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Formulation and evaluation of bi-layered tablet of divalproex sodium

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Abstract
Objective: To Formulate and Evaluate bi-layered tablet of Divalproex Sodium.
Method: Divalproex sodium is broad-spectrum anticonvulsant. It increases the availability of gamma-amino butyric acid (GABA), an inhibitory neurotransmitter, The bilayer tablet of Divalproex sodium were prepared by using sodium starch glycolate, croscarmellose sodium, lactose, microcrystalline cellulose, polyvinyl pyrrolidone, magnesium stearate, talc, hydroxyl propyl methyl cellulose, as Excipents using wet granulation by using different Superdisintegrants.
Result: In the present work, formulation and evaluation of bi-layered tablet of Divalproex sodium was carried out. In the project, different formulations of immediate release and sustained release layer have been prepared separately. From above formulations best formulation of each immediate and sustained release layers were selected according to the dissolution profile and bi- layered tablet were prepared.
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 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, *in vitro* drug release and drug polymer interaction.

Keywords: Patient acceptance, Bi-layer tablets, flexibility

Introduction
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 [2].
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. Bi-layered 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 [1].

Advantage of Bi-layered tablets [3]
1. Bi-layered execution with optional single-layer conversion kit.
2. Cost is lower compared to all other oral dosage form.
3. Greatest chemical and microbial stability over all oral dosage form.
4. Objectionable odor and bitter taste can be masked by coating technique.
5. Flexible concept.
6. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
7. Easy to swallowing with least tendency for hang-up.
8. Suitable for large scale production.

Disadvantage of Bi-layered tablets
1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character,
2. Bitter tasting drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients.

Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate as a tablet that will still provide adequate or full drug bioavailability

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Advantage of Bi-layered tablets over conventional tablets [4]

1. Blood level of a drug can be held at consistent therapeutic level for improved drug deliver, accuracy, safety and reduce side effects.
2. Reduction of adverse effect can be accomplished by targeting the drug release to the absorption site as well as controlling the rate of release, enabling the total ddrug content to be reduced.
3. Patient convenience is improved because fewer daily doses are required compated to traditional systems. Patient compliance is enhanced leading to improved drug regimen efficacy.
4. Bi-layered tablets readily lend themselves to repeat action products; where in one layer provide initial dose, the other layer provide maintenance dose.

Ideal characteristics of Bi-layered tablets [5]

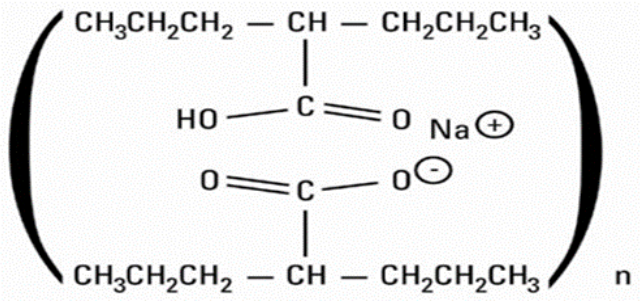
1. A Bi-layered tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.
2. It should have sufficient strength to with stand mechanical stock during its production packaging, shipping and dispensing.
3. It should have the chemical and physically stability to maintain its physical attributes over time. The Bi-layered tablet must be able to release the medicinal agents in a predictable and reproducible manner.
4. It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost- effective dosage forms [6]. Bi-layered tablet concept has long been utilized to develop sustained released formulation. The pharmacokinetic advantage relies on the criterion that, drug release from the fast releasing layer leads to a sudden rise in the blood concentration. However the blood level is maintained at steady state as the release from sustained layer. Particularly bilayer tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation, and release profile [7]. After stoke and dementias, epileptic seizures constitute the 3rd most frequent neurologic disorders encountered in elderly in developed countries [8]. The aim of the present research work was to develop the different immediate and sustained release formulation of Divalproex sodium and compare their release profile, from above formulation select a best formulation for manufacturing bi-layered tablet. Hence, in the present research investigation attempt was made to formulate and evaluate bi-layered tablet of Divalproex sodium.

Drug Profile

Divalproex Sodium [9-12]

Chemical structure



Structure of Divalproex sodium

Divalproex sodium contains not less than 98% and not more than 102% of available valproic acid, $C_8H_{16}O_2$.

Chemical Name: 2-propyl-pentanoic acid sodium salt(2:1). Sodium hydrogen bis(2- propylvalerate) oligomer.

CAS Number: 76584-70-8

Brand name: Depakote, Depakote CP, Depakote ER, Epival, Stavzor.

Category: Anticonvulsant.

Molecular Formula: $C_8H_{16}O_2C_8H_{15}O_2Na$

Molecular weight: 310.41.

Description: Odorless, white or off-white crystalline powder.

Melting Point: 222 °C.

Solubility: soluble in ethanol (95%), methanol, Isopropyl alcohol, partially soluble in water, ether.

Storage: Store protected from moisture at a temperature not exceeding 30 °C.

Mechanism of action

Divalproex sodium is broad-spectrum anticonvulsant. It increases the availability of gamma- amino butyric acid (GABA), an inhibitory neurotransmitter. It has inhibitory action against GABA transaminase which breakdown GABA, it leads to increased concentration of GABA in the synapses. Other propose mechanisms of action that account for their anticonvulsant properties is it either enhance the action of GABA or mimic its action at postsynaptic receptor sites. It also block voltage gated sodium channels and T-type calcium channels, and cause inhibitory activity in the brain.

Pharmacokinetics

Absorption: Rapid absorption from gastrointestinal tract.

Distribution: Protein binding 80-90%

Metabolism: Metabolized almost entirely by the liver.

Excretion: Both bile and urine

Half Life: 9-16 hours

Bioavailability (oral): 84%

Materials and Methods

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 50 °C 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 1.

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 °C 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 no 2.

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 prepared formulations

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

Weight Variation Test [13]

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 [14]

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 [15]

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.

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

Tablet thickness [16]

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 [17]

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 °C. 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 [17]

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 °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.

Result and Discussion

Post-Compression Evaluation Parameters

The selected formulation of immediate and sustained release layer was prepared as bi- layered tablet and the post-compression parameters tabulated in 3 & Hardness and friability showed 7.05±0.15 and less than 1% respectively indicating the stability against physical stokes. Thickness was found to be 5.75±1.83 mm and content of uniformity 99.23±0.53 indicate uniform distribution of drug in both layer. In vitro drug release showed in table no 3.

In-vitro dissolution study

In vitro drug release profile of the immediate release and sustained release formulations were given in table no 5 and 6 respectively. Among all formulations of immediate release layer, formulation IF1, IF2, IF3 and IF4 showed the least drug release 80.40, 83.44, 82.68 and 94.82 respectively in 20 min as they consist of 5% SSG, 6% SSG, 5% CD and 6% CD

respectively. Formulation IF6 releases 98.62% drug in 20 min. The release profile of the formulation IF6 was believed be due to combination of SSG and CD. The result indicated that increase in the concentration of Superdisintegrants and combination of super disintegrants increases the release profile of drug. In sustained release formulation, the formulation SF1 (15% HPMC K4M) showed highest release in 16 hours compare to the formulations SF2 and SF3 (17.5 and 20% HPMC K4M) which showed the drug release of 97.81 and 84.11% in 18 hours. The formulations SF4 and SF5 containing 15% and 17.5% of HPMC K100M showed 98.82 and 97.69% drug release in 18 hours. SF8 was selected as best sustained release formulation based on dissolution profile as they showed more than 90% after 18 hours. The formulations found to contain combination of HPMC K4M and HPMC K100M in ratio 1:1 of the concentration 17.5% of total weight. The formulation SF9 showed floating behavior which consists of polymers in 20% of total weight so withdrawn the batches from the dissolution studies.

Discussion

Divalproex sodium a broad spectrum antiepileptic drug was chosen as a model drug as it is a right candidate for immediate as well as sustained release formulations. Both immediate and sustained release formulations were prepared by wet granulation method using PVP K30 solution as binding agent. Six batches (IF1-IF6) of immediate release layer and nine batches (SF1-SF9) of sustained release layer were developed by altering the excipients ratio as given in table number 13 and 14 respectively. Immediate release tablet were prepared by using Superdisintegrants such as sodium starch glycolate and croscarmellose sodium and Sustained release tablet were prepared by using polymer like HPMC K4M and HPMC K100M.

The tablets were evaluated for weigh variation, friability, thickness, drug content and *in vitro* dissolution parameters using standard procedure as shown in tablet number 24. Best formulations for preparation of bi-layered tablet were selected depending upon the dissolution profile as all the formulation showed good content uniformity, friability, hardness and other physical parameters.

The selected formulation of immediate and sustained release layer was prepared as bi- layered tablet and the post-compression parameters tabulated in 3. Hardness and friability showed 7.05±0.15 and less than 1% respectively indicating the stability against physical stokes. Thickness was found to be 5.75±1.83 mm and content of uniformity 99.23±0.53 indicate uniform distribution of drug in both layer. In vitro drug release showed in table no 4. The release pattern of the drug from bi-layered tablet showed same as the individual layer tablets of immediate and sustained release.

Table 1: 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

Table 2: Formulation of sustained release layer (SRL

-	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

Table 3: 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	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	-

Table 4: 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

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

Table 6: *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

Table 7: Dissolution study of Bi-layered Tablet

Time in min	% CDR	
	BTF	
	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

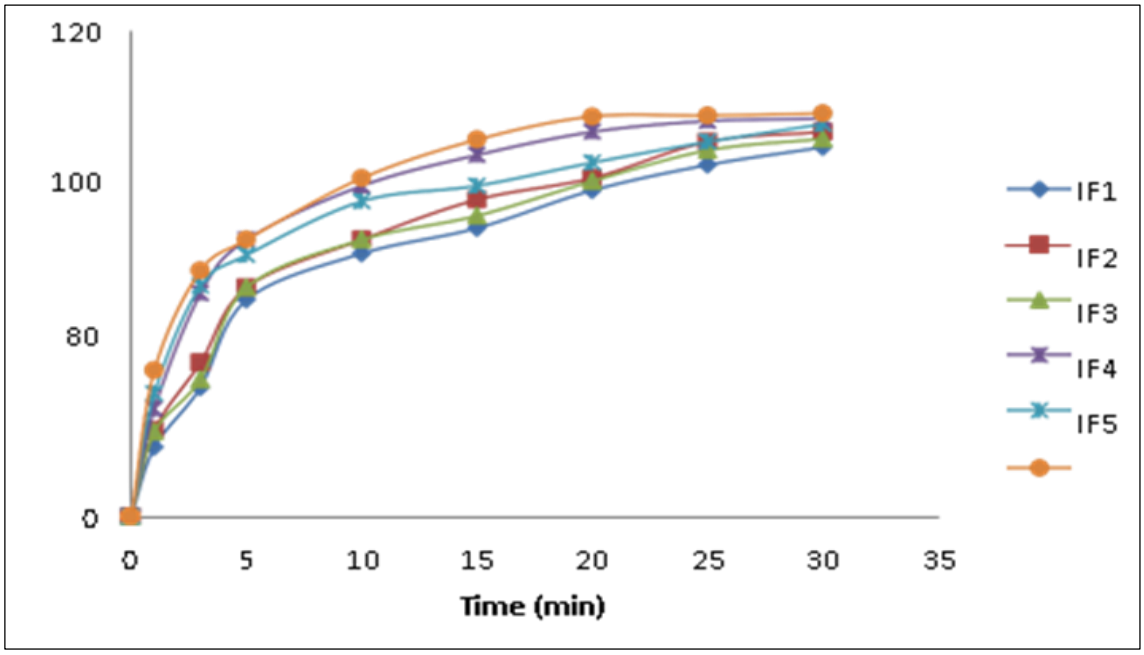


Fig 1: Release profile of immediate release layer

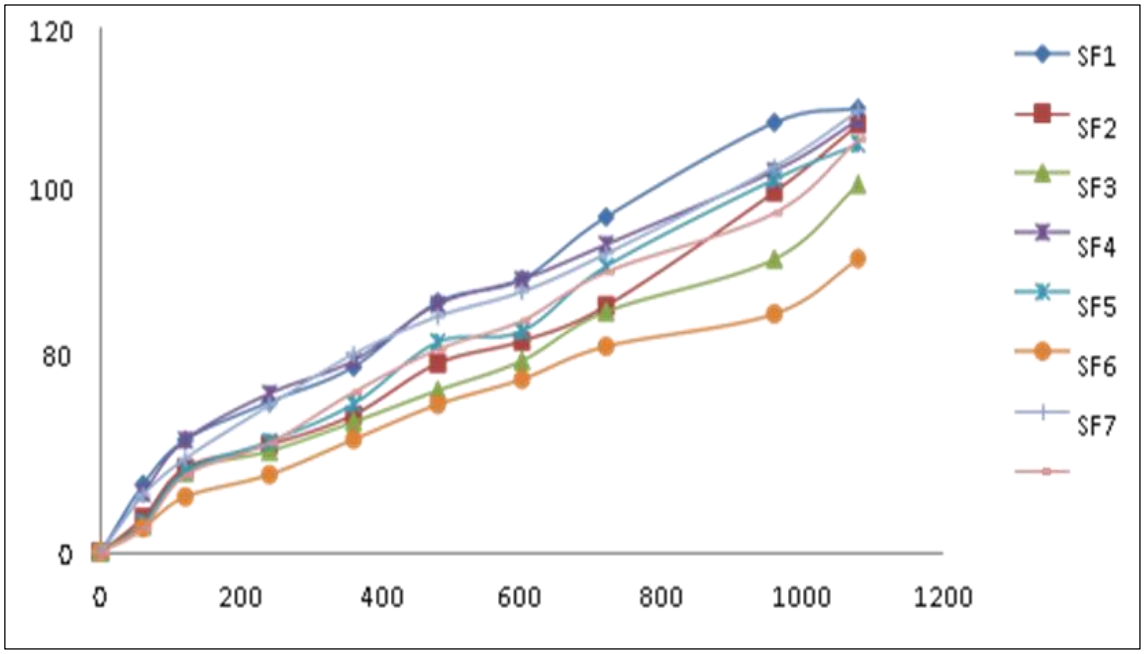


Fig 2: Release profile of sustained release layer

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, *in vitro* drug release and drug polymer interaction. 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.

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Conflict of Interest

The study is a self-sponsored and the authors declare no conflict of Interest.

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