for IRL and SRL

Batch code	Weight variation Mean ± SD	Hardness (kg/cm^2) Mean ± SD	Friability (%) Mean ± SD	Thickness Mean ± SD	Drug content (%) Mean ± SD	*In vitro* disintegration time (sec) Mean ± SD
IF1	250.10±1.61	6.36±0.04	0.54±0.02	2.91±0.05	98.64±1.25	73.32±2.53
IF2	251.56±1.99	6.18±0.06	0.65±0.04	2.88±0.02	99.63±0.92	48.35±3.08
IF3	249.10±1.58	5.92±0.04	0.77±0.05	2.86±0.05	98.15±1.15	120.34±1.53
IF4	250.5±1.62	4.19±0.11	0.56±0.06	2.93±0.12	97.68±1.84	91.65±2.05
IF5	251.47±2.50	4.12±0.06	0.64±0.08	2.95±0.07	99.45±1.33	59.35±2.06
IF6	250.08±1.85	4.57±0.13	0.65±0.05	2.88±0.06	99.56±1.85	37.36±1.54
SF1	301.71±1.10	6.25±0.08	0.37±0.03	3.27±0.03	98.52±0.81	-
SF2	300.63±1.35	5.15±0.05	0.43±0.04	3.32±0.02	98.45±1.24	-
SF3	302.35±1.32	4.56±0.04	0.48±0.02	3.31±0.05	97.63±0.62	-
SF4	302.61±1.46	5.35±0.12	0.34±0.08	3.35±0.08	99.32±1.13	-
SF5	302.12±2.21	4.32±0.05	0.36±0.05	3.34±0.12	98.61±1.02	-
SF6	302.45±1.50	6.15±0.06	0.45±0.04	3.38±0.02	97.45±1.26	-
SF7	303.30±1.56	6.78±0.03	0.48±0.08	3.26±0.08	99.48±1.05	-
SF8	301.29±1.61	6.15±0.03	0.36±0.02	3.32±0.04	99.52±1.22	-
SF9	302.50±1.12	6.57±0.01	0.33±0.01	3.34±0.07	98.49±0.95	-

Table 14: 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	551.71±0.72	7.08±0.12	0.37±0.20	6.25±0.60	99.20±0.61

***In-vitro* dissolution study**

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

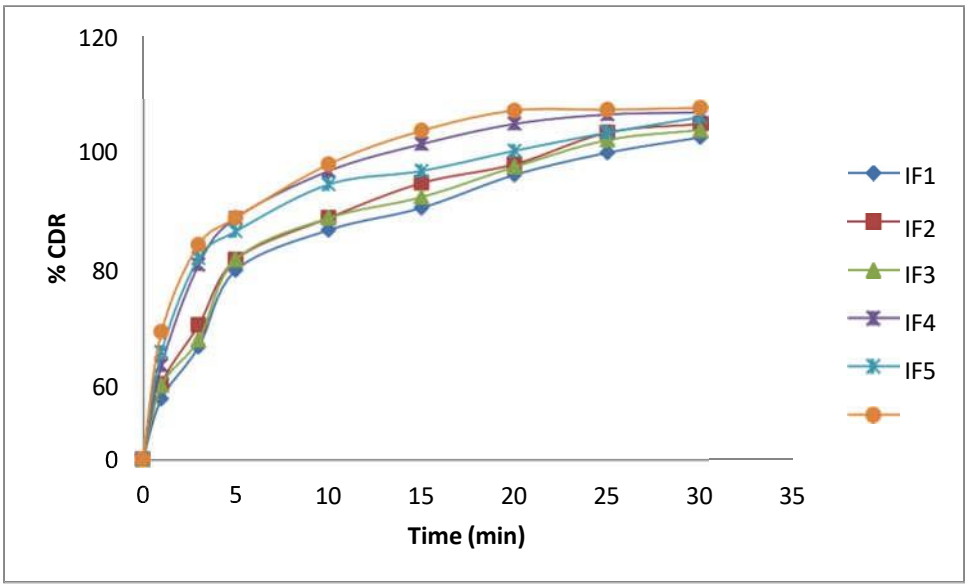

Figure 10: Release profile of immediate release layer

Table 16: *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	13.469±1.222	6.741±1.281	5.558±1.591	15.408±1.222	7.905±1.234	6.017±1.508	13.006±1.994	5.391±0.882
120	25.637±0.732	18.521±1.421	12.635±0.751	25.634±1.764	19.263±1.532	18.231±1.281	21.351±1.317	17.527±1.114
240	33.235±1.164	25.279±1.003	17.697±1.151	34.323±2.715	24.502±1.083	23.091±1.547	33.589±1.503	24.917±1.426
360	38.852±1.521	33.852±1.835	25.742±1.427	42.342±0.632	31.362±1.321	29.735±0.941	45.247±0.941	36.518±0.831
480	56.674±2.061	47.993±0.539	33.733±2.378	57.151±1.196	43.141±1.974	36.936±1.251	53.869±1.510	46.331±0.891
600	62.316±1.839	50.491±0.694	39.513±1.114	62.342±0.412	48.234±0.826	43.752±1.423	59.523±1.163	52.852±0.792
720	70.315±2.001	65.327±1.779	47.031±1.480	76.620±1.642	56.263±2.227	54.964±2.137	68.215±0.906	64.017±0.710
960	87.123±0.645	86.182±0.467	54.439±2.565	98.183±0.352	82.430±1.267	66.957±1.402	88.053±0.676	77.498±0.918
1080	98.822±1.325	97.692±0.844	67.057±1.191	101.512±1.093	97.816±0.630	84.113±1.317	100.859±2.165	94.298±0.560

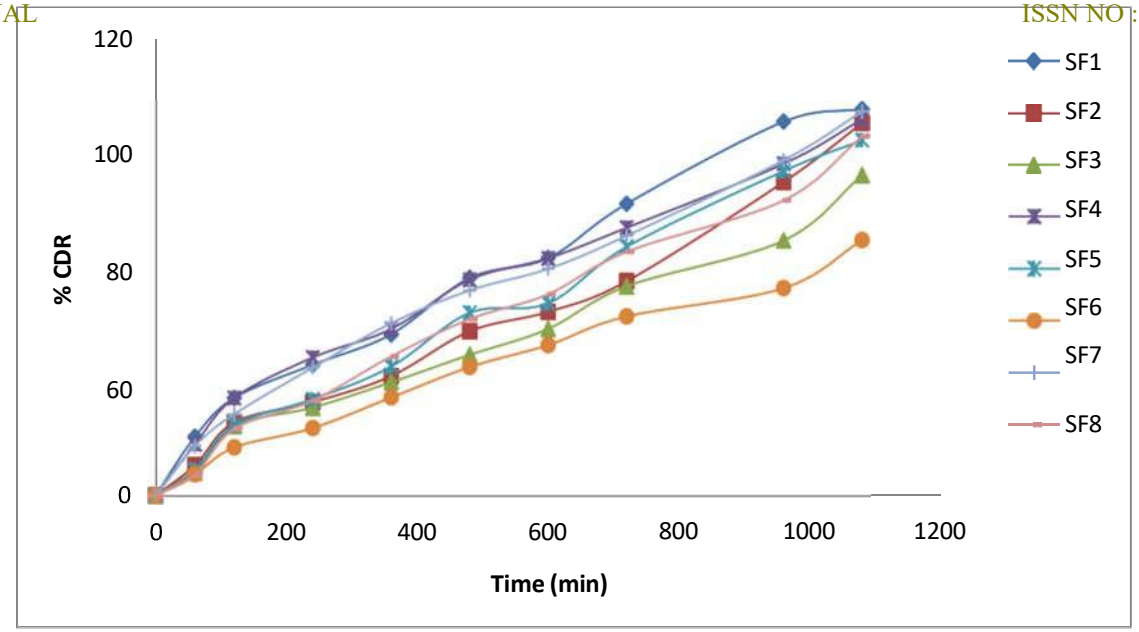

Figure 11: Release profile of sustained release layer

Table 17: Dissolution study of Bi-layered Tablet

Time in min	% CDR	
	BTF	
	IRL	SRL
0	0.000±0.000	0.000±0.000
10	83.454±1.053	-
20	98.368±1.152	-
30	99.420±0.752	-
60	-	5.386±1.035
120		17.523±0.858
240	-	23.472±1.523
360		36.168±0.632
480	-	46.061±0.828
600		52.862±0.845
720	-	64.776±0.522
960	-	76.152±0.945
1080	-	95.823±0.616

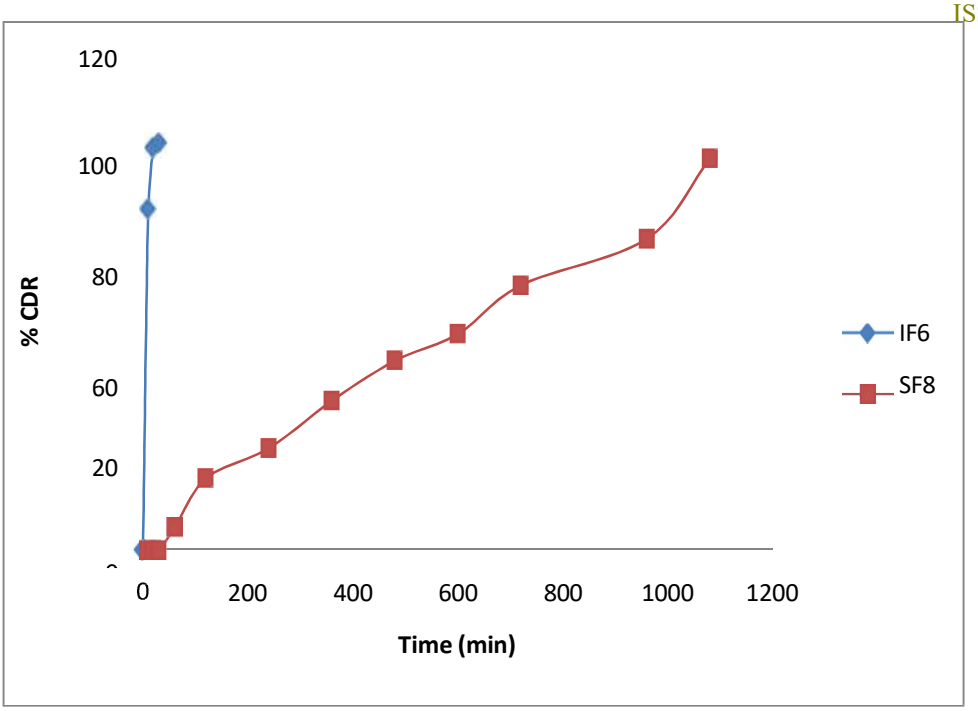

Figure 12: Release profile of Bi-layered Tablet

Kinetic Release

For immediate release tablets

Table 18: Kinetic release for IRL

FORMULATION CODE	KINETIC MODELS				
	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer n	Korsmeyer R^2
IF1	0.8231	0.9819	0.9643	0.8711	0.6336
IF2	0.7068	0.9850	0.9059	0.8424	0.5642
IF3	0.836	0.9816	0.9689	0.8915	0.6657
IF4	0.8228	0.9844	0.9677	0.8694	0.6263
IF5	0.7101	0.9606	0.9055	0.804	0.5134
IF6	0.6838	0.9795	0.8942	0.8036	0.5123

Zero order Kinetics for IRL

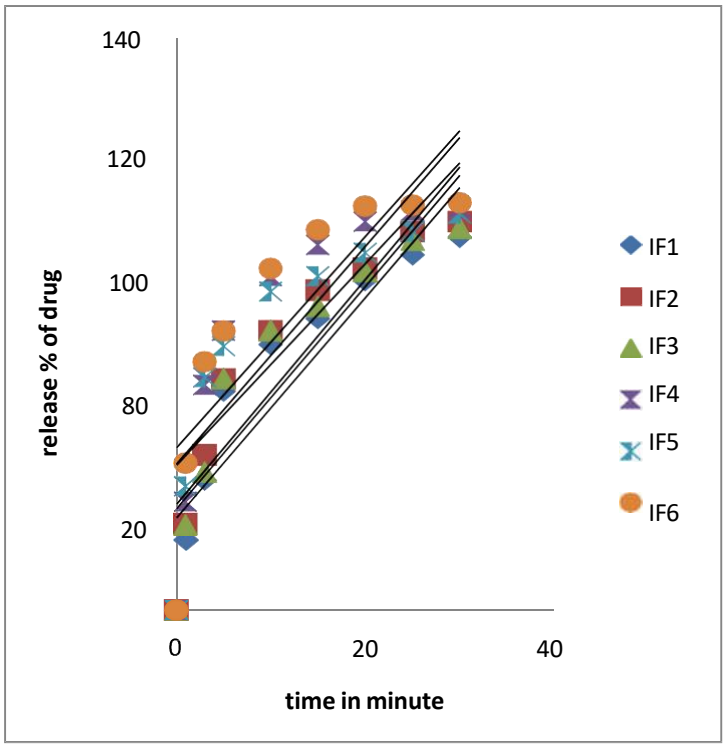

Figure 13: Zero order Kinetics for IRL

First order Kinetics for IRL

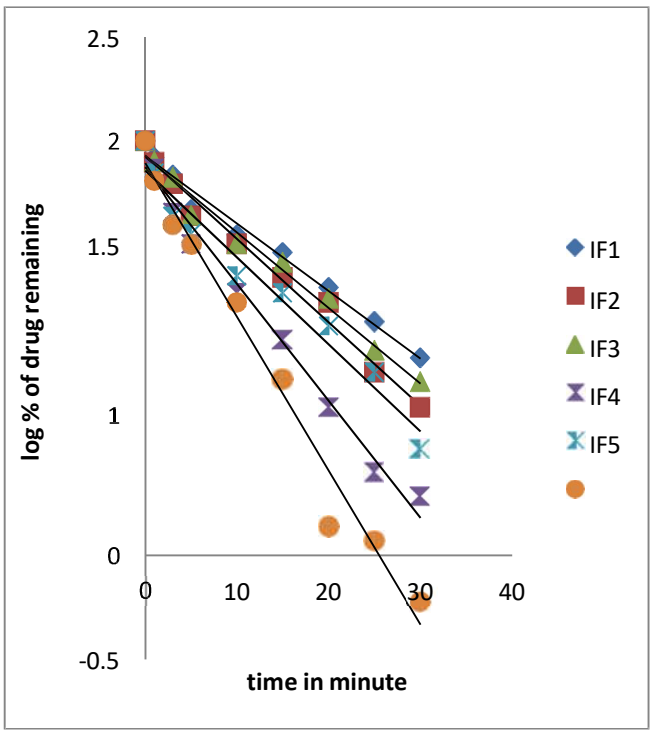

Figure 14: First order kinetics for IRL

Higuchi release kinetic for IRL

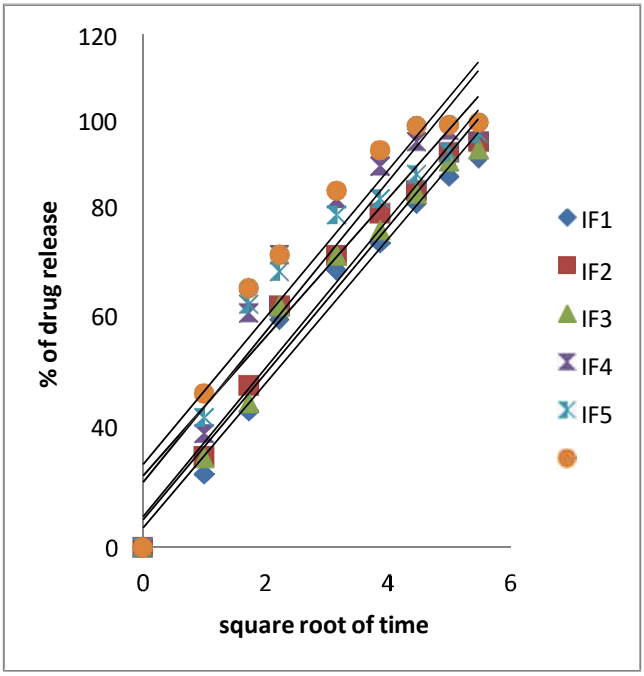

Figure 15: Higuchi release kinetics for IRL

Korsemeyer-peppas release Kinetics of IRL

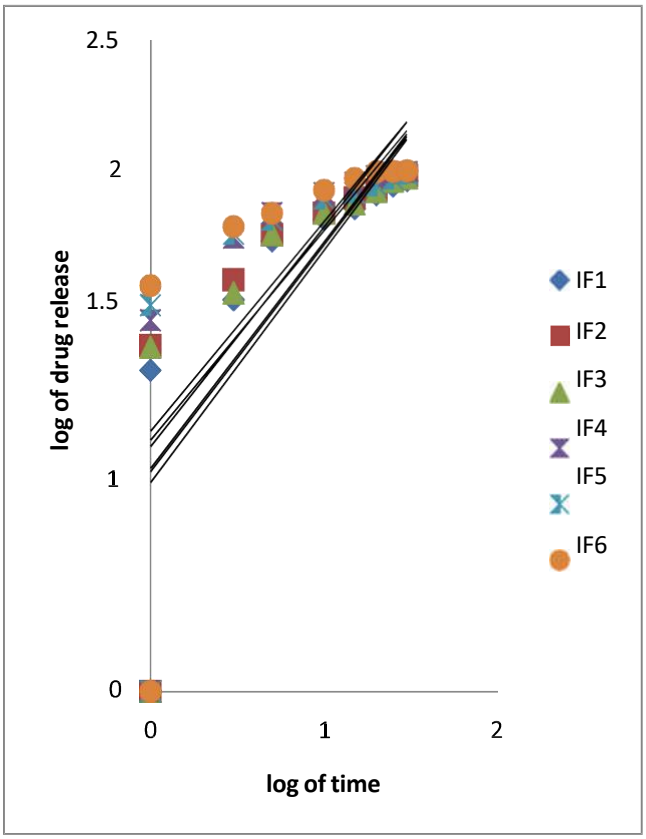

Figure 16: Korsemeyer-peppas release Kinetics for IRL

For sustained release layer

Table 19: Kinetic release for SRL

FORMULATION CODE	KINETIC MODELS				
	Zero order R^2	First Order R^2	Higuchi R^2	Korsmeyer n	Korsmeyer R^2
SF1	0.9736	0.7718	0.9794	0.6510	0.9983
SF2	0.9918	0.8975	0.9404	0.6571	0.9736
SF3	0.9847	0.8975	0.9518	0.6064	0.9692
SF4	0.9821	0.8296	0.9653	0.6549	0.9975
SF5	0.9838	0.7303	0.9074	0.6426	0.9794
SF6	0.9838	0.8986	0.9297	0.6296	0.9699
SF7	0.9827	0.7693	0.9685	0.6528	0.9987
SF8	0.9878	0.7922	0.9421	0.6631	0.9610

Zero order kinetics for SRL

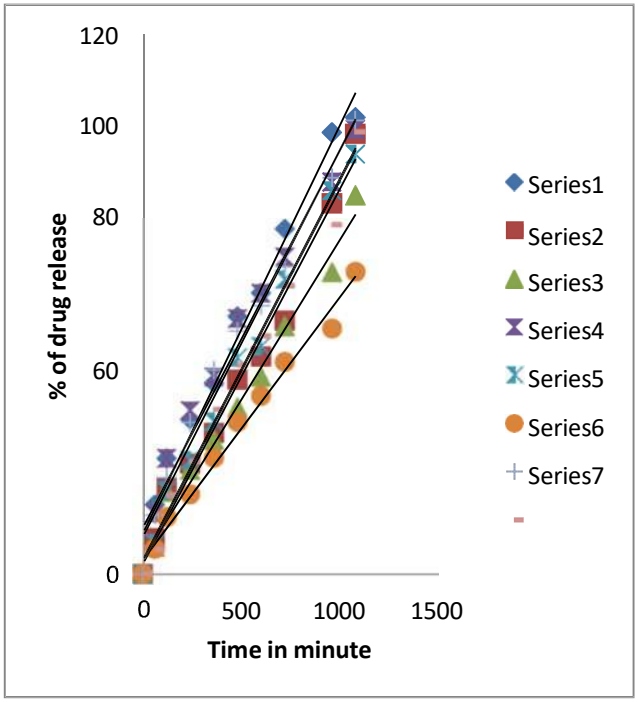

Figure 17: zero order kinetics for SRL

First order kinetics for SRL

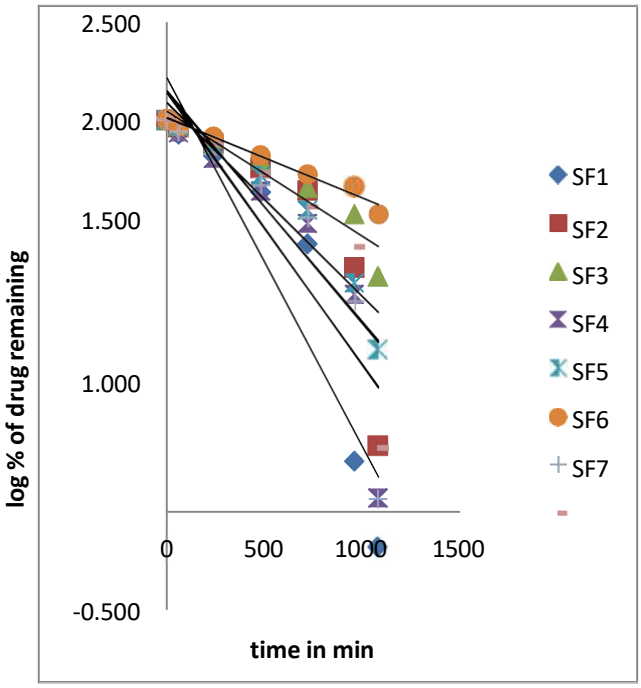

Figure 18: First order kinetics for SRL

Higuchi Model for SRL

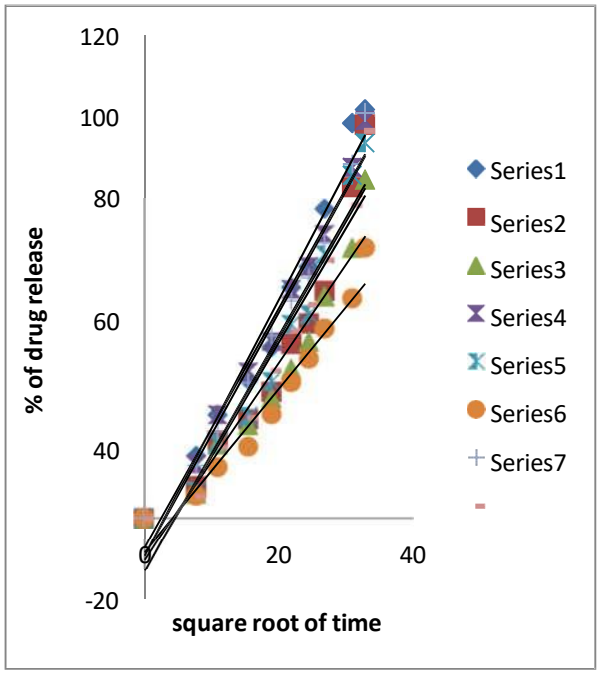

Figure 19: Higuchi Model for SR

Korsmeyer's peppas release kinetics for SRL

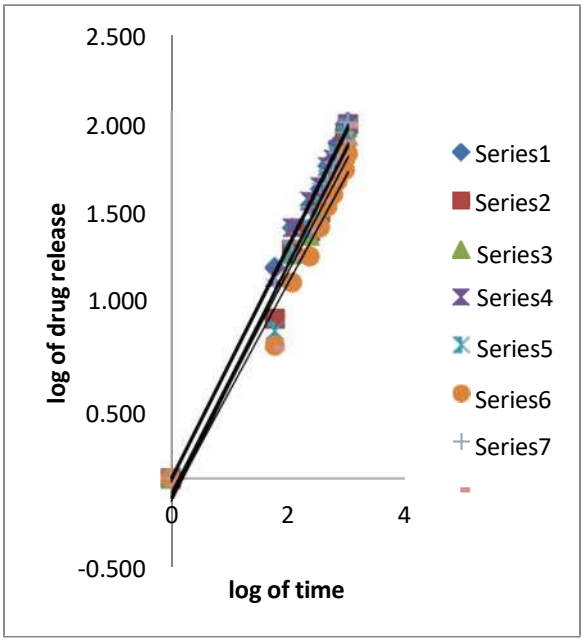

Figure 20: Korsmeyer's peppas release kinetics for SRL

Stability Studies:

Table 20: Stability data

Stability period	40^0C / 75% RH				
	Hardness Mean ± SD	% Friability Mean ± SD	% Drug content Mean ± SD	Drug release	
				IRL (30 min)	SRL (1080 min)
Initial	7.08±0.62	0.37±0.02	99.28±0.538	99.418	95.828
1 month	7.05±0.45	0.45±0.01	99.31±0.750	99.586	95.425
2 month	6.38±0.46	0.53±0.05	98.90±0.796	99.141	94.732
3 month	5.36±0.63	0.71±0.06	96.98±0.925	98.725	94.386

The bi-layered tablets were subjected to short term stability study, storing the formulationat 40^0C / 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 super disintegrants such as sodium starch glycolate and croscarmellosefor immediate release layer and polymer like HPMC K4M and HPMC K100M for sustained release layer .Bi-layered tablet of Divalproex sodium were subjected to hardness, weight variation, friability, drug content uniformity, *in vitro* drug release and drug polymer interaction.

According to the *in vitro* 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. The hardness of the prepared tablets was found to be in the range of 5.36 to 7.08 kg /cm^2.The friability of the prepared tablet was found to be less than 1%.The percentage drug content was uniform in all the formulations of prepared bi-layered tablets .*In vitro* drug release pattern of the bi-layered tablets were same as individual layertablets.

The stability study showed that no significant changes in tablets after 3 months study. Based on the observations, it can be concluded that the formulated bi-layered tablets of Divalproex sodium using super disintegrants, release retardant polymers and different excipients was capable of exhibiting all the properties of bi-layered tablet. They are thus reducing the dose intake, minimize dose related adverse effect, cost and ultimately improve the patient compliance and drug efficiency.

Reference

1. Notari, R.,Biopharmaceutics and Clinical Pharmacokinetics, An Introduction, 3rd Ed., Marcel Dekker Inc. New York, 1980,152-54.
2. Vinay K, Prajapati SK, Girish CS, Mahendra S, Neeraj k. Sustained release matrix type drug delivery system. IRJP 2012;1(3):934-60.
3. Kumar V, Sharma A, Sharma A, Joshi G, Dhillon V. Recent Advances In Novel Drug Delivery System for Delivery Of Anti- Hypertensive Drugs. Int J D D Res. 2011;3(1):252-59.
4. Basu B, Bagadiya A, Makwana S, Vipul V, Batt D,Dharamsi A. Formulation and evaluation of fast dissolving tablets of cinnarizine using superdisintegrant blends and subliming material. J Adv Pharm Technol Res. 2011;2(4):266-73.
5. http//www.pharmacopeia.cn/v29240/USP29nf24s0-c115/587.htm/
6. The Indian Pharmacopoeia, Government of India Ministry of health and family welfare, the indian pharmacopoeia commission Ghaziabad, 2014;vol.II:959.
7. Pahade AA, Jadhav VM, Kadam VJ. Formulation and Development of a Bilayer Sustained Released Tablets of Isosorbide Mononitrate. Int J Pharma Bio Sci. 2010;1(4):305-14.

8. Sandeep N. & Gupta M.M, Immediate Drug Release Dosage Form: A review. Journal ofDrug Delivery & therapeutics. 2013;3(2):155-61.

9. Pahwa R, Gupta N. A Review: Superdisintegrants in the development of orally disintegratingtablets. Int J Pharm Sci Res. 2011;2(11):2767-2780.

10. Chugh I, Seth N, Rana A.C. Oral sustained release drug delivery system. International Research Journal of Pharmacy 2012;3(5):57-62.

11. Singh A, Sharma R, Jamil F. Sustained Release Drug Delivery System: a Review. Int ResJ Pharma. 2012;3(9):21-4.

12. Chien YW. Fundamentals of controlled-release of drug administration in: J. Swarbrick (Ed.), Novel Drug Delivery System Marcel Dekker, New York, 1982, pp. 465–574.

13. www.usp.org/sites/default/files/usp-pdf/EN/USPNF/revisions/divalproexsodium extended-releasetablets.pdf

14. www.chem.wisc.edu/courses/342/fall2004/melting_point.pdf

15. Rama, Bhoot MR. Formulation and Evaluation of Bilayer Tablet of two Incompatible Drugs Amlodipine Besilate and Losartan Potassium.Int Res J pharma. 2012;4(9):136-42.

16. Shivanand K, Raju S.A. Jaykar B. Mucosdhesive Bilayered Buccal Tablets of Tizanidine Hydrochloride. Int J pharma tech Res. 2010;2(3):1861-9.

17. Patil SS, Hiremath D, Basha KM, Udupi R.H. Design and In-vitro Evaluation of Gastro Retentive Bilayer Floating Tablets of Rosiglitazone Maleate. Int J Pharma Bio Arch.2012;3(1):204-10.

18. Hadi MA, Rao NGR, Firangi S. Mini-Tablets Technology: An Overview. Am J Pharma Tech Res. 2012;2(2):128-49.

19. Ahmed NVH, Hiharika G, Deepak P, Shaaz Nazan, Afroz AM. Formulation Design, Characterisation and in vitro Evaluation of Bi-layered Tablets Containing Telmisartan and Hydrochlothizide. Int J Bio Pharma. 2013;4(1):1-9.

20. Tehseen N, Rao V, Hdi MA. Design and Characterization of twice Daily Mini-Tablets Formulation of Pregabalin. Int J Pharma Sci. 2013;5(1):168-75.

21. Barthwal PAR, Ganarajan, Kothiyal P. Formulation and Evaluation of Sustain Release Bilayer Tablets of Metformin and Gliclazide. Int J Pharma Chem Sci. 2013;2(4):1965-70.

22. Kumari LP, Vasanth PM, Suresh K, Ramesh T, Malothu R. Formulation and Evaluation of Bi-layer Floating of Tablets Quinapril HCL. Int J Pharma P. 2013;4(1):34-40.

23. Patel HP, Karwa P, Patel NJ. A Noval Approch to Sustained Zolpidem Tartrate Release: Compressed Mini-Tabets. Int J Pharma Sci Rev Res. 2011;7(2):53-8.

24. Velasco MV, Castellanos MRJ, Munoz A, Castellano I, Goni I, Gurruchaga M. In Vitro Evaluation of Sustained-release Matrix Tablets Prepared with New Modified Polymeric Cabohydrates. Int J Pharma. 1996:107-15.

25. Shibu B.S, Suresh S, Saravanan C. Formulation and Evaluation of Extended Release Tablet of Divalproex Sodium using Different Polymers as Release Retarding Agent. Int J Pharma Devel Tech. 2014;4(3):145-50.

26. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic Modeling on drug Release

From Controlled Drug Delivery Systems. Acta Poloniae Pharma-drug Res. 2010;67(3):217-23.

27. Shyamala Bhaskaran. Industrial Pharmacy. Ist ed. New Delhi. Birla Publications Pvt.Ltd; 2010.P.46-69.