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Research Article

Developing and Testing A Two-Layered Divalproex Sodium Tablet

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Abstract

Objective: to create and assess a bi-layered Divalproex Sodium tablet. Method: A broad-spectrum anticonvulsant is divalproex sodium. It makes the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) more readily available. Sodium starch glycolate, croscarmellose sodium, lactose, microcrystalline cellulose, polyvinyl pyrrolidone, magnesium stearate, talc, and hydroxyl propyl methyl cellulose were used as excipients in the wet granulation process with various superdisintegrants to create the bilayer tablet of Divalproex sodium.

Result: Divalproex sodium bi-layered tablet formulation and evaluation were completed in this work. Various immediate release and sustained release layer formulations have been created independently for the project. The best immediate and sustained release layer formulations from the aforesaid formulations were chosen based on the dissolution profile, and a bi-layered tablet was created.

Conclusion: The current study used the wet granulation method to create a bi-layered tablet of Divalproex sodium. The sustained release layer was made of polymers such HPMC K4M and HPMC K100M, while the immediate release layer was made of super disintegrants like sodium starch glycolate and croscarmellose. Each layer's best formulation was chosen for the bi-layered tablet, and it was then made. Divalproex sodium bi-layered tablets were tested for hardness, weight fluctuation, friability, homogeneity of drug content, in vitro drug release, and drug polymer interaction.

Keywords: Bi-layer tablets, flexibility, Divalproex sodium etc.

Introduction :

In order to improve patient convenience and compliance, the pharmaceutical industry has been more interested in creating a single dose form that combines two or more active pharmaceutical ingredients (API) during the past ten years. In order to prevent chemical incompatibilities across APIs through physical separation and to facilitate the creation of distinct drug release patterns, bi-layered tablets may be the best choice **[1]**.

Bi-layer tablets are made with a drug layer that releases the drug immediately and a second layer that releases the drug later, either as a second dose or in a prolonged release fashion. A bi-layered tablet can be used to segregate two incompatible substances, release two medications in succession, or create a sustained release tablet with a maintenance dose in the second layer and an instant release as the initial dose. Achieving a constant state medication level in the blood for a certain amount of time is the main objective of therapy. **[2]**

Advantage of Bi-layered tablets [3]

- Bi-layered execution with optional single-layer conversion kit.
- Cost is lower compared to all other oral dosage form.
- Greatest chemical and microbial stability over all oral dosage form.
- Objectionable odor and bitter taste can be masked by coating technique.
- Flexible concept.
- 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.
- Easy to swallowing with least tendency for hang-up.
- Suitable for large scale production.

Disadvantage of Bi-layered tablets

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

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.

Materials and Methods[6-13]

Hausner'sratio:

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

The tablets prepared were evaluated for the following parameters:

- *Weight variation*
- *Hardness*
  Friability
- *Drug content*

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.[13]

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.[14]

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.[15]

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Percentage friability was calculated by using the formula.

$$\text{Hausner'sratio} = \frac{weight\ initial - weight\ final}{weight\ initial} \text{X100}$$

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 metric scale is read first then read "hundred 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.[16]

Result and Discussion

Determination of λ max

The λ max of Divalproex sodium was found to be 210 nm in methanol and phosphate buffer pH.Standard curve of Divalproex sodium. The absorbance was measured in a UV spectrophotometer at 210 nm against methanol.

Table: 1 Spectrophotometric data of Divalproex Sodium

S. No.	Cone. (µg/ml)	Absorbance			Mean± SD
		Trial 1	Trial2	Trial 3	
1	0	0.000	0.000	0.000	0.000±0.000
2	5	0.049	0.042	0.045	0.047±0.003
3	10	0.096	0.094	0.097	0.096±0.003
4	15	0.144	0.143	0.147	0.143±0.003
5	20	0.184	0.187	0.186	0.188±0.002
6	25	0.239	0.236	0.236	0.237±0.002

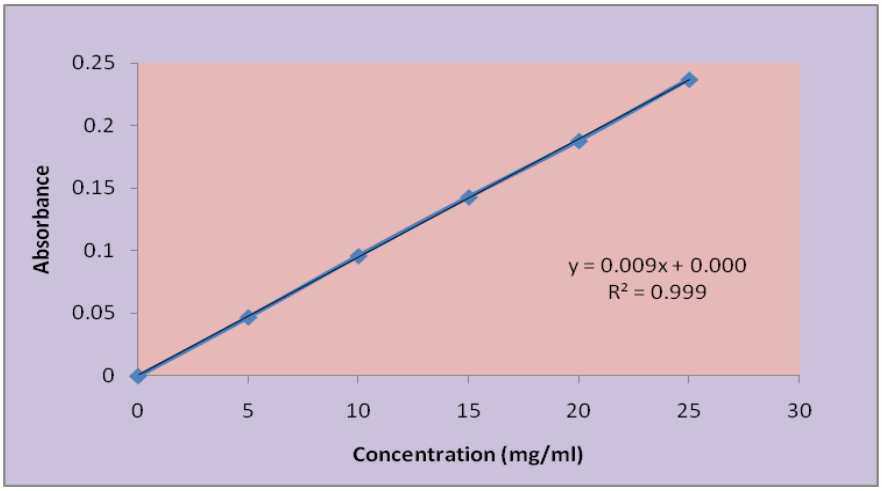

Figure: 1 Standard graph of Divalproex sodium

Table :2 Solubility of divalproex sodium

Solvents	Solubility (mg/ml)
Distilled water	7.34
Methanol	48.44
Chloroform	54.23
Phosphate buffer pH 6.8	29.73

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 the given table. The result shows maximum solubility in chloroform.

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 results found to be 219223°C.

Conclusion

the sustained release layer was made of polymers like HPMC K4M and HPMC K100M. Each layer's best formulation was chosen for the bi-layered tablet, and it was then made. Divalproex sodium bi-layered tablets were tested for hardness, weight fluctuation, friability, homogeneity of drug content, in vitro drug release, and drug polymer interaction. Based on the observations, it can be said that the Divalproex sodium bi-layered tablets that were created with the use of super disintegrants, release retardant polymers, and various excipients were able to display every characteristic of a bi-layered tablet. As a result, they are lowering dosage intake, minimizing side effects associated with it, lowering costs, and eventually increasing patient compliance and medication effectiveness

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Table: 3 Dissolution study of Bi-layered Tablet.

Time m mm	% CDR	
	BTF	
	IRL	SRL
0	0.000±0.000	0.000±0.000
10	82.423±1.062	-
20	97.351±1.146	-
30	98.321±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

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

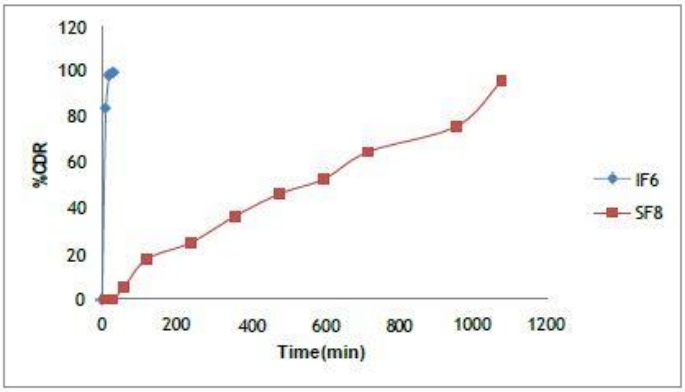

Figure: 2 Release profile of Bi-layered Tablet

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