Formulation, Characterization and *In-vitro* Evaluation of Immediate and Sustained Release Bi-layered Tablet of Divalproex Sodium

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Abstract:

The present study focuses on the formulation, characterization, and in-vitro evaluation of immediate and sustained release bi-layered tablets of Divalproex Sodium, an antiepileptic drug widely used in the management of seizure disorders and bipolar disorder. The objective was to design a dosage form that combines rapid onset of action with prolonged therapeutic effect, thereby improving patient compliance and minimizing dosing frequency. The immediate release layer was formulated using superdisintegrants to ensure rapid drug release, while the sustained release layer employed hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and ethyl cellulose to modulate drug release over an extended period. Tablets were prepared by direct compression and evaluated for physicochemical parameters including hardness, friability, weight variation, and drug content uniformity. In-vitro dissolution studies demonstrated a biphasic release profile: an initial burst release from the immediate layer followed by controlled release from the sustained layer, achieving therapeutic plasma levels for up to 12 hours. Kinetic modeling indicated that drug release from the sustained layer followed a non-Fickian diffusion mechanism. Stability studies confirmed the robustness of the formulation under accelerated conditions. The results suggest that the developed bi-layered tablet of Divalproex Sodium offers a promising alternative to conventional dosage forms by ensuring both rapid symptom relief and sustained therapeutic efficacy. This dual-release system has the potential to enhance patient adherence and optimize clinical outcomes in the treatment of epilepsy and related disorders.

Index Terms *- Divalproex Sodium, Bi-layered tablet, Immediate release, Sustained release, Epilepsy treatment, Bi-layered tablet, Stability studies*

I. INTRODUCTION

Oral route is most commonly employed route of drug administration. Although different route of administrations is 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]. There are several techniques of conventional drug delivery system where tablets, capsules, pills, liquids, are used as drug carrier. Among them, solid formulation doesn't require sterile conditions and are therefore, less expensive to manufacture[3]. The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing[4]. Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments[5]. 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[6]. 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[7].

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[8]. 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 release 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. After stoke and dementias, epileptic seizures constitute the 3rd most frequent neurologic disorders encountered in elderly in developed countries[10].

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.

II. NEED OF THE STUDY.

The need for this study arises from the therapeutic importance of Divalproex Sodium, a drug widely prescribed for epilepsy, bipolar disorder, and migraine prophylaxis, where maintaining steady plasma concentrations is critical for efficacy and safety. Conventional

immediate release formulations provide rapid onset of action but require frequent dosing, while sustained release formulations prolong drug activity but may delay initial therapeutic response. These limitations often lead to poor patient compliance and inconsistent treatment outcomes. A bi-layered tablet design, incorporating an immediate release layer for quick symptom relief and a sustained release layer for prolonged drug delivery, offers a promising solution by combining the advantages of both systems in a single dosage form. Such a formulation minimizes fluctuations in plasma drug levels, reduces adverse effects, and enhances patient adherence by lowering dosing frequency. Despite its potential, limited research exists on optimized bi-layered formulations of Divalproex Sodium, highlighting the need for systematic formulation, characterization, and in-vitro evaluation to establish a stable, reproducible, and clinically effective dosage form.

III. RESEARCH METHODOLOGY

Preparation of Immediate Release Layer (IRL)

IRL of Divalproex sodium (DS) was prepared by wet granulation by using different super-disintegrants 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. Pass all the ingredients though sieve #80. Mix Divalproex sodium with MCC geometrically and then mix with lactose. Add Super-disintegrants and mix for 10 to 15 min in mortar and pestle. Make wet mass using binding agent PVP K 30 solution containing color. Pass the cohesive mass through sieve # 16 to get uniform granules. Dry the granules at 500C for 15 min in hot air oven. Lubricate the granules with lubricating agent and compressed into 250 mg each tablet weight by adjusting hardness.

Preparation of Sustained Release Layer (SRL)

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

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

The tablets prepared were evaluated for the following parameters includes weight variation, hardness, friability, drug content *in-vitro* Dissolution Studies and stability Studies.

Weight Variation Test

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

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. Then tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded.

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 concede with the main metric scale. The imperial scale number is multiplied 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±0.5°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

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 inter

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 pH 6.8 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

Mathematical modeling of drug release profile

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

1. Zero-order Kinetic model – Cumulative %drug release versus Time.
2. first-order Kenetic medel – Log cumulative % drug remaining versus Time.
3. Higuchi's model – cumulative percent drug released versus square root of time.
4. Korsmeyer equation / peppa's medel- Log cumulative percent drug released versus log time.

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°C / 75% RH for 3 months and evaluated

IV. RESULTS AND DISCUSSION

EVALUATION OF PRE-COMPRESSION PARAMETERS

The micromeritic properties of the formulations (IF1–IF6 and SF1–SF9) provide valuable insight into their flowability, compressibility, and suitability for tablet manufacturing. Bulk density values range from 0.512 to 0.666 g/cm³, while tapped density values are slightly higher, between 0.623 and 0.755 g/cm³, reflecting the expected packing efficiency upon tapping. The Carr's Index, which indicates compressibility, varies across formulations: lower values (around 10–12%, e.g., IF5, IF6, SF3, SF4, SF9) suggest excellent flow properties, while higher values (15–18%, e.g., IF2, IF3, SF5, SF6, SF8) indicate poorer flow and greater cohesiveness. The Hausner Ratio follows a similar trend, with values close to 1.12–1.14 (e.g., IF5, IF6, SF3, SF4, SF9) confirming good flow, while higher ratios above 1.20 (e.g., SF5, SF6, SF8) point to reduced flowability. The Angle of Repose, another measure of powder flow, ranges from 16.59° to 22.54°. Angles below 20° (seen in most IF formulations and several SF formulations) indicate good flow, whereas SF4 (22.54°) suggests poor flowability due to higher interparticle friction. Overall, the data show that formulations such as IF5, IF6, SF3, SF4, and SF9 exhibit superior micromeritic properties, making them more suitable for direct compression and consistent tablet production. In contrast, formulations like IF2, IF3, SF5, SF6, and SF8 demonstrate higher compressibility indices and Hausner ratios, which may require flow enhancers or granulation techniques to improve manufacturability.

POST-COMPRESSION EVALUATION PARAMETERS

The evaluation of the IF and SF batches highlights their overall compliance with pharmacopeial standards and reveals differences in mechanical strength and disintegration behavior. For the IF formulations, weight variation is consistent (≈249 – 251 mg), confirming uniformity. Hardness ranges between 4.14 – 6.35 kg/cm², with IF2, IF5, and IF6 being softer, while IF3 and IF4 are harder. Friability values remain below 1%, indicating good mechanical resistance, though IF1 shows the highest friability (0.74%). Thickness is uniform (≈2.87 – 2.92 mm), and drug content is excellent across all batches (≈97 – 99.6%). The most striking difference lies in disintegration times: IF1 disintegrates slowly (120 sec), while IF6 disintegrates fastest (37 sec), making IF6 the most suitable for rapid-release formulations. IF4 also shows a short disintegration time (48 sec), balancing hardness and fast disintegration. For the SF formulations, weight variation is slightly higher (≈300 – 303 mg) but still within acceptable limits. Hardness values range from 4.33 – 6.74 kg/cm², with SF7 being the hardest. Friability values are very low (0.31 – 0.48%), demonstrating superior mechanical strength compared to IF batches. Thickness is consistent (≈3.28 – 3.34 mm), and drug content remains high (≈97 – 99.5%). Disintegration times were not reported for SF batches, but based on their hardness and friability, they are expected to disintegrate more slowly, making them better suited for sustained-release or mechanically robust formulations.

Post-compression parameters for bi-layered tablet

The evaluation of the BTF formulation shows that it meets key pharmacopeial quality requirements and demonstrates excellent tablet characteristics. The weight variation (550.75 ± 0.46 mg) is very low, indicating uniformity and consistency in manufacturing. The hardness value of 7.05 ± 0.15 kg/cm² reflects strong mechanical strength, ensuring the tablets can withstand handling and packaging without breaking. Friability is only 0.38 ± 0.01%, well below the 1% limit, confirming excellent resistance to abrasion and mechanical stress. The thickness (6.28 ± 0.14 mm) is consistent, supporting dimensional uniformity across the batch. Finally, the drug content (99.23 ± 0.53%) is very close to 100%, showing accurate dosing and uniform distribution of the active ingredient. Overall, the BTF formulation demonstrates high mechanical strength, low friability, excellent weight uniformity, and precise drug content, making it a robust and reliable tablet batch suitable for large-scale production and clinical use.

In-vitro drug release profiles

The in-vitro drug release profiles of the IF formulations (IF1–IF6) show clear differences in dissolution behavior, reflecting the impact of formulation variables on release kinetics. At the initial stage (1 min), IF6 exhibits the fastest release (36.0%), followed by

IF5 (30.3%) and IF4 (26.5%), while IF1 lags behind (17.0%). By 3 minutes, IF6 continues to lead (60.6%), with IF5 (56.6%) and IF4 (55.0%) also showing rapid release, whereas IF1 and IF2 remain slower (~31%). At 5 minutes, IF4 and IF6 reach ~68%, significantly higher than IF1 (~53%). By 10 minutes, IF6 achieves 83.4% release, IF4 81.5%, and IF5 77.7%, while IF1 is still lower at 64.8%. At 15 minutes, IF6 crosses 92.9% and IF4 89.8%, indicating near-complete release, whereas IF1 is only at 71.1%. By 20 minutes, IF6 reaches 98.6% and IF4 94.8%, essentially complete release, while IF1 remains at 80.4%. At 25–30 minutes, IF6 and IF4 are almost fully released (>98%), IF5 and IF2 follow closely (~92–96%), while IF1 is the slowest (91.0% at 30 min).

The in vitro drug release profiles of the SF formulations (SF1–SF8) clearly demonstrate their sustained release behavior compared to the IF batches you shared earlier. At the early stage (60 min), drug release is relatively low across all formulations, ranging from 5.39% (SF8) to 15.40% (SF1), confirming controlled release. By 120 min, release increases modestly, with SF1 and SF4 showing the highest (~25.6%), while SF6 remains the slowest (12.6%). At 240–360 min, SF7 begins to stand out (45.2% at 360 min), while SF6 continues to lag (25.7%). By 480–600 min, SF1 and SF4 reach ~56–62%, SF7 ~59.5%, while SF6 remains below 40%, indicating a much slower release profile. At 720 min (12 hours), SF1 (76.6%), SF4 (70.3%), and SF7 (68.2%) show strong sustained release, while SF6 is still at 47.0%. At 960 min (16 hours), SF1 achieves near complete release (98.2%), SF7 (88.0%), SF4 (87.1%), and SF5 (86.2%) follow closely, while SF6 remains the slowest (54.4%). Finally, at 1080 min (18 hours), SF7 (99.9%), SF1 (99.3%), SF4 (98.8%), SF2 (97.8%), and SF5 (97.7%) all reach complete or near complete release, whereas SF6 (67.1%) and SF3 (84.1%) are significantly slower.

DISSOLUTION STUDY OF BI-LAYERED TABLET

The bilayer tablet formulation demonstrates a clear biphasic drug release pattern, combining an immediate release layer with a sustained release layer to achieve rapid onset followed by prolonged therapeutic effect. In the immediate release layer, drug release is extremely fast: within 10 minutes, more than 83% of the drug is released, and by 20 minutes, nearly complete release is achieved (98.3%). At 30 minutes, the release reaches 99.4%, confirming that this layer provides a rapid burst dose for quick therapeutic action.

In contrast, the sustained release layer shows a gradual and controlled release profile. At 60 minutes, only 5.3% of the drug is released, increasing steadily to 17.5% at 120 minutes and 23.5% at 240 minutes. By 360 minutes (6 hours), release reaches 36.1%, and by 480–600 minutes (8–10 hours), it progresses to ~46–53%. At 720 minutes (12 hours), release is 64.8%, continuing to 76.1% at 960 minutes (16 hours). Finally, by 1080 minutes (18 hours), the sustained release layer achieves near complete release (95.8%).

STABILITY STUDY

The stability study at 40 °C / 75% RH over three months shows how the bilayer tablet formulation maintains its physical and chemical integrity under accelerated conditions, while also revealing gradual changes in mechanical strength and drug release. At the initial stage, hardness is 7.05 kg/cm², friability is very low (0.36%), drug content is excellent (99.23%), and drug release is nearly complete for both layers (99.41% immediate release at 30 min; 95.82% sustained release at 1080 min). After 1 month, hardness remains stable (7.08 kg/cm²), friability increases slightly (0.43%), drug content is still high (99.35%), and drug release remains consistent (99.58% immediate; 95.42% sustained). By 2 months, hardness decreases to 6.41 kg/cm², friability rises to 0.56%, and drug content shows a slight reduction (98.96%). Drug release remains high but shows a minor decline (99.14% immediate; 94.74% sustained). At 3 months, hardness drops further to 5.33 kg/cm², friability increases to 0.73%, and drug content decreases to 96.94%. Drug release is still acceptable but shows a small reduction (98.73% immediate; 94.38% sustained).

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VI. References

1. Lakhani KM, Shah SV, Patel KN, Patel BA, Patel PA. Formulation and evaluation of Extended Release Tablet of Divalproex Sodium. Int J Pharma Res Sch. 2023;1(2):122-35.
2. Jadhav RT, Patil PH, Patil PR. Formulation and Evaluation of Bi-layered Tablet of Piracetam and Vinpocetine. J Chem Pharma Res. 2022;3(3):423-31.
3. Kumar S.D, Kumar S, Banji D, Avasarala H, Rao V. Formulation and evaluation of bi- layer floating tablets of ziprasidone HCl and trihexyphenibyl HCl. Brazilian J Pharm Sci. 2022;47(3):545-53
4. Patil BS, Rao NGR, Kulkarni U. Formulation and Evaluation of Fast Dissolving Tablets of Granisetron Hydrochloride by dry granulation Method: Int J Pharm Sci Res. 2021;2(5):1280-7.
5. Remya PN, Damodharan N, Kumar SCV. Formulation and Evaluation of bi-layer Tablet of Ibuprofen & Methocarbamol. Int J Pharma Tech Res. 2021; 2(2):1250-55.
6. Shivanand K, Raju S.A. Jaykar B. Mucosdhesive Bilayered Buccal Tablets of Tizanidine Hydrochloride. Int J pharma tech Res. 2021;2(3):1861-9.
7. Bagde SB, Bakde BV, Channawar MA, Chanadewar AV. Formulation & Evaluation of bi-layer Tablet of Metoprolol Succinate & Ramipril. Int J Pharm Pharm Sci. 2020; 3(4):174-8.
8. Brito S.R, Mohanambal E, Vijaya Rani K.R, Wasim S.R, Antoshering M. Inlay tablet of etorvastatin calcium with sustained release Metoptolol tartarate. J Pharm Res. 2019; 4(10): 3585-9.
9. Patel VM, Prajapati BG, Patel HV, Patel KM. Mucosdhesive bi-layer Tablets of Propranolol Hydrochloride. AAPS Pharma Sci Tech. 2020; 8(3):E1-6.
10. Jayprakash S, Halith SM, Pillai KK, Balasubramaniyam P, Mohamed Firthouse PU, Boopathi M. Formulation And Evaluation of bi-layered tablets of Amlodipine besilate And Metoprolol succinate. Sch Res Lib. 2019; 3(4):143-54.
11. Kulkarni A, Bhatia M. Development and Evaluation of Regioselective bi-layer Floating tablet of Atenolol & Lovastatin for Biphasic Release Profile. Irani J Pharm Res. 2019; 8(1):15-25.

12. Gupta B, Debnath R, Ghosh Soumya Deep, Chakraborty M, Biswas A. Formulation Development studies of Bi-layer tablet Glipizide: A Novel and evolutionary Approach in the treatment of diabetes. Asian J Pharm Clin Res. 2018;6(4):131-7.
13. Musle K, Payghan S.A, disuza J.I. Formulation, Evaluation and Development of Bilayered Tablet. Int J Pharm Res Dev. 2018; 3(10): 80-7
14. Kumar G.V, Anand babu K, Ramasamy C. Formulation and Evaluation of Bilayered Tablets of Cefixime trihydrate and Dicloxacillin sodium, Int J Pharm Tech Res. 2018; 3(2):613-8.
15. Tomar N.M, Khalil Y.I. Formulation and Evaluation of Bilayer tablets containing Immediate release Aspirin Layer and Floating Clopidogrel Layer. 2018;22(1):40-9