

BILAYER TABLET: REVIEW**Vinod Usnale^{*1}, Nishigandha Nadiwade² and Akshay Bendsure³**¹Mauli Collage of Pharmacy, Udgir.²Channabasweshwar Pharmacy Collage, Latur.³Gurukrupa Institute of Pharmacy, Majalgaon.**ABSTRACT**

Bilayer 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. Bilayer tablet is better than the traditionally used mouthwash, sprays, gels. So use of bilayer tablet is a very different aspect for anti-inflammatory and analgesic. 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. Bilayer tablet is improved beneficial

technology to overcome the shortcoming of the single layered tablet. There is various application of the bilayer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bilayered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper nonadhesive layer its delivery occurs into the whole oral cavity.

KEYWORDS: Bi-layer Tablet, Maintenance Dose, anti-inflammatory and analgesic, sustained release.

1. INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs. The goal of any drug delivery system is to provide a therapeutic amount of the drug at the site an effective throughout the entire duration of therapy and then maintain the desired drug concentration.^[1] Conventional dosage form produces wide range of fluctuation in drug concentration in the blood stream and tissues which leads to reduction or loss in drug

Article Received on
10 July 2017,

Revised on 31 July 2017,
Accepted on 21 August 2017

DOI: 10.20959/wjpr201710-9376

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effectiveness or increased incidence of side effects with subsequent undesirable toxicity and poor efficiency. However, sustained or controlled drug delivery systems can decrease the frequency of the dosing and also increases effectiveness of the drug by localization at the site of action, reducing the dose required and providing uniform drug delivery.^[2] Different approaches have been proposed to formulate sustained release tablets for retaining dosage form in stomach. These include bioadhesive or mucoadhesive systems,^[3] swelling and expanding systems^[4,5] floating systems^[6,7] and other delayed gastric emptying devices. In recent years, a growing interest has developed in designing drug delivery systems that include an immediate release (IR) component to extended release (ER) dosages. The addition of an IR component allows one to design delivery systems having optimal pharmacokinetic profiles and enables the combination of different drugs thereby improving patient compliance.^[8] In certain conditions (migraine and sleeping disorders), drug treatment may be advantageous to be delivered in a biphasic manner rather than a single phase extended release preparation. In the first phase of drug release, the immediate release dose fraction (also called loading-dose) reaches a therapeutic drug level in the blood plasma quickly after administration, while the second extended release phase (called the maintenance-dose) provides the dose fraction, required to maintain an effective therapeutic level for a prolonged period. Examples of such systems can be found as bilayer tablets, drug layered matrices or combinations of immediate and extended release multiparticulates.

Bilayer tablet is new concept for successful development of sustained release formulation along with various features to provide a way of successful drug delivery system that include an immediate release (IR) layer and an Sustained release (SR) layer. Immediate release layer provide therapeutically effective plasma drug concentration for a short period of time and Sustained release (SR) layer maintain uniform drug levels over a sustained period to reduce dosing intervals and side effects, increase the safety margin for highly-potent drugs and thus offer better patient compliance. It also includes bimodal drug delivery profile (fast release / slow release / fast release).^[9]

This type of system is used primarily when maximum relief needs to be achieved quickly and it is followed by a sustained release phase to avoid repeated administration. Suitable candidate drugs for this type of administration include nonsteroidal anti-inflammatory drugs (NSAIDs) and antihypertensive, antihistaminic, and antiallergic agents, anti psychotics, hypnotics.^[10] Generally, conventional extended dosage forms delay the release of therapeutic

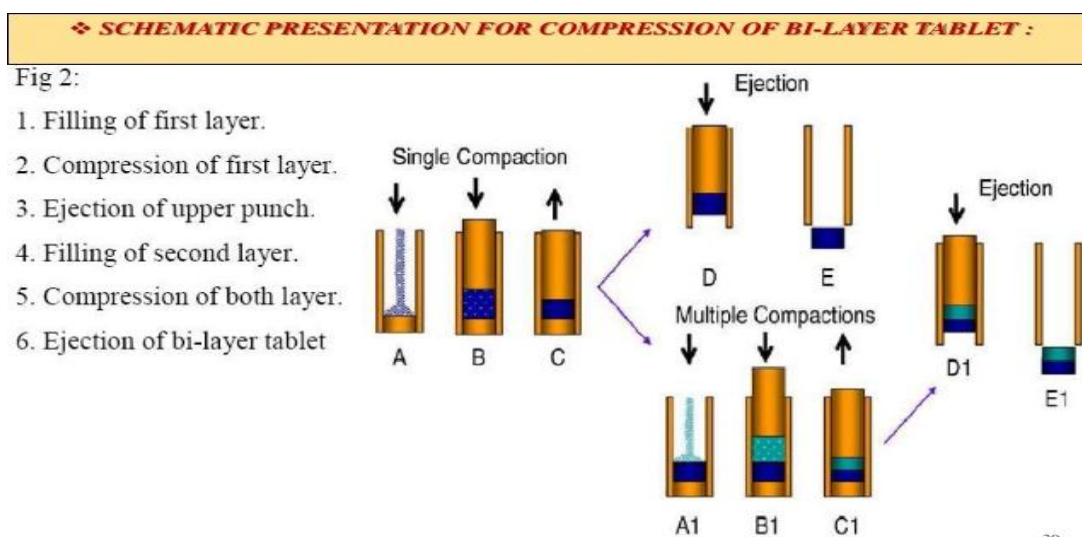
systemic levels and do not provide a rapid onset of action. Immediate release DDS are intended to disintegrate rapidly and exhibit instant drug release. They are associated with a fast increase and decrease and hence fluctuations in drug plasma levels which leads to reduction or loss in drug effectiveness or increased incidence of side effects. Administration of the DDS several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolism and excretion. In many therapies, extended-release preparations are considered desirable but for many drugs, significant daily variations in pharmacokinetics and/or drug effects have been demonstrated on human beings. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and absorption varies along the gastrointestinal (GI) tract.^[11] A constant plasma concentration may not be obtainable even though a dosage form with a zero-order In-vitro release is administered. It is conceivable that a delivery system that can provide a release profile with an initial burst of release followed by a relatively steady release or an accelerated release at a late stage may offer a better solution. Such a release profile, namely pseudo zero-order release with initial burst or bimodal release may compensate for the lower absorption rate in the stomach and the large intestine.^[12,13] Moreover, for some drugs (such as NSAIDs, antihypertensive, antihistaminic, anti-allergic agents) a prompt disposition of a fraction of the dose should be reached in the shortest time possible to relieve the symptoms of the disease and then the continuation of the drug effect should be prolonged for some hours to optimize the therapy. For these types of drugs, extended release formulations generally lead to a delayed appearance of effective plasma levels and they cannot provide a prompt disposition of the dose immediately after administration. To fulfill the specific therapeutic needs of the different diseases, new drug delivery devices are required for a more accurate time-programmed administration of the active ingredients. On the basis of these considerations, a new oral delivery device was proposed, in the form of a double-component tablet, one portion is formulated to obtain a prompt release of the drug with the aim of reaching a high serum concentration in a short period of time. The second portion is a prolonged-release layer which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing component leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer.



Fig 1: Bilayer Tablet.

Bilayer 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. Bilayer tablets have been developed to achieve controlled delivery of different drugs with pre defined release profiles. In the last decade interest in developing a combination of two or more API's in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance. Several pharmaceutical companies are presently developing bi-layer tablets, for a variety of reasons patent extension, therapeutic, marketing to name a few. To decrease capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. This article explains about different techniques of bi-layer tablet and why development and production of quality bi-layer tablets need to be carried out on purpose built tablet presses to conquer common bilayer problems, such as layer separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, reduced yield etc. There are various applications of the bi-layer tablet consists of monolithic partially coated or multilayered matrices.

Schematic Presentation for Compression of Bi-Layer Tablet



Conventional dosage form produces wide range of fluctuation in drug concentration in the blood stream and tissues with subsequent undesirable toxicity and poor efficiency. This dynamic such as repetitive dosing and erratic absorption led to the concept of controlled drug delivery systems.

The aim in designing sustained or controlled delivery systems is to decrease the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or provide uniform drug delivery. The main objective of sustained release drug delivery is to make sure safety and to improve effectiveness of drugs as well as patient compliance. Several pharmaceutical companies are presently developing bi-layered tablets for a variety of reasons: patent extension, therapeutic and marketing purpose. Formulation of layers are done by using more than one rate controlling polymer, thus enabling different types of drug delivery of one or more drugs where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract.

1.1 Need of developing bi-layer tablets^[14,15,16]

For the supervision of fixed dose combinations of drugs, prolong the drug product life cycle, manufacture novel drug delivery systems such as floating or mucoadhesive bilayer tablets for gastro - retentive drug delivery systems.

1. Controlling the delivery rate of either single or two different active pharmaceutical ingredients (API'S).
2. To adapt the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable / erodible barriers for controlled release.
3. To separate incompatible API's with each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property).

1.2 Advantages of bi-layer tablets^[17,18]

1. Bi-layer execution with optional single layer conversion kit.
2. Low cost compared to other dosage forms.
3. Greatest chemical and microbial stability compared to other oral dosage forms.
4. Objectionable odor and taste can be masked by coating technologies.
5. Flexible concept.
6. Offer greatest precision and the least content uniformity.
7. Easy to swallow with least hang up problems.
8. Fit for large scale production.

9. Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs.
10. Bi-layer tablets can be designed in such a manner as to modify release as either of the layers can be kept as extended and the other as immediate release.
11. Expansion of a conventional technology.
12. Prospective use of single entity feed granules.
13. Separation of incompatible components.
14. Patient compliance is improved leading to improve drug regimen efficiency.
15. Patient compliance is improved because fewer daily dosages are required compared to traditional delivery system.
16. Maintain physical and chemical stability.
17. Product identification is easy.
18. Easiest and cheapest to package and strip.

1.3 Disadvantages of bi-layer tablets

1. Complexity and bi-layer rotary presses are expensive.
2. Insufficient hardness, layer separation, reduced yield.
3. Imprecise individual layer weight control.
4. Cross contamination between the layers.
5. Difficult to swallow in case of children and unconscious patients.
6. Some drugs resist compression into dense compacts, due to amorphous nature, low density nature.
7. Drugs with poor wetting, slow dissolution properties, optimal absorption high in GIT may difficult to manufacture as a tablet that will still provide ample drug bio availability.

1.4 General properties of bi-layer tablet dosage forms

1. It should have graceful product identity free of defects like chips, cracks, discoloration and contamination.
2. Should have sufficient strength to with stand mechanical shock during its production, packaging, shipping and dispensing.
3. Should have physical and chemical stability.
4. The bi-layer tablet must release drug in a expectable and reproducible manner.
5. Must have a chemical stability shelf life, so as not to follow alteration of the medicinal agents.

1.5 Bilayered tablets: Quality and GMP Requirements^[22]

To produce a quality bi-layered tablet, in a validated and GMP way, it is important to select a bilayered tablet press is 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.
- High yield.
- Precise and individual weight control of the two layers.

2. Introductions to Drug Delivery System

2.1 Introduction to formulation^[23]

Bi-layer tablets are tablets made by compressing several different granulations fed into a die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for two or three layers. More are possible but the design becomes very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes. (Pujara N, et al., (2012), Bhandari A, et al. (2011)).

2.1.1 Layer thickness

Layer thickness can be varied within reasonable proportions within the limitations of the tablet press. Thinness is dependent on the fineness of the granulation.

2.1.2 Sizes and Shapes

Size is limited by the capacity of the machine with the total thickness being the same as for a single-layer tablet. Many shapes other than round are possible and are limited only by the ingenuity of the die maker. However, deep concavities can cause distortions of the layers. Therefore, standard concave and flat-face beveled edge tooling make for the best appearance, especially when layers are of different colors.

2.1.3 Granulations

For good-quality tablets with sharp definition between the layers, special care must be taken as follows:

- a. Dusty fines must be limited. Fines smaller than 100 mesh should be kept at a minimum.

- b. Maximum granule size should be less than 16 mesh for a smooth, uniform Scrape-off at the die.
- c. Materials that smear, chalk, or coat on the die table must be avoided to obtain clean scrape-off and uncontaminated layers.
- d. Low moisture is essential if incompatibles are used.
- e. Weak granules that break down easily must be avoided. Excessive amounts of lubrication, especially metallic stearates, should be avoided for better adhesion of the layers.
- f. Formulation of multilayer tablets is more demanding than that of single layer tablets. For this reason, selection of additives is critical.

2.1.4 Tablet layer press

A tablet multiplayer press is simply a tablet press that has been modified so that it has two die-filling and compression cycles for each revolution of the press. In short, each punch compresses twice, once for the first layer of a two-layer tablet and a second time for the second layer. Three-layer presses are equipped with three such compression cycles. There are two types of layer presses presently in use one in which each layer can be ejected from the press separately for the purpose of weight checking, and the second in which the first layer is compressed so hard that the second layer will not bond to it, or will bond so poorly that upon ejection the layers are easily separated for weighing. Once the proper weight adjustments have been made by adjusting the die fill, the pressure is adjust to the proper tablet hardness and bonding of the layers. Once hazard of layer tablet production is the lack of proper bonding of layers. This can result in a lot of 100,000 tablets ending up as 200,000 layers after several days if the layers are not sufficiently bonded. In a two layer tablet press, two hoppers above the rotary die table feed granulated material to two separate feed frames without intermixing. Continues, gentle circulation of the material through the hoppers and feed frames assures uniform filling without segregation of particle sizes that would otherwise carry over to the second layer and affect layer weight, tablet hardness, and, in the case of differently colored granulations, the press with three hoppers for the tree granulations instead of two. (Pujara N, et al., (2012), Bhandari A, et al., (2011)).

2.1.5 Limitations of the single-sided press

Various types of bi-layer presses have been designed over the years. The simplest design is a single-sided press with both chambers of the double feeder separated from each other. Each chamber is gravity- or forced-fed with a different powder, thus producing the two individual

layers of the tablet. When the die passes under the feeder, it is at first loaded with the first-layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps (two = pre- and main compression).

The two layers in the die mix slightly at their interface and in most cases bond sufficiently so that no layer-separation occurs when the tablet is produced. This is the simplest way of producing a bi-layer tablet. The limitations of such single-sided press are,

- No weight monitoring/control of the individual layers
- No distinct visual separation between the two layers

The fact that it is not possible to monitor and control the weight of the Individual layers raise the question whether we consider this production GMP Individual layer-weight control on a single-sided press requires some form of measurement of the first layer and of the total tablet. The first control loop indirectly monitors weight and controls the fill depth of the first layer. The second loop indirectly monitors the total tablet weight, but adjust only second-layer fill depth. In general, compression force is used to monitor tablet- or layer-weight. But to do so it is necessary to apply a compression force to the first layer before adding the second layer-powder. To apply a compression force to the first layer prior to adding the second layer, it is necessary to use two separate powder feeders with a compression station in- between. This can be achieved on a single-sided press by installing an additional feeder between the pre- and main- compression station. Very often the precompression roller must be reduced to a much smaller size in order to create the pace required for the second feeder. Additional limitations of such single-sided press are,

- Very short first layer-dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems. This may be corrected by reducing the turret-rotation speed (to extend the dwell time) but with the consequence of lower tablet output.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

To eliminate these limitations, a double-sided tablet press is preferred over a single-sided press. A double-sided press offers an individual fill station, pre compression and main compression for each layer. In fact, the bi-layer tablet will go through 4 compression stages before being ejected from the press.) (Pujara N, et al., (2012), Bhandari A, et al., (2011)

2.1.6 Limitations of “compression force” - controlled tablet presses

Separation of the two individual layers is the consequence of insufficient bonding between the two layers during final compression of the bi-layer tablet. Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression of the tablet. Bonding is severely restricted if the first layer is compressed at a too-high compression force. The low compression force required when compressing the first layer unfortunately reduces the accuracy of the weight monitoring/control of the first layer in the case of tablet presses with “compression force measurement”. Most double-sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main-compression of that layer. (Pujara N, et al., (2012), Bhandari A, et al., (2011)).

2.2 Introduction to Immediate Release formulation

The drug substances contained in an immediate release pharmaceutical composition are suitably a drug substance which has a very low solubility under acidic conditions, i. e. under conditions similar to those present in the stomach and/or drug substances which have a pKa value below about 5.5 such as in a range of from about 4 to about 5. The compositions have been designed in such a manner that two important requirements are obtained, namely i) that the pharmaceutical composition releases the drug substance very fast under acidic conditions whereby the drug substance will become dissolved and, accordingly, available for absorption already almost immediately upon entrance into the stomach. ii) The mechanical strength of a composition according to the invention is sufficiently high to withstand normal handling of a pharmaceutical composition and to enable the composition to be coated using traditional coating equipment well known by a Person skilled in the art. A composition use in those cases in which a fast onset of a therapeutic and/or prophylactic effect is desired, e. g. in connection with acute pain or mild to moderate pain. Accordingly, suitable therapeutically and/or prophylactically active substances may inter alia be found in the class of drug substances denoted nonsteroid anti-inflammatory drug substances Generally, however, the rationale which lies behind the kind of compositions which have been described to enable an immediate release of a drug substance is to employ a traditional formulation approach such as, Plain tablets which have a disintegration time in water of at the most about 30 Min, A traditionally formulated granulate or

- Loose powder of the drug substance itself.
- By doing so the immediate release part of the composition is intended to release the drug substance in a manner which corresponds to a plain tablet.

Formulation or the like and the term "immediate" is in such a context intended to denote that the release of the drug substance is faster than the release from a sustained release composition. drug substance has a low solubility in an acidic medium having a pH of from about 1 to about 3, i.e. a pH corresponding to the pH in the stomach, the traditional formulation approach will lead to a pharmaceutical composition which has a suitable fast disintegration time but not necessarily a suitable fast dissolution rate of the drug substance under acidic conditions, i.e. a plain tablet will rapidly disintegrate into granules but the dissolution of the drug substance from the composition and/or the disintegrated composition under acidic conditions may be unsuitable low due to the solubility properties of the drug substance itself. The availability of a drug substance with respect to absorption, i.e. entrance into the circulatory system, is dependent on the presence of the drug substance in dissolved form as it is generally accepted that only dissolved substances are capable of passing the mucous membranes in the gastro-intestinal tract. Therefore, it is important that the dissolution of the drug substance is suitably fast even under acidic conditions in order to enable a fast and initial absorption so that a true fast or immediate therapeutic response is obtainable. (Surendra G et al., (2008), Banu H, et al.,(2011))^[24]

For drug substances which are weak acids it is very important to ensure a proper bioavailability of the drug substance already under acid conditions in order to achieve a true rapid therapeutic effect. However, the various approaches disclosed with respect to achievement of a combination of a rapid effect do not seem to take all the above-mentioned factors into account and, hence, there is a need for developing compositions which enable a true rapid onset of the therapeutic effect. To this end, we have especially focused on compositions comprising a drug substance belonging to the class of drug substances normally denoted NSAIDs, but other drug substances having a low solubility in acidic medium and/or a pKa below about 5.5 may as well be suitable for use in a composition according to the invention. Moreover, patients suffering from acute pain, mild to moderate pain and/or inflammatory conditions and/or related conditions very often require a dosage and a formulation which enable a fast onset of the therapeutic effect of the NSAID substances. The release from the dosage form must be safe, predictable and reliable. Furthermore, from a

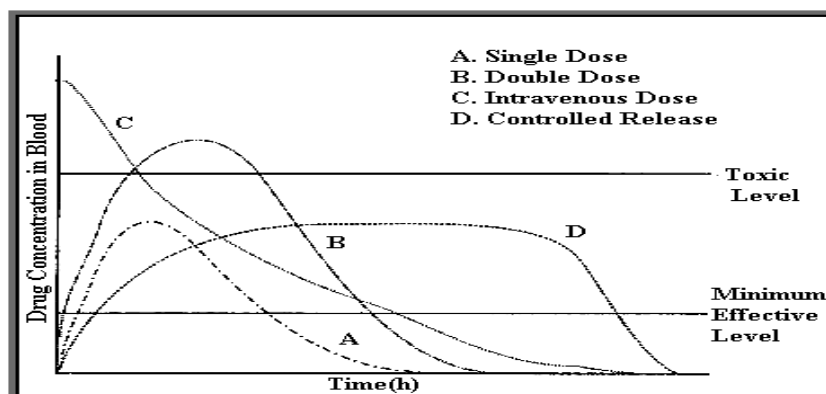
technical point of view, the release rate and the release pattern of the active drug substance from the composition should not significantly change during the shelf life of the composition. A change in the release rate and/or release pattern may have a significant impact on the in vivo performance of the composition. Thus, the development of a pharmaceutical composition which is suitable for rapid release of the active substance seems surprisingly to be a balance of on the one hand to obtain a composition which is sufficient robust to withstand normal handling and on the other hand to enable a fast release and dissolution of the active drug substance in an acidic aqueous medium. (Surendra G et al., (2008), Banu H, et al., (2011)).

2.3 Introduction to Sustained Release Formulation

For decades an acute or chronic illness is being clinically treated through delivery of drugs to the patients in form of some pharmaceutical dosage forms like tablets, capsules, liquids, creams, pills, aerosols, injectables, and suppositories. However, these conventional dosage forms have some drawbacks. Multiple daily dosing is inconvenient to the patient and can result in missed doses, made up doses and patient incompliance with the therapeutic regimen. When conventional immediate release dosage forms are taken on schedule and more than once daily, there are sequential therapeutically blood peaks and valley associated with taking each dose. It should be emphasized that the plasma level of a drug should be maintained within the safe margin and effective range. For this proper and calculated doses of the drug need to be given at different time interval by conventional dosage form. To achieve and maintain the concentration of administered drug within therapeutically effective range, it is often necessary to take drug dosage several times and this result in a fluctuating drug level in plasma. (Chien Y. W, 1992))^[25] Greater attention has been focused on development of sustained or controlled release drug delivery systems with concomitant recognition of the therapeutic advantages of controlled drug delivery. Controlled drug delivery systems have been introduced to overwhelm the drawback of fluctuating drug levels associated with conventional dosage forms.

A variety of materials and approaches have been proposed which could be effectively used in designing and construction of systems with potential to provide Predictable, precise and reproducible pattern of controlled release or even site-specific drug delivery. A sustained release system delivers the active agent at slower rate than the conventional dosage form but the release is substantially affected by external environment. Various terms like ‘smart’,

intelligent', 'novel', therapeutic have been assigned to controlled release systems.(Hoffman A., (1998), Hui H. W., Robinson J. R., Lee V.H.L.).^[26]



Graph No 1: Drug levels in the blood with I.V. administration and controlled release delivery.

2.3.1 Modified release dosage form

A modified release dosage form is one for which the drug release characteristics of time course and/ or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments or promptly releasing dosage form. Delayed release and extended release are two types of modified release dosage forms. (USP, 1995).^[27]

2.3.2 Delayed release dosage form

A delay release dosage form is one that releases a drug(s) at time other than promptly after administration.

2.3.3 Extended release dosage form

Extended release dosage form is one that allows at time least a two-fold reduction in dosage frequency or significant increase in patient compliance or therapeutic performance as compared to that presented in conventional dosage form. The term controlled release prolonged action and sustained release are used synonymously with extended release. Advantages and disadvantages are listed below. (Lachman L., Lieberman H. A., Kanig J. L., (1986)).^[28]

2.3.4 Advantages of sustained release formulations

- Reduction in dosing frequency
- Reduced fluctuation in circulatory drug levels

- Avoidances of night time dosing
- Increased patient compliance
- More uniform effect
- Decreased side effects like reduced GI irritation
- Effective utilization of drug. (Yie W. C., (2005))^[29]

2.3.5 Disadvantages of sustained release formulations

- High cost
- Unpredictable or poor in vivo in vitro correlation
- Dose dumping
- Reduced potential for dosage adjustments
- Increased first pass clearance
- Poor systemic availability in general. (Yie W. C., (2005))

2.3.6 Biological factors influencing oral sustained-release dosage form design

1) Biological half-life

Therapeutic compounds with short half-lives are excellent candidates for sustained-release preparations, since this can reduce dosing frequency. (Jain N. K., (2002), Vyas S. P., Khar R. K., (2002)) 2).^[30]

2) Absorption

The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. If a drug is absorbed by active transport, or transport is limited to a specific region of the intestine, sustained-release preparations may be disadvantageous to absorptions. (Jain N. K., (2002), Vyas S. P., Khar R. K., (2002)).

3) Metabolism

Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period, allowing more complete conversion of the drug to its metabolite. (Jain N.K., (2002), Vyas S. P., Khar R. K., (2002)).

2.3.7 Physicochemical factors influencing oral sustained-release dosage form design

1) Dose Size

In general, single dose of 0.5 – 1.0 g is considered maximal for a conventional dosage form. This also holds true for sustained-release dosage forms. Another consideration is the margin of safety involved in administration of large amounts of drug with a narrow therapeutic range. (Jain N.K, (2002), Vyas S. P., Khar R. K., (2002)).

2) Ionization, pKa, and aqueous solubility

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKa of the compound and the absorptive environment. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of drug in the aqueous media. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form, meaning that the solubility of the drug may change several orders of magnitude during its release. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml. (Jain N.K., (2002), Vyas S. P., Khar R. K., (2002)).

3) Partition coefficient

Compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. Furthermore these compounds can usually persist in the body for long periods, because they can localize in the lipid membranes of cells. (Jain N. K., (2002), Vyas S. P., Khar R. K., (2002)).

4) Stability

Orally administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transit in the GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. (Jain N. K., (2002), Vyas S. P., Khar R. K., (2002)).

2.3.8 Drug selection for oral sustained release drug delivery systems

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug from the GI tract, the general absorbability, the drug's molecular weight, solubility at different pH and

apparent partition coefficient. The pharmacokinetic evaluation requires knowledge on a drug's elimination half-life, total clearance, absolute bioavailability, possible first-pass effect, and the desired steady concentrations for peak and trough. (Jain N. K., (2002), Vyas S. P., Khar R. K., (2002)).

2.3.9 Basic kinetics of controlled drug delivery

In order to establish a basis for discussion of the influence of drug properties and the route of administration on controlled drug delivery, following mechanisms need a fair mention,

- Behavior of drug within its delivery systems
- Behavior of the drug and its delivery system jointly in the body.

The first of the two elements basically deal with the inherent properties of drug molecules, which influence its release from the delivery system. For conventional systems, the rate-limiting step in drug availability is usually absorption of drug across a biological membrane such as the gastro intestinal wall. However, in sustained/controlled release product, the release of drug from the dosage for the rate limiting instead; thus, drug availability is controlled by the kinetics of drug release than absorption. (Jain N. K., (2002), Vyas S. P., Khar R. K., (2002)).

Table 1: Parameters for drug selection for SR drug delivery system.

Parameter	Preferred value
Molecular weight/ size	< 1000
Solubility	> 0.1 mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

2.3.10 Factors influencing the *in vivo* performance of sustained release dosage formulations

There are various factors that can influence the performance of a sustained release product. The physiological, biochemical, and pharmacological factors listed below can complicate the evaluation of the suitability of a sustained release dosage formulation. (Jain N. K., (2002), Vyas S. P., Khar R. K., (2002)).

Physiological

- Prolonged drug absorption

- Variability in GI emptying and motility
- Gastrointestinal blood flow
- Influence of feeding on drug absorption.

Table 2: Pharmacokinetic parameters for drug selection controlled drug delivery.

Parameter	Comment
Elimination half life	Preferably between 0.5 and 8 h
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution V_d	The larger V_d and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration C_{ss} av	The lower C_{ss} av and smaller V_d , the loss among of drug required


Pharmacokinetic/biochemical

- Dose dumping
- First- pass metabolism
- Variability in urinary pH; effect on drug elimination
- Enzyme induction/ inhibition upon multiple dosing

Pharmacological

- Changes in drug effect upon multiple dosing
- Sensitization/ tolerance

2.4 Introduction to hydrophilic matrix tablet

A hydrophilic matrix, controlled release system is a dynamic one involving polymer wetting, polymer hydration, gel formation, swelling, and polymer dissolution. At the same time, other soluble excipients or drugs will also wet, dissolve, and diffuse out of the matrix while insoluble materials will be held in place until the surrounding polymer/excipients/drug complex erodes or dissolves away. The mechanisms by which drug release is controlled in matrix tablets are dependent on many variables. The main principle is that the water-soluble polymer, present throughout the tablet, hydrates on the outer tablet surface to form gel layer.  (Hoffman A., (1998))^[31]

Throughout the life of the ingested tablet, the rate of drug release is determined by diffusion (if soluble) through the gel and by the rate of tablet erosion. With soluble drugs, the primary

release mechanism is by diffusion through the gel layer. With insoluble drugs, the primary mechanism is by the tablet surface erosion.

As increasing viscosity of the polymer yields slower drug release as a stronger more viscous gel layer is formed, providing a greater barrier to diffusion and slower attrition of the tablet, with insoluble drugs. The fine tuning of modified release systems may be achieved by blending of different viscosity grades of polymer where the desired dissolution rate is not obtained with a single polymer.

A fast rate of hydration followed by quick gelation and polymer/polymer coalescing is necessary for a rate-controlling polymer to form a protective gelatinous layer around the matrix. This prevents the tablet from immediately disintegrating, resulting in premature drug release. Fast polymer hydration and gel layer formation are particularly critical when formulating with water-soluble drugs and water-soluble excipients. (Hui H. W., (2005).^[32]

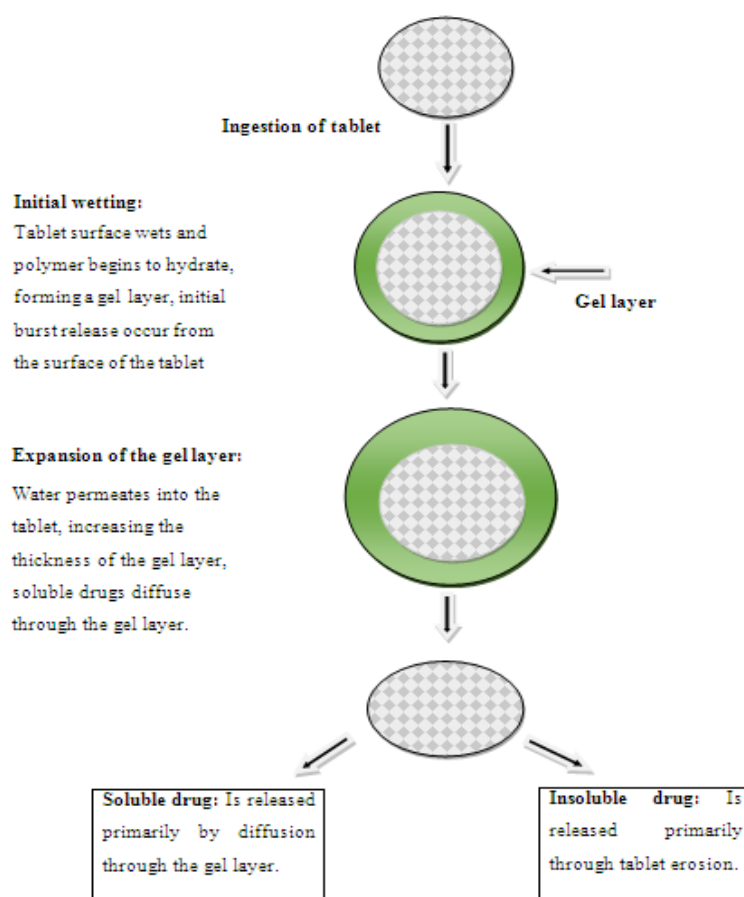


Figure 3: Drug release from hydrophilic matrix tablet.

Hydrophilic matrix tablet using HPMC were prepared and evaluated. They found that the type and amount of HPMC could affect the release rates as well as kinetics from the

swellable matrices. Several investigators investigated the drug release rates and release kinetics from carbomer matrix tablets.

Tablets exhibiting zero-order release mechanisms could be obtained at several different levels of concentration of different carbomers, such as Carbopol 934P, 971P and 974P. The results indicated that drug release from the carbomer matrix tablets could occur, both by diffusion through low microviscosity pores and by a swelling controlled mechanism. As the amount of the carbomers in their respective formulations increased, drug release rate decreased and the release mechanism gradually changed from anomalous type of release to the Case II transport mechanism. Other factors responsible for the reduction in the number and/or size of low microviscosity pores, such as higher pH that increased polymer swelling and decreased drug release, tended to shift the release profiles towards the swelling controlled, Case II type release mechanism. (Jantzen G. M., Robinson J. R., (1996), Jain N. K., (2002).^[33]

CONCLUSION

Bilayer tablet is improved beneficial technology to overcome the shortcoming of the single layered tablet. There is various application of the bilayer tablet it consist of monolithic partially coated or multilayered matrices. 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. The preparation of tablets in the form of multi layers is used to provide systems for the administration of drugs, which are incompatible and to provide controlled release tablet preparations by providing surrounding or multiple swelling layers. Bi-layer tablet quality and GMP-requirements can vary widely.

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