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# CONTEMPORARY APPROACHES FOR BI-LAYER TECHNOLOGY OF DRUGS THROUGH ORAL ROUTE: AN OVERVIEW

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**ABSTRACT:** Bi-layer tablet technology for bimodal release of drug and co-administration of drugs via oral route has been engaged a significant place in the field of drug delivery technology. At present, several pharmaceutical companies are developing bilayer tablet for co-administration of drugs to improve the therapeutic efficacy as well as to reduce the chances of drug-drug interaction. This review indicates the different aspects of drug release mechanism, different strategies of drug release, various techniques for bilayer tablet, and the influence of different process and formulation parameters must be considered during the development of bilayer tablet. Bi-layer 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.

**INTRODUCTION:** Bi-layer tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system.

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 [1].

Oral drug delivery system is considered to be one of the most convenient and commonly employed drug delivery system as it poses some specific advantageous characteristics, such as ease of administration, least aseptic constraints and flexibility in the design of the dosage form.

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Another revolution towards the oral drug delivery is the modified release dosage forms which have huge advantages over immediate release formulations of the same drug. There are different methods for the designing of this modified dosage form, some of them are film coated pellets, tablets, capsules or more sophisticated and complicated delivery systems such as osmotically driven systems, systems controlled by ion exchange mechanism, systems using three dimensional printing technology and systems using electrostatic deposition technology.

The modified release products are usually designed to provide slow and continuous delivery of drug over the entire dosing interval and improve patient compliance and convenience [2, 3].

Recently, the most common widely used controlled delivery system is the matrix type where the drug is uniformly entrapped in to the polymer [4]. In formulation of oral controlled release formulation, hydrophilic polymers are most frequently used as polymeric retardant materials due to their ease of

manufacturing, relatively low cost, favorable *in vivo* performance and versatility in controlling the release of drug with wide range of physicochemical properties [5].

The another new drug delivery concept is the control release of drug form the dosage form where the drug is released from the dosage form in a constant manner in respect to time but without depending upon the initial concentration of the drug and hence the release of drug from this type of dosage form follows zero order release kinetics. This drug delivery system has been widely used as drug delivery system for the drugs having low therapeutic index to reduce the dose dumping.

To alter the kinetics of drug release from inherent non-linear behavior to linear include the use of geometry factors (solid units having spherical, cylindrical, conical, biconcave, biconvex, donut shapes, hemisphere with cavity, core in cup, circular sectioned cylinder, rings, oval bi-dose divisible tablets etc.), films, erosion/dissolution controlled and swelling controlled mechanisms, non-uniform drug loading and matrix-membrane combination [6].

From the word 'Bilayer Tablet' indicates that it is a solid oral dosage form, usually round, spherical, oval or biconcave in shape and consist of one or more than one medicaments designed in a two layers system which can be suitable for combination therapy and biphasic release therapy.

In case of combination therapy the two layers of this tablet is consist of two different medicaments and in case of bi-phasic release bilayer tablet both the layers content same drugs but the drug from one layer is immediately release and the drug release from the second layer is released for an extended period of time to maintained the therapeutic concentration of drug within therapeutic window.

For the formulation of layers from different polymers manipulation has been done over more than one rate-controlling polymers and thus allow different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then as a controlled rate or by targeted drug delivery in the GI tract using pH dependant polymers so in the formulation of bilayer tablets the polymer plays a very important role.

Multi-layered matrix tablet comprises a matrix core containing the active solute(s) and one, or more barriers (modulating layers) incorporated during the tabletting process. The function of the modulating layers is to delay the interaction of active solute with dissolution medium by limiting the surface available for the solute release and at the same time controlling solvent penetration rate through the matrix [7, 8, 9].

**FIGURE 1: IN CASE OF COMBINATION THERAPY THE DRUG 1(RED PORTION) AND DRUG 2 (WHITE PORTION) ARE DIFFERENT BUT IN CASE OF SUSTAINED RELEASE THE DRUG 1 IS THE LOADING DOSE WHERE AS THE DRUG 2 IS THE MAINTENANCE DOSE OF A DRUG.**

**Advantages of Bilayer Tablet:** Before explaining the advantages of bilayer tablet, here are the advantages of the tablet dosage form over the dosage form are as follows:

- Tablet is a unit dosage form and they offer the greatest compatibilities of all oral dosage forms for the greatest dose precision and the least content variability.
- The cost is approximately lower than any other oral dosage form.
- These are very compact in nature.
- In genera the packaging procedure for tablets are easier and cheaper.
- Swallowing of tablets is very easy.
- They are better suited to large scale production.
- Chemically, mechanically and microbiologically tablets are very stable. The advantages of the 'bilayer tablet' over the other conventional

preparations of oral solid dosage forms comprise.

- When the two different layers of the tablet content two different drugs, then the tablet can be easily used in combination therapy.
- This formulation can be use to deliver separate two incompatible substance.
- In case of drags having a low half life, each of the two layers of the tablet respectively content a loading dose and maintenance dose of the same and thus increase the bioavailability of the drug.
- Frequency of the dose administration is reduced which ultimately improve the patient compliance.
- In case of a conventional dosage form due to variation of the dose interval the plasma drug concentration may differ (under medication or over medication), but in this dosage form the plasma drug concentration is always constant, which ultimately provide a more effective action of the drug.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of high availability drug can be reduced by formulation in an extended action form. The safety margin of high potency drugs can be increased and the local and systemic adverse effects can be reduced in sensitive patients.

**Limitations of Bilayer Tablet:** From the above mentioned advantage of bilayer tablets it is quite clear that in pharmaceutical industry it is a great revolution, but there are certain limitations in the formulation and use of bilayer tablets, such as:

- One of the major challenges in bilayer formulation is lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack and layer separation.
- If the compacted layers are too soft or too hard, they will not bind securely with each other which can lead to compromised mechanical integrity and also the separation of the layers.
- Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers.
- The adjacent layers of a bilayer tablet are bonded together by mechanical means, so the factors influences the stress state is very important. The mechanical properties of each layer and the tablet, and compression parameters along with specialized techniques and compression condition plays a very important role for the same.
- Administration of sustained release bilayer tablet does not permit the prompt termination of therapy.
- The physician has a less flexibility on adjusting the dose regimens.

**GMP requirements for Bi-Layer Tablet:** To produce a quality bi-layer tablet, in a validated and GMP-way, it is very important to follow the following criteria for the selection of bilayer press. These requirements seem obvious but are not so easily accomplish. The press should be capable of:

- Preventing capping and separation of the two individual layers that constitute the bi-layer tablet;
- Providing sufficient tablet hardness;
- Preventing cross-contamination between the two layers;
- Producing a clear visual separation between the two layers;
- Manufacturing products of high yield;
- Accurate and individual weight control of the two layers.

**Release Mechanism:** Normally the drug release from hydrophilic swellable matrices depends on the polymer macromolecular coupling, relaxation and the drug diffusion [10, 11] and all of these are responsible on the rate at which water may penetrate into the device. Hydration rate, swelling of the polymer and modification of the polymer matrix are the basics for the multilayered drug delivery design. These factors are very effective at the primary or initial phase of the drug dissolution but with the respect of time as swelling proceeds linearization of the release profile occurs.

To achieve this objective, coating of the matrix tablets with an inert impermeable film has been performed. Coating plays a very important role in the drug release from the multilayered preparations. The release rate of the drug from tablets is observed by *in vitro* release rate study. The release rate of the drug is inversely proportional to the extent of coating. The release of the drug is primarily dependant on the swelling of the polymer which is again controlled by reducing the drug release surface by the coating material.

When a tablet is coated partially, it does not swell and retain its initial size and shape and maintain the release retardation continuously through the entire dissolution process [8]. On the other hand, when the tablet is subjected to water immersion the polymer barrier which is inert in nature have a tendency to crack and separated out from the core within hours. This effect is resulted from volume expansion of core upon water immersion due to polymer swelling.

The outer barrier layer does not expand while the core is swelling as a result a stress is generated in the outer barrier layer. When the outer barrier is sellable polymer then the both barrier and core swell simultaneously without any internal stress during the dissolution process. Multilayer compression process can be used for the application of barriers. One notable example of this phenomena is the double layer or three layer tablets in which only one layer contains the active ingredient (active core), while other layers are barrier layers.

**Bimodal Release Profile:** To design constant drug absorption, the dosage form should be able to release the drug in a varying manner; thereby the release can compensate the change in the drug absorption in the different part of the gastrointestinal tract and provide a control release of the drug. This kind of release pattern can be obtained with the help of bimodal release system. This release system is consisted of an initial rapid release layer, which is then followed by a period of slow and constant release, and again a second phase of rapid drug release [12].

Control release system is considered that the system should release the drug in a zero-order rate, thereby to maintain the plasma drug concentration in a constant level. An additional layer known as the fourth layer containing initial dose rapidly disintegrates to produce a quick dissolution onset which ultimately provide a concentration gradient to compensate the poor absorption in stomach. With the help of barrier layers from the sustained release portion drug release is controlled. The pH of the large intestine initiates the second rapid drug release.

**Advantages of this system over others systems**: This dosage form can produces rapid drug release during the initial phase and in the later phase compensate the relatively slow drug absorption in the stomach and large intestine and

- It can be used to design programmed pulse release oral drug delivery systems for the therapeutic agents that can perform more effectively or give more therapeutic activity when drug levels at the site of action undergo periodic changes.

**Techniques for Bilayer Tablet:**

**Osmotic-controlled release oral delivery system:** In this technology the system is consist of mainly two or three layer among which one or more layer are of the drug and other layers are consist of push layer. The drug layer mainly consists of poorly soluble drug along with diluents, low molecular weight polymer, suspending agent and osmotic agent. The push layer is constructed of a higher molecular weight osmopolymer and an osmagent.

A semi permeable membrane surrounds the tablet core. In this technology the medication is sandwiched with an osmotic agent that swells when it takes up water. The sandwich is then coated with a semi permeable membrane .Then a laser is used to drill a tiny hole through the membrane.

In the stomach, water passes through the membrane into the pill, causing the osmotic material to swell, which pushes the drug out of the hole. This delivers the drug to the body at a constant rate instead of all at once, as happens when a traditional pill dissolves. Products manufactured using this technology are Glucotrol Xl and procardia XL both of which are composed of a bilayer tablet core and Concerta is compose of a trilayer tablet core.

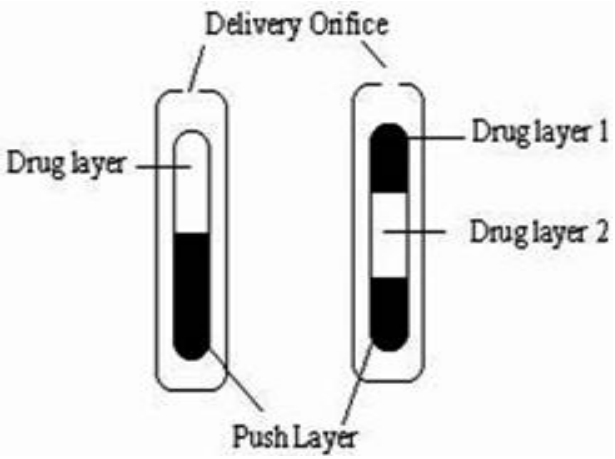


**FIGURE 2: OROS PUSH PULL TECHNOLOGY OF BILAYER AND TRILAYER TABLET PREPARATION**

**DUREDUS Technology:** DUREDAS or Dual Release Drug Absorption System (**Elan Corporation**) utilizes bilayer-tabletting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct-compression steps that combine an immediate-release granulate (for rapid onset of action) and a controlled-release hydrophilic matrix complex within one tablet.

The immediate release layer, release the drug immediately after going into the GIT (stomach or intestine) in a diffusion and dissolution manner and the controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid.

As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner.

A further extension of the Duredus technology is the production of controlled-release combination dosage forms whereby two different drugs are incorporated into the different layers, and the drug release of each is controlled to maximize therapeutic effect of the combination.

Again both immediate release and controlled release combinations of the two drugs are feasible. The DUREDAS™ technology was initially employed in the development of a number of over the counter controlled release analgesics.

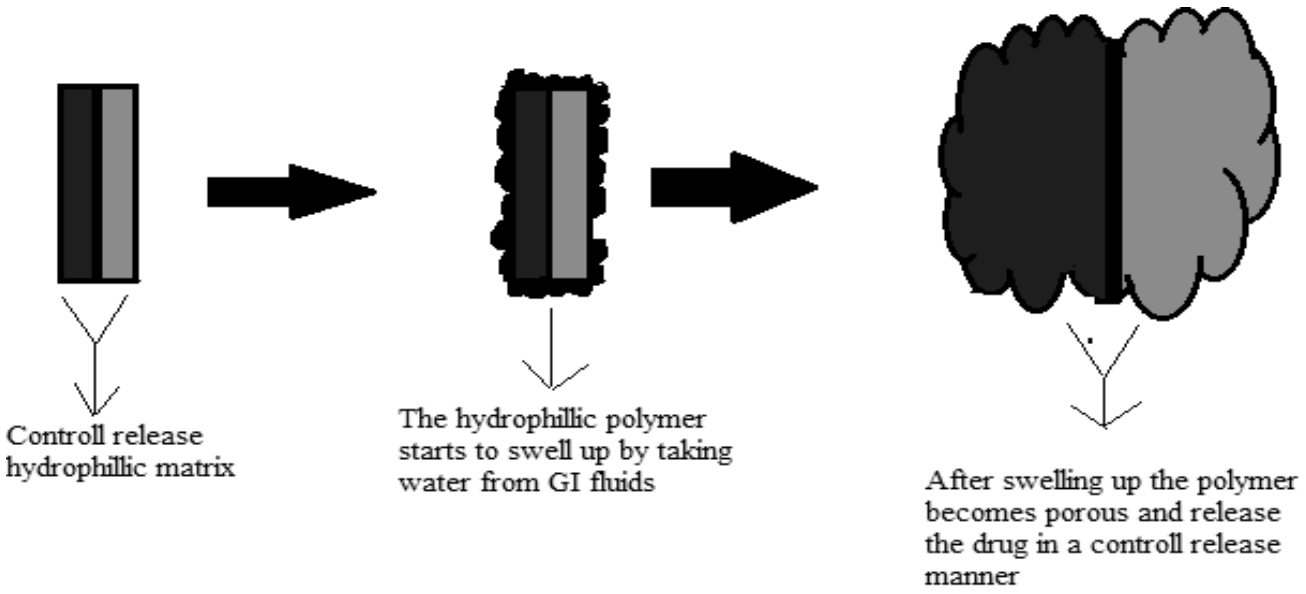


**FIGURE 3: DUREDAS TECHNOLOGY CONSISTS OF CONTROL RELEASE AND IMMEDIATE RELEASE LAYER**

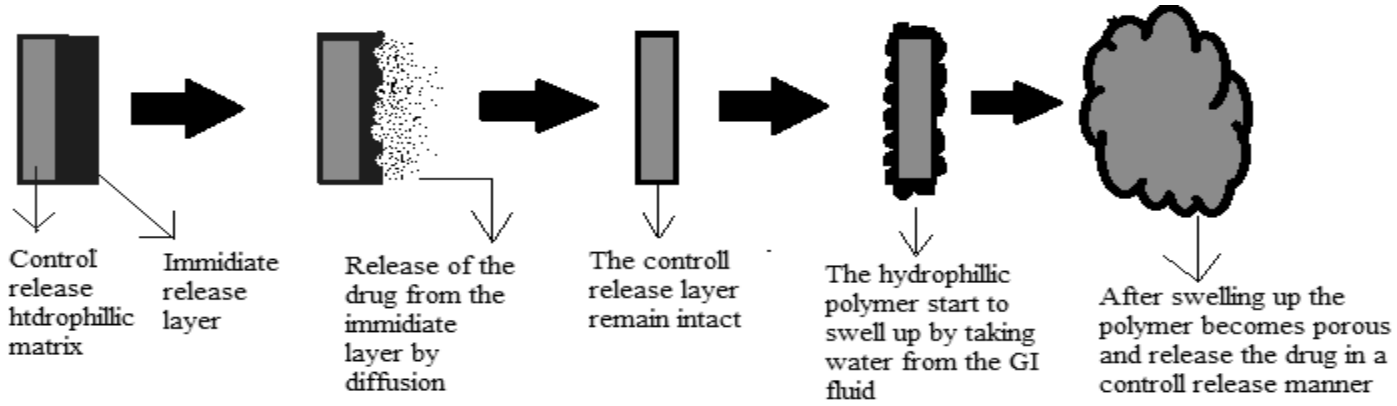


**FIGURE 4: DUREDAS TECHNOLOGY CONSIST OF TWO CONTROL RELEASE LAYERS**

**Process and Formulation Parameters:** As the initial dose layer do not affect the intermediate slow release or the second rapid phase or constant phase release, this layer is not necessary to be considered in the formulation process. Multi-layered tablet consisting of a core and one or more barrier layers should be taken into account while determining the parameters involved in the processing. The following factors should be considered for the process and formulation.

**Parameters dealing with the layer consisted of therapeutically active substances:** During granulation of therapeutically active substances some basic factors are to be considered which includes percentage of the liquid used in granulation, time required for massing step, temperature of the outlet air during the drying step and milling screen apertures as well as the interaction between the amount of granulation liquid and the outlet temperature [13].

While the impact of these factors on the final products has to be considered and the responses can be classified into four categories:

- Granules properties (e.g., flowability, bulk density, ability to settle, particle size distribution),
- Extensometric responses (e.g. Cohesion index, lubrication index, ejection strength, plasticity, elasticity),
- Physical characteristics of tablet (e.g. Thickness, weight variation, hardness, friability) and
- Analytical results (e.g. Content uniformity, *in vitro* profile).

**Compression process:** The significant parameters in the compression process are turntable speed and compression forces equivalent to first, second and main layers. The tablet crushing strength response improves when the turret compression speed on the main compression force is increased. But these parameters (within a particular range) do not influence the content uniformity and the release performances in multi-layered, press coated and, bimodal delivery systems [8, 14]. But in the case of press coated tablet intended for distant destination (e.g. colon targeting) the release rate and lag time are dependent on the compression force.

The release rate of drug decreases and the lag time increases with increasing compression force till a critical point. After this point increasing compression force does not provide further reduction in porosity. There is necessity of increasing the lag time more than 10 h in the gastric fluid under some physiological conditions [15] and also there is need for suppression of release in the intestinal fluid for more than 3 h in order to obtain colon targeting.

To achieve these certain additives, which have poor wettability, are added to the outer shell polymer to prevent the penetration of dissolution medium into the pores in the outer shell.

For example, magnesium stearate or calcium stearate were added to the hydroxyl propyl methyl cellulose acetate succinate (HPMCAS) polymer to increase the lag time [16].

Press coated tablets intended for colon targeting mainly depends on compression force when poor wettable additives are used.

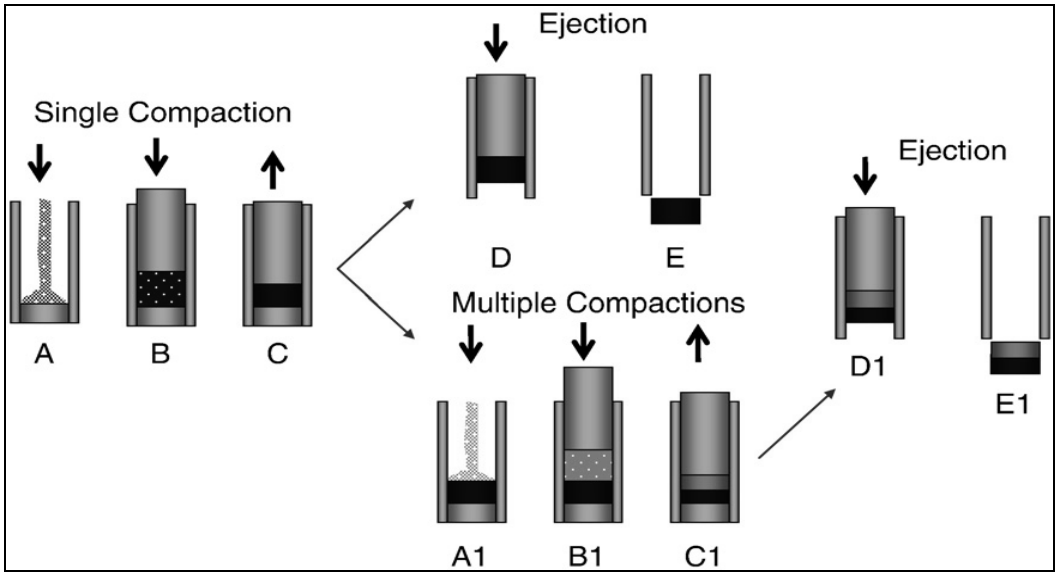


**FIGURE- 5: SCHEMATIC DIAGRAM SHOWING THE MANUFACTURE OF SINGLE AND BI-LAYER TABLETS UTILIZING UNIAXIAL COMPACTION. A — DIE FILLING, B — COMPRESSION, C — DECOMPRESSION, D — LOWER PUNCH REMOVAL AND REAPPLICATION OF LOAD TO THE UPPER PUNCH, E — TABLET FULLY EJECTED. 1 REFERS TO THE FINAL COMPACTION CONDITIONS [25]**

**Hardness of compressed tablet:** 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 of each formulation was measured by Veego hardness tester. The hardness was measured in kg/cm$^2$.

Hardness of tablet is expressed in terms of tensile strength. The tensile strength of the tablet is calculated by the formula, according to Fell and Newton [17]:

$$\sigma = \frac{2P}{\pi Dt} \qquad (1)$$

where r = tensile strength (kg/cm$^2$), D= tablet diameter (cm), t = tablet thickness (cm), P= force applied to fracture (kg). The porosity of the tablets decreased by the rise of tensile strength which is ultimately depends on the compression load. Since the compression force (particular range) does not affects the release rate, therefore, hardness of the tablet (generally in layered construction) has less significance in the formulation [8].

**Polymer concentration in core:** Polymer is one of the most vital factors that control the release of drug from the tablets. With the increase of the polymer concentration usually the dissolution rate of the tablet is decreased. This consideration does not affect the drug release in layered tablets as considerably in the bimodal tablet because the solubility of certain polymers depends on the pH of the surrounding medium. For example, the effect of decreasing HPMC amounts in the inner layer of bimodal delivery system is not significant in pH 1.2 but in pH 7.4 & 6.8 drug release increases with decrease in the amount of polymers [14].

At high pH values a less dense polymer network dissolves more quickly than a tight structure, leading to increased drug release rate. At low pH HPMC is not soluble, thus there is no effect on the breakdown of the polymer network. Therefore, concentration of pH sensitive retard polymers in the core should be controlled more closely.

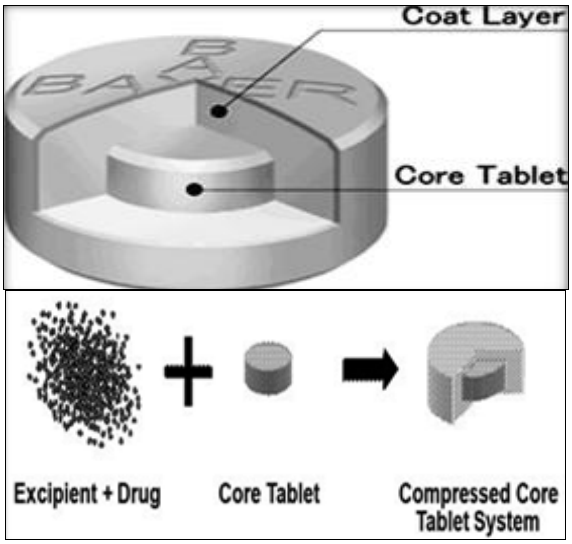


**FIGURE 6: COMPRESSED CORE TABLET SYSTEM AS BIPHASIC DELIVERY SYSTEM [25]**

**Polymers used in bi-layer tablets:** Polymers are the most widely used for controlled-release drug formulations. Typical products used in controlled release include METHOCEL K100 Premium LV, K4M Premium, K15M Premium, K100M Premium, E4M Premium, and E10M Premium CR. All of these products are available in controlled-release (CR) grades, which are specially produced, ultra-fine particle size materials. Polyethylene glycols (PEGs) are used experimentally in biodegradable polymeric matrices used in controlled-release systems. Guar Gum, xanthan gum, Carbomer, Kollidon SR is also used in bi-layer tablets.

**Diluents:** Filler or diluents used in the core of the tablet, has a great influence on the drug release rate because of its solubility. On contact with the release medium, the filler diffuses out from the device and thereby affect the drug release rate by increasing the porosity of polymers. Depending upon the amount of the filler the amount of the polymer is adjusted to keep the tablet weight constant. Examples of such filler are lactose, Starch 1500.

**Combinations of Bilayer Tablets: Table 1** indicates the different formulations of bilayer tablet containing combination of two drug and their specific uses. Table 2 indicates the different formulation of bilayer tablet containing the same drug in both fast release layer and sustained release layer.

**TABLE 1: BILAYER TABLETS CONTAINING TWO DRUGS IN AN INDIVIDUAL LAYER-[17, 18, 19, 20,]**

| Drug | Drug | Purpose |
|---|---|---|
| Metformin hydrochloride | Glimepiride | Improve oral therapeutic efficacy with optimal control of plasma drug level |
| Metformin hydrochloride | Pioglitazone | Reduce frequency of administration and improve patient compliance |
| Paracetamol | Diclofenac sodium | Reduce dose frequency and decrease incidence of GI side effects |
| Tramadol | Acetaminophen | Prolonged release up to 12 h and improve patient compliance |
| Salbutamol | Theophylline | Enhance patient compliance and prolong bronchodilation |
| Metoprolol succinate | Amlodipine besylate | Lower doses of drug to reduce patient blood pressure, minimize dose dependent side effects and adverse reactions |
| Diltiazem hydrochloride | Lovastatin | Improve patient compliance and better disease management |
| Atorvastatin calcium | Nicotinic acid | Develop potential dosage form |
| Metoclopramide hydrochloride | Ibuprofen | Effective treatment of migraine and avoid chemical incompatibility between drugs |

**TABLE 2: BILAYER TABLETS CONTAINING THE SAME DRUG IN AN IMMEDIATE RELEASE LAYER AND SUSTAINED RELEASE LAYER.[21, 22, 23, 24]**

| Drug | Fast release layer | Sustained release layer |
|---|---|---|
| Indomethacin (Floating tablet) | Ac-di-sol | HPMCK4M |
| Propanolol Hcl (Bucoadhesive tablet) | Ethylcellulose | Sodium alginate and carbopol 971P |
| Guaifenesin (Matrix tablet) | Microcrystalline cellulose, Sodium starch glycolate | Metalose 90SH, Carbopol 934 |
| Atorvastatin calcium (Mucoadhesive buccal tablet) | Ethylcellulose | Carbopol 934P, Sodium CMC, Hydroxyethylcellulose, Sodium alginate |
| Propanolol HCl (Matrix tablet) | Sodium starch glycolate | Ethylcellulose, Eudragit RLPO and Eudragit RSPO |
| Zolpidem tartarate (Matrix tablet) | Cross -carmellose sodium | HPMC K100M |
| Fenoverine (Floating tablet) | Cross-carmellose sodium | HPMC K4M, HPMC K100LV |
| Verapamil hydrochloride (Floating tablet) | Cross-povidone, Sodium starch glycolate | HPMC K15M, HPMC K100M, Carbopol 971P |

**CONCLUSION:** This concept demonstrates a wide technology for various applications such as quick/slow, bimodal delivery of active ingredients because it allows the defined modulation of drug release process even for drug characteristics by extreme physicochemical properties. By considering various formulation parameters it is possible to get the appropriate release kinetics. The system has the advantages of relatively low cost and potentially feasible to large scale production using layered tablet process.

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