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Design development and evaluation of bi-layered tablet of Divalproex sodium

Vikas Kumar*[1], Girendra Gautam[1], Abhay Kumar[2], Sonali Dasgupta[2]
[1]Bhagwant Institute of Pharmacy, Muzaffarnagar, (U.P.) – India
[2]Sanjivani Institute of Technology & Management, College of Pharmacy, Bahraich, (U.P.) – India

Abstract

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 formulation of bi-layered tablet of Divalproex sodium containing immediate release layer and sustained release layer by 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.. *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.. 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 superdisintegrants 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. Finally Bi-layered tablets were prepared by double compression of selected sustained release layer and immediate release layer of Divalproex sodium.

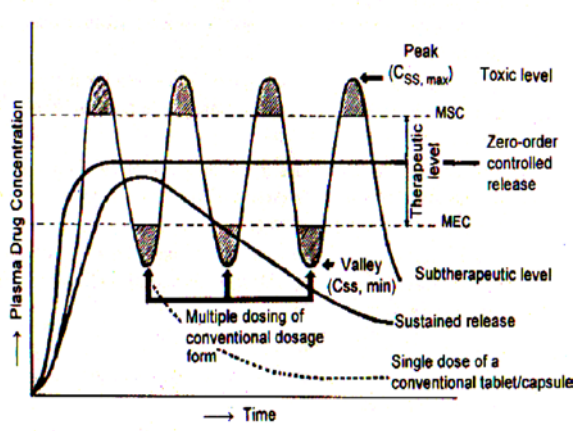
Key-words: Bi-layered tablet, epilepsy, wet granulation, Divalproex sodium, immediate release, sustained release

Introduction

Oral route is most commonly employed route of drug administration 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. 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. 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. There are different types of tablets are available in market conventional tablet, immediate tablet, fast dissolving tablet, controlled release tablet, sustained release tablet, delayed release tablet. Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. For immediate release formulation, superdisintegrants play key component.

*** Corresponding Author**
Vikas Kumar
gk100781@gmail.com

Superdisintegrants 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. Categories of the drug which are preferable for immediate release are analgesic and antiinflammatory drugs such as Ibuprofen, Diclofenac sodium. Anti-coagulants such as Dicoumarol, Dipyridamol. Anti-Depressants such as Amoxapiine. Anti-diabetic such as Glipizide. Antihypertensive drug such as Amlodipine, Minoxidil, Nifedipine are most preferable for the immediate release. 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.



Hypothetical Plasma Concentration vs. Time Profile

Advantages of sustained release dosage forms

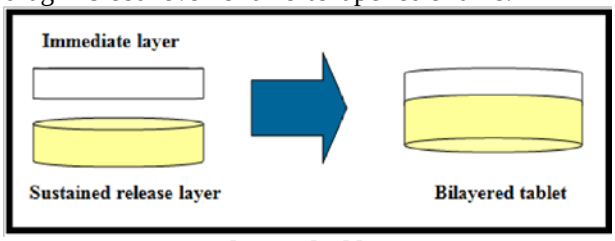
- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
- Better control of drug absorption can be attained.
- The characteristic blood variation due to multiple dosing of conventional dosage forms can be reduced.
- The total amount of drug administered can be reduced thus:
- Improve efficiency in treatment.

Disadvantages of sustained release formulation

- Administration of sustained release medication does not permit the prompt termination of therapy.
- Flexibility in adjustment of dosage regimen is limited.
- Controlled release forms are designed for normal population; i.e., on the basis of average drug biological half-lives.
- Economic factors must also be assessed, since more costly process and equipment are involved in manufacturing of many controlled release dosage forms.

Mechanism of drug release from matrix

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. In the last decade, interest in developing a combination of two or more active pharmaceutical ingredients (API) in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bi-layered 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. Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, either as second dose or in an extended release manner. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. The basic goal of therapy is to achieve a steady state drug in blood level for an extent period of time.



Bi-layered tablet

Material and Methods

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.

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.

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 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.

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.

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

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

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

% COMPRESSIBILITY INDEX

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.

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

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 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.

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/cm^2. 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.

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.

***In-vitro* 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 ± 0.50^0C. 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.

***In vitro* 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 ± 0.5^0C 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.

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 40^0C / 75% RH for 3 months and evaluated periodically.

Results and Discussion

Determination of λmax
The λ_{max} of Divalproex sodium was found to be 210 nm in phosphate buffer pH 6.8.

Standard curve of Divalproex sodium.
The absorbance was measured in a UV spectrophotometer at 210 nm.

Table 1: Spectrophotometric data of Divalproex Sodium

S.no.	Conc. (µg/ml)	Absorbance
1	0	0.000
2	5	0.046
3	10	0.098
4	15	0.146
5	20	0.187
6	25	0.237

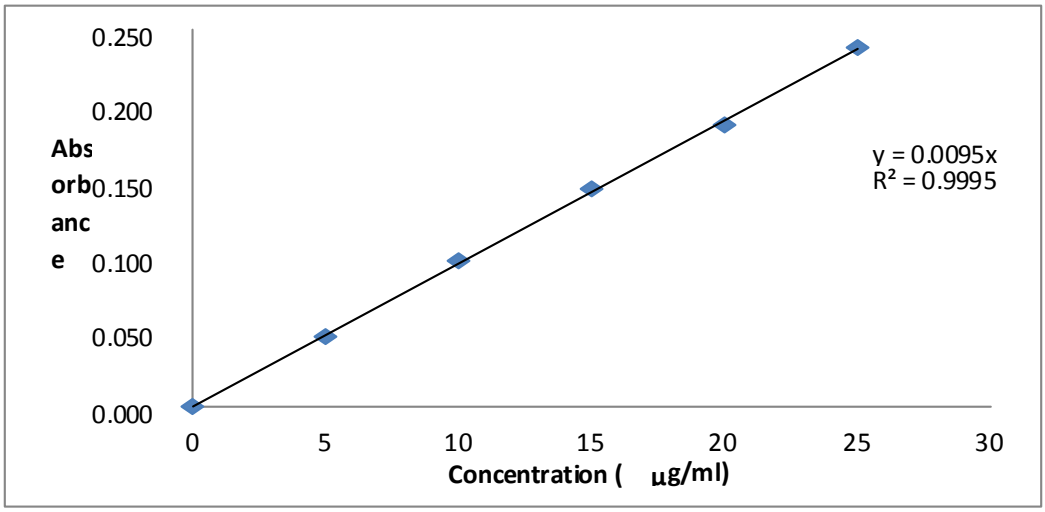


Figure 1: Standard graph of Divalproex sodium

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 are shown in table 5. The result shows maximum solubility in chloroform.

Table 2: Solubility of Divalproex sodium

Solvents	Solubility (mg/ml)
Distilled water	7.35
Methanol	48.45
Chloroform	55.24
Phosphate buffer pH 6.8	29.73

Table 5: *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

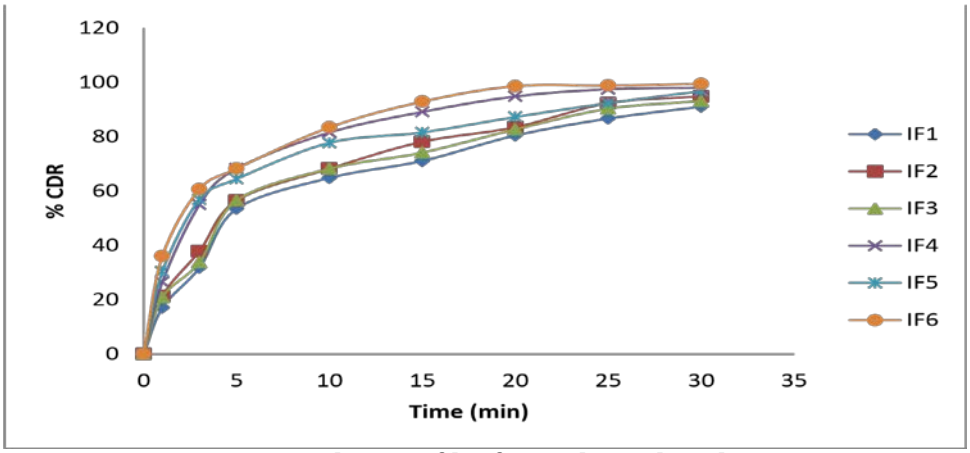


Figure 2: Release profile of immediate release layer

Table 6: *In vitro* dissolution study of SRL

Time in min	% CUMULATIVE DRUG RELEASE					
	SF1	SF2	SF3	SF4	SF5	SF6
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
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
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
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
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
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
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
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
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
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

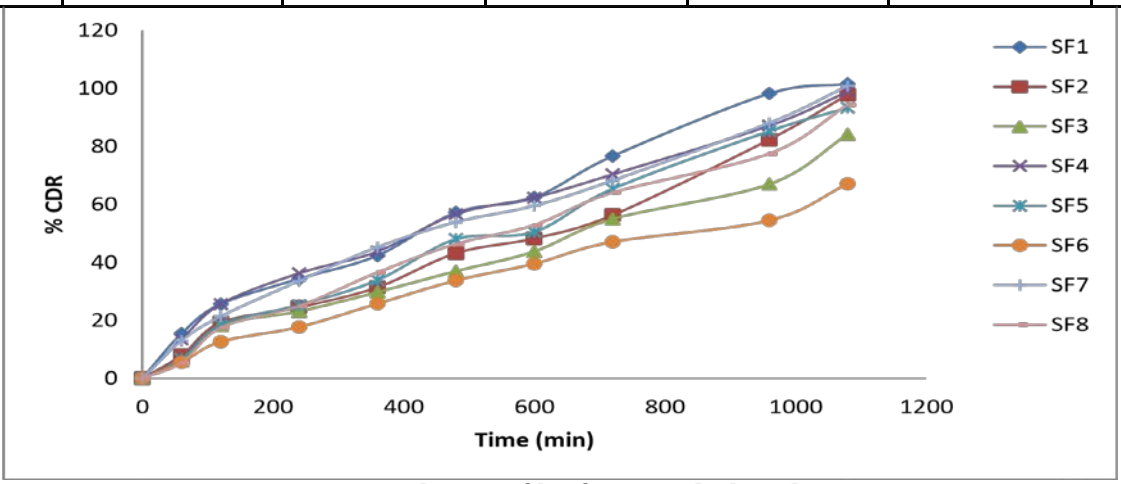


Figure 3: Release profile of sustained release layer

Table 7: Dissolution study of Bi-layered Tablet

Time in min	% CDR	
	B	TF
	IRL	SRL
0	0.000±0.000	0.000±0.000
10	83.424±1.063	-
20	98.351±1.147	-
30	99.413±0.731	-
60	-	5.384±1.032
120		17.512±0.853

240	-	23.483±1.520
360		36.164±0.638
480	-	46.054±0.825
600		52.854±0.841
720	-	64.781±0.527
960	-	76.149±0.952
1080	-	95.823±0.614

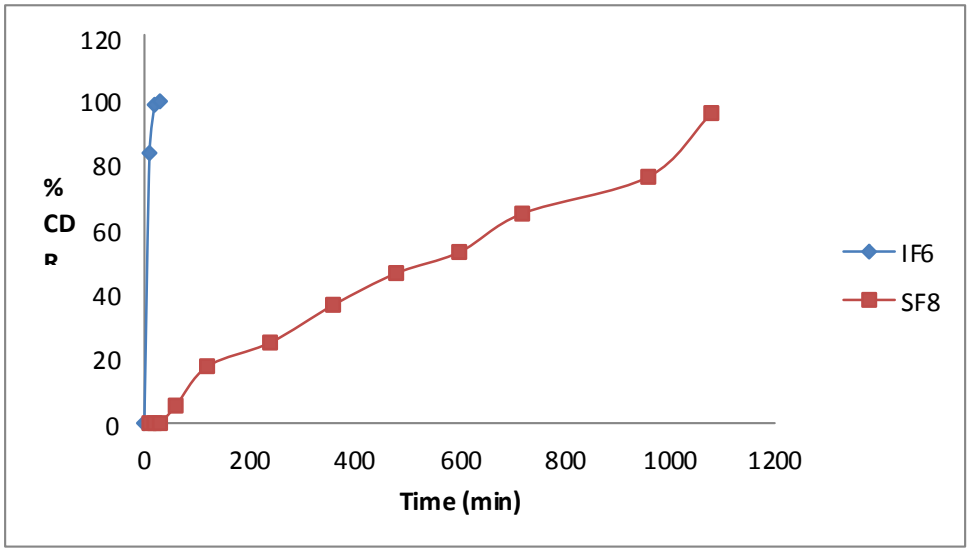


Figure 4: Release profile of Bi-layered Tablet

Table 8: Stability data

Stability period	40^{0}C / 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 40^{0}C / 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

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 40^0C / 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

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