INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Paper

Formulation and Evaluation of By-Layered Tablet

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ARTICLE INFO

Published: 28 Mar. 2025
Keywords:
Layered Tablet, patent extension, therapeutic efficacy, marketing
DOI:
10.5281/zenodo.15101573

ABSTRACT

Several pharmaceutical companies are currently developing bi- layer tablets for a variety of reasons like patent extension, therapeutic efficacy, marketing etc. This technology has been used to reduce capital investment. Modified tablet presses have been used to develop bilayer tablets in order to overcome problems associated with tablets like layer separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, reduce yield etc. When high production output is required a modified tablet, press is used.

INTRODUCTION

Since many decades' treatment of acute and chronic disorders have been done with the help of conventional drug delivery systems like tablets, capsules, solutions, suspensions, creams, ointments, suppositories, liquids and injectable. These types of conventional therapy are most widely used and it is available commonly on prescription as well as over the counter. The conventional therapy is regarded as prompt release therapy. In order to maintain and achieve drug concentration within effective therapeutic range the conventional therapy has to be administered several times in a day and slight delay causes fluctuation in drug concentration which leads to poor patient compliance as well as poor aesthetic value. In order to avoid fluctuation or disadvantages of conventional therapy several new techniques have been developed to improve patient compliance which is capable of controlling rate of drug delivery to the site of action. Oral route is one of the best and most widely used routes for administering drug to site of action. Tablets and capsules are the most widely used conventional therapy for the patients because they can be easily administered without any problem.

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablets in which one layer is immediate release which act as loading dose and second layer is sustained release which act as maintenance dose. Bilayer tablet is the most recent form of tablet which comprises of combination of immediate release tablets and sustained release tablets. It is a type of once a day oral dosage form which acts immediately upon administration and provides the action for prolonged period of 12-24hrs. Bilayer tablets can be an excellent technique to avoid all types of incompatibilities between drugs, API and excipients etc.

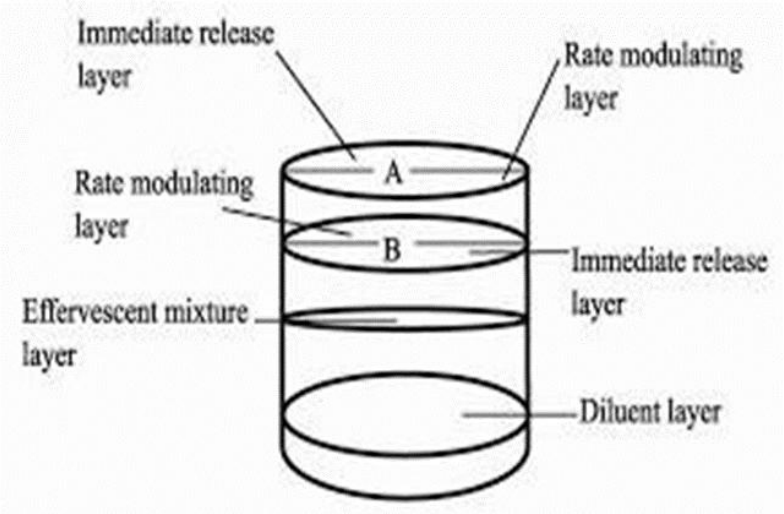


Figure 1: Bi-layer tablet

Advantages of bilayer tablet

- Release of both drugs start immediately.
- Combination of incompatible drugs can be easily composed
- Combination of different release profile drugs can be formulated.
- Pill burden can be reduced by reducing dose of individual drug due to additive effect.
- Side effects can be reduced by using combination of drugs which can nullify the adverse effects of each other.
- Provides elegance to the products.
- Treats different disorders in same patient at the same time by administering one pill.
- This type of tablet only allows synergistic combination.

Limitations of bilayer tablet

- Capping
- Hardness problem
- Layer separation
- Order of layer sequence
- Cross contamination between layers
- Elastic mismatch of adjacent layers.

Ideal candidates of bilayer tablet

- Drugs which produces additive or synergistic effect i.e. antiasthamatic drugs like salbutamol + theophylline.
- Drugs having opposite side effects may reduce the side effects of each othere.g. omeprazole + NSAIDS, hydrochlorothiazide + amiloride.
- Incompatible drugs.
- Low biological half-life (ideal for modified release bilayer).
- Unstable at intestinal pH (ideal for bilayer floating).
- High first pass metabolism with low biological half-life (ideal for buccoadhesive bilayer).

Approaches for bilayer tablet

It consists of two drugs in same tablet having different layers. One layer is immediate release layer and other layer is sustained release layer.

Different types of bilayer tablet

- Bilayer modified release tablet
- Bilayer floating tablet
- Bilayer buccoadhesive tablet.

Bilayer modified release tablet

This type of bilayer tablet consists of two different types of release profile layers. One layer is immediate release layer in which drug will release 90% of concentration within 30 minutes. Other layer is sustained release layer where drug will release slowly up to 12-24 hrs.

e.g. Metaclopramide HCl+ Ibuprofen.

Bilayer floating tablet

This type of bilayer tablet consists of such type of combination of drugs which are sensitive to gastrointestinal pH. One layer of drug gets metabolized in stomach, while other layer gets degraded in intestine.

e.g. Rosiglitazone Maleate.

Bilayer buccoadhesive tablet This type of bilayer tablet consists of drugs which have mucoadhesion and have the property to get attached to mucous membrane of buccal region and sustain the release of drug.

e.g.Propanolol HCl

Reasons for selecting bilayer tablet by pharmaceutical industry

- To get synergistic effects.
- To inhibit drug interaction.
- Drug incompatibility.
- Patent extension.
- Therapeutic justification.
- To reduce capital investments.
- To get sustained release tablets preparation in combination in which one layer is immediate release form and second layer may be extended release form.

Various techniques of bilayer tablet

- OROS push pull technology.
- L-OROS tm technology.
- EN SOL TROL Technology.
- DUROS technology.
- Dual release drug delivery system.

MATERIALS AND METHODS

Preparation of IRL IRL of Divalproex sodium (DS) was prepared by wet granulation by using different Super disintegrates 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 Super disintegrates 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.

Dual release drug delivery system

This tablet provides immediate release and sustained release of two drugs in one dosage form.

Prefomulation studies to be carried out before formulation of bilayer tablet

- Solubility of drug.
- Particle size determination.
- Bulk density.
- Tapped density.
- Carr's index
- Hausner's ratio.
- Angle of repose.
- Drug excipients compatibility studies.

Solubility of drug

The solubility of drugs to be formulated as bilayer tablets should be determined in various types of mediums like distilled water, 0.1N HCl, 0.1 N NaOH, ethanol, methanol, PBS pH 6.8, PBS pH 7.2 etc.

Particle size determination.

Particle size can be determined by two methods. It can be either determined with the help of Malvern particle size analyzer or by sieving on a mechanical sieve shaker.

Bulk density

Weigh accurately 25g of drug and pass through sieve no 20. Transfer it in a 100ml graduated measuring cylinder. Without disturbing measuring cylinder note the initial apparent volume (Vo).

Calculate bulk density by the following formula: -

$$\text{Bulk density} = \frac{Weight\ of\ drug}{Bulk\ volum}$$

Tapped density

Weigh accurately 25g of drug, pass through sieve # 20 and transfer it in a 100ml graduated measuring cylinder. Measure initial volume (Vo), now tap the cylinder for about 100 times. Then measure final volume (V1).

Calculate the tapped density by the following formula: -

$$\text{Tapped density} = \frac{Weight\ of\ drug}{Tapped\ volume}$$

Hausner 's ratio

It is ratio of tapped density and bulk density. It can be calculated by the formula: -

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

Carr's index

It is a measure for compressibility index developed by carr and Neumann. It can be calculated by the formula: -

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

Angle of repose

Weigh 10g of drug accurately. Prepare an assembly consisting of tripod stand, funnel and paper. Pour the drug through the funnel freely and now calculate height and diameter of heap with scale and pencil. Angle of repose can be calculated by the formula: -

$$\text{Angle of repose} = \tan^{-1}\frac{h}{r}$$

Drug –excipient compatibility studies

This test is carried out to find out a stable storage condition for drug in solid state. In this method different excipients were selected and mixed separately with drug in proportion generally used for tablet formulation. Three mixtures of each set is prepared for measurement at different RH and temperatures. Keep for one month in same condition and check for colour changes in each combination. This is mainly determined by FT-IR study or DSC.

Formulation of bilayer

tablet Bilayer tablet is formulated by mainly two methods: -

Wet granulation method

Direct compression method.

Wet granulation method

Weigh all drugs and excipients accurately and pass through sieve# 100. Prepare binder solution. Wet massing of mixture with the binder solution is done in a pestle mortar. Screen wet mass with the help of sieve# 10. Dry the granules. After drying blend with the help of lubricants and disintegrants to produce running powder. Compress the mixture into tablets with the help of flat punch.

Direct compression method

Weigh accurately all the excipients and drugs and pass through sieve# 100. Mix all the components in a pestle mortar and compress them in the form of tablet directly.

Compression cycle of bilayer tablet

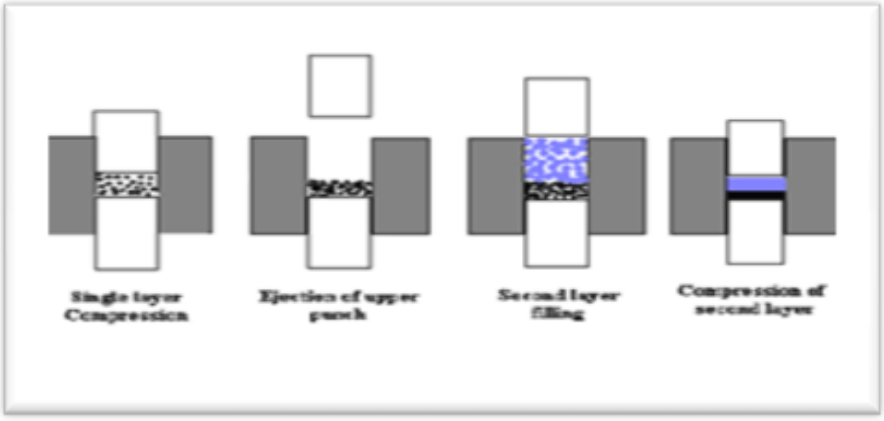


Figure 2: Compression cycle of bilayer table

Steps for compression cycle of bilayer tablet

- Filling of first layer.
- Compression of first layer.
- Ejection of upper punch.
- Filling of second layer.

- Compression of both the layers together.
- Ejection of bilayer tablet.

Drug release kinetics

Drug release mechanism from a bilayer tablet can be determined as follows. In vitro release profile of all sustained release layers can be expressed with the help of higuchi model and korsemeyer's Peppas equation. The data of in vitro dissolution are put into these two equations and calculated properly. Similarly, in vitro release profiles of immediate release layer can be determined in same manner. Both of them do not follow zero order or first order release profiles.

Characterization of bilayer tablet

- Appearance.
- Weight variation.
- Thickness.
- Hardness.
- Friability.
- Disintegration time.
- Dissolution time

Appearance

The general appearance of bilayer tablet was identified visually in terms of shape, size, color, presence or absence of odor, taste and surface texture.

Weight variation

Weigh 20 tablets accurately. Determine average weight of tablets. The individual weight of each tablet was compared with average tablet weight.

Thickness

Randomly tablet was selected and its thickness was measured by using vernier caliper scale.

Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet can be determined with the help of Monsanto hardness tester. The hardness was measured in kg.

Friability

Friability is a measure of tablet strength. Friability can be determined with the help of Roche friabilator. Twenty tablets are weighed accurately and placed in tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 minutes the tablets are weighed and percentage loss in tablet weight is calculated.

% loss = initial weight of tablets – final weight of tablets/ initial weight * 100

Disintegrationtime

6 tablets are taken in disintegration apparatus with distilled water or suitable medium at 370C. Calculate time at which tablet gets converted to soluble particles. Disintegration time for immediate release tablets and bilayer tablets was determined. Disintegration time for immediate release tablets should not be more than 15 minutes.

Dissolution time

Dissolution profile is evaluated with the help of USP paddle apparatus. 900ml of suitable dissolution mediums are taken in vessel maintained at 370C at 75rpm. The dissolution was carried out for about 12 hrs. 5ml of sample was withdrawn at regular time intervals, and 5ml of fresh medium is inserted in vessel. Absorbance is recorded for each sample at specific lambda maxima for the combination drugs.

Applications of bilayer tablet

- Hypertension e.g. Propanolol hydrochloride and hydrochlorothiazide.
- Diabetes e.g. Metformin and glimepiride, Metformin and glipizide.
- Analgesics e.g. aceclofenac and COX inhibitors.
- Antipyretics e.g. ibuprofen and Metaclopramide HCl

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.

The above studies lids to following conclusions:

- FTIR and DSC studies indicated that the drug is compatible with all the excipients.
- Both immediate and sustained release layer were prepared by wet granulation method and punched separately. The prepared tablets of both layers were evaluated for post compression parameters.
- According to the *in vitro* dissolution profile date one formulation of each layer were selected for bi-layered tablet. IF6 from immediate release formulations as they showed 98.62 % drug release within 20 minute. SF8 from sustained release formulation as they showed 94.29 % drug release within 18 hours.
- The bilayer tablets were prepared using the selected immediate and sustained release layer. The prepared tablets were found to be good and free from chipping and capping.
- The hardness of the prepared tablets was found to be in the range of 5.85 to 7.05 kg /cm^2
- The low values of the standard deviation of average weight of the prepared tablets indicate weight uniformity within the batches prepared.
- The friability of the prepared tablet was found to be less than 1%.
- The percentage drug content was uniform in all the formulations of prepared bi-layered tablets.
- *In vitro* drug release pattern of the bi-layered tablets were same as individual layer tablets.
- The stability study showed that no significant changes in tablets after 3 months study.

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HOW TO CITE: Rajni Dubey, Saniya Mubarik*, Bhaskar Kumar Gupta, Mariya Beg, Formulation and Evaluation of By-Layered Tablet, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 3, 2848-2895. https://doi.org/10.5281/zenodo.15101573