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# Review Paper on Multi -Layered Tablet of Divalproex Sodium

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**ABSTRACT:-** 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<sup>1</sup>. 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. There are several techniques of conventional drug delivery system where tablets, capsules, pills, liquids, are used as drug carrier. Among them, solid formulation do not require sterile conditions and are therefore, less expensive to manufacture. 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.

**KEYWORDS:** - Bi-layered tablet, Multi-layered, Divalproex Sodium

## I. INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing<sup>4</sup>. Tablets are solid dosage forms containing medicinal substances with or without suitable diluents<sup>5</sup>. 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<sup>6</sup>. 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 [1, 2].

### Advantage of the tablet dosage

- They are unit dosage form and great dose precision and the least content variability.
- Cost is lowest of all oral dosage form.
- Lighter and compact.
- Easiest and cheapest to package and strip.
- Easy to swallow.
- Objectionable odour and bitter taste can be masked by coating technique.
- Suitable for large scale production.

### Disadvantages of tablet dosage form

- Difficult to swallow in case of children and unconscious patients.
- *Some drugs resist compression into dense compacts, owing to amorphous nature, lower density character.*
- *Drug with poor wetting, slow dissolution properties, optimum absorption in GIT may be difficult to formulate.*

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. 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 [3, 4].

**Advantages of Immediate Release Drug Delivery System**

- Improved compliance
- Improved stability, bioavailability
- Suitable for controlled/sustained release actives
- Allow high drug loading
- Ability to provide advantages of liquid medication in the form of solid preparation
- Adaptable and amenable to existing processing and packaging machinery
- Cost-effective
- Improved solubility of the pharmaceutical composition

Categories of the drug which are preferable for immediate release are analgesic and anti-inflammatory 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 [5, 6].

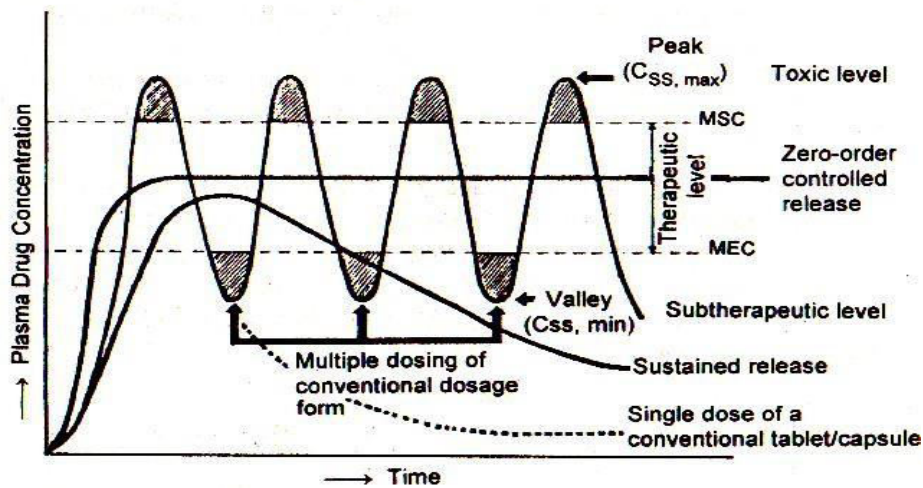


Figure 1: A Hypothetical Plasma Concentration Vs Time Profile Advantages of sustained release dosage forms

- 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:
  - Maximizing availability with dose.
  - Minimize or eliminate local side effects.
  - Minimize or eliminate systemic side effects.
  - Minimize drug accumulation with chronic dosing.

- Safety margin of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced and sensitive patients.
- 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.

## II. LITERATURE REVIEW

**Lakhani KM et al. [7]**, designed an oral Extended release matrix tablet of Divalproex sodium, by a direct compression method using HPMC K100M and Eudragit L100 as matrix forming polymer. Prepared tablets were evaluated for various physicochemical parameters like hardness, thickness, friability, weight variation, content uniformity and *in vitro* drug release. The drug release profile was optimized by using 3<sup>2</sup> full factorial designs where, HPMC K100M and Eudragit L100 were taken as the independent variables. Among all ten formulations, batch F8 containing HPMC K100M 15% and Eudragit L100 10% was found to be optimized formulation as it has almost identical dissolution profile with marketed product.

**Vamsy KA et al. [8]**, have prepared extended release Tablets of Divalproex sodium, by a direct compression technique. They formulated 5 different formulations using various polymer like HPC-HF, HPMC K4M, HPMC K15M, HPMC K100M in different proportion. FTIR studies shown that the drug and excipients were compatible with each other. Compressed tablets were evaluated for weight variation, hardness and *in vitro* dissolution using paddle (USP type II) method. Among the five formulations, batch DERT-V containing 19.5 of HPMC K100M and % of HPMC K4M taken as ideal formulation of extended release tablets for 18 hours release as it fulfill all the requirements for extended release tablet.

**Jadhav RT et al. [9]**, have developed bi-layered tablet of Piracetam and Vinpocetine. Both of layers were prepared by wet granulation method using PVP K-30 and maize starch as granulating agent respectively. Formulated tablets were evaluated for thickness, weight variation, hardness, friability, drug content and *in vitro* drug release. Drug content was evaluated using HPLC method. Among all the formulations, tablets of batch P2 of Piracetam and V2 of Vinpocetine was taken as optimized formula and formulated as bi-layered tablet due to its higher dissolution rate and complied all official specifications. The selected batches were kept for stability study at 40°C and 75% RH for 3 months.

**Kumar S.D et al. [10]**, was formulated the bi-layered floating tablet of ziprasidone Hcl as immediate release and Trihexyphenidyl Hcl as sustained release. HPMC K4M / HPMC K15M used as polymer for sustained release of the drug and sodium bicarbonate as the floating layer. IR shows that no any interaction among the drugs and excipients. The final tablets were evaluated for the different parameter like Hardness, thickness, friability, weight variation, disintegration & dissolution. Release profile of the tablet was carried out by using USP XXIII dissolution apparatus. Among the 20 formulation F1 F2 F11 and F12 are optimized formulation.

**Shivanand K et al. [11]**, have prepared bi-layer buccal tablets of Tizanidine hydrochloride (TZD HCl), by a direct compression method, using mucoadhesive polymers carbopol 934(CP), HPMC K4M, HPMC K15M and sodium carboxymethylcellulose along with ethyl cellulose as an impermeable backing layer. FTIR and DSC found to be compatible with selected polymers. Bi-layered buccal tablets containing CP and HPMC K4M in the ratio 1:1 (BT1) had the maximum percentage of *in-vitro* drug release in 6 hours. A modified balance method was used for determining the *ex-vivo* mucoadhesive strength. The bioadhesive strength exhibited by the HPMC K4M and Na CMC tablets can be considered satisfactory for maintaining them in the oral cavity.

**Remya PN et al. [12]**, have prepared Ibuprofen and Methocarbamol bi-layered tablets by wet granulation process by using povidone k-30 as binder. The *in-vitro* disintegration time was found in the range of 3.23 to 7.34 min. sec.

Among the formulations tablets of formulation-8 was taken as optimized formula due to its higher rate of dissolution. The percentage drug release for formulation F8 shows the better drug release between 95.1 to 97.2%. It was concluded that Ibuprofen, Methocarbamol bi-layer tablets can be prepared successfully as it satisfies all the criteria as a bi-layered tablet and would be alternative to the currently available conventional tablets.

**Patil SS et al. [13]**, have developed gastro retentive bi-layer floating tablets of Rosiglitazone maleate by using different super disintegrants and controlled release layer using hydroxypropyl methylcellulose K100M (HPMC K100M) by direct compression method. Among various super disintegrants used, croscarmellose at the concentration of 8% was found sufficient to cause rapid drug release whereas 50% HPMC of the total weight of the tablet effectively controlled the drug release over a period of 24hrs. Sodium bicarbonate at the concentration of 14 %w/w reduced the buoyancy lag time to less than 3 minute for the optimized tablet (F5). The total floating time for different formulations was in the range of 10-28hrs. Release profiles of formulation F5 indicated that, increasing the polymer concentration has drastically retarded the release of rosiglitazone maleate over a period of 24hrs. Tablets followed diffusion controlled first order kinetics. During the stability period optimized formulation was found to be stable with respect to physico-chemical and drug release characteristics.

**Patel VM et al. [14]**, prepared bi-layer buccal tablets by homogeneously mixing the drug with CP, Na-alginate, PVP K-30, D-mannitol, and PEG 4000 in a glass mortar for 15 minutes and the mixture (100 mg) was then compressed by using a direct compression method. Tablets containing Na-alginate and CP in the ratio of 5:1 (F2) had the maximum percentage of *in vitro* drug release without disintegration in 12hrs. The formulation F4 was optimized based on good bioadhesive strength ( $28.9 \pm 0.99$  g) and sustained *in vitro* drug permeation ( $68.65\% \pm 3.69\%$  for 12hrs). The formulation F4 was applied to rabbit oral mucosa for *in vivo* studies. The formulation inhibited Isoprenaline-induced tachycardia. The studies conducted in rabbits confirmed the sustained release as compared with intravenous administration.

**Bagde SB et al. [15]**, developed ten batches of ER/IR bi-layer tablets of Metoprolol succinate and Ramipril by using wet granulation and dry granulation technique, respectively. Hydroxypropylmethylcellulose K100M and sodium carboxymethylcellulose was used for extended release of Metoprolol succinate. FTIR and DSC studies shown that the drug and excipients were compatible with each other. Compressed tablets were evaluated for weight variation, hardness, and *in vitro* dissolution using paddle (USP type II) method. Among the ten formulations, F showed compliance with US pharmacopoeial standards, extended the release of drug for 20hrs with 99.6% drug release and subjected to stability studies for 1 month at 40°C/75% R.

**Jayaprakash S et al. [16]**, developed bi-layered tablet of Amlodipine besilate immediate release layer by direct compression method and Metoprolol succinate sustained release layer were prepared by wet granulation method. In the formulation of immediate release sodium starch glycolate and pregelatinised starch were used as super disintegrant and PVP K30 as binder was used for sustained release layer. An *in-vitro* drug release study shows that optimized formulation showed 9.96%, 35.56%, 52.12%, 90.46% release for Metoprolol succinate in 1, 4, 8, 20hrs respectively. However, Amlodipine besilate released 98.28% at the end of 30 minutes. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug and release follows first order kinetics.

**Kasid I et al. [17]**, developed bi-layer tablets of optimized Gliclazide sustained release layer and Lisinopril fast dissolving layer by double compression method. Lisinopril was formulated as fast dissolving layer using sodium starch glycolate, croscarmellose sodium as super disintegrants. Gliclazide was formulated as sustained release layer using different polymer matrix like hydroxyethylcellulose, hydroxypropylcellulose, and ethylcellulose and evaluated for physical parameter along with *in vitro* release studies. The *in vivo* antidiabetic activity suggested that Lisinopril potentiate hypoglycemic effect of Gliclazide and blood glucose level was constantly maintained up to 24hrs. The FTIR study conducted using a combination of drugs along with excipients and polymers revealed that combination can be safely prepared.

**Kulkarni A et al. [18]**, developed bi-layer regioselective floating tablets of Atenolol for sustained release and Lovastatin for immediate release by direct compression method. The immediate release layer of Lovastatin comprised sodium starch glycolate as a super disintegrant and the sustained release layer of Atenolol comprised HPMC K100M and xanthan gum as the release retarding. Sodium bicarbonate was used as a gas generating

agent was used for formulation of the bilayer tablets. Roentgenography study shows all formulations floated for more than 12hrs. More than 90% of Lovastatin was released within 30 min. The release of Atenolol was found to follow a mixed pattern of Korsmeyer-Peppas, Hixson-Crowell and zero order release models. The optimized formulation was found to be buoyant for 8hrs in stomach. Therefore, biphasic drug release pattern was successfully achieved through the formulation of floating bi-layer tablets in this study.

**Brito S.R et al. [19]**, was design a dual retard technique of once daily inlay tablet of atorvastatin calcium as immediate release and Metoprolol tartarate as Sustained release formulation. For immediate release Sodium starch glycolate, cross povidone and croscarmellose are used as the super disintegrants and for the sustained release guar gum, Eudragit, and HPMC are used as the polymer. Differential scanning calorimetry shows no interaction among the drug and the used excipients. Formulated tablet are evaluated for the thickness, Hardness, weight variation, disintegration, swelling erosion behavior, *in vitro* release and stability studies. Six formulations (F1-F6) were prepared among that F4 shows expected release pattern and follows zero order.

### III. CONCLUSION

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.

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