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Review Article

A REVIEW ON BILAYER TABLETS CONTAINING PARACETAMOL AS SR LAYER AND N-ACETYL CYSTEINE AS IR LAYER

Premanjali Divya[1], Dr. Manish Kumar Gupta[2], Vijay Sharma[3]

[1] M.Pharm. Research Scholar, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

[2] Professor and Principal, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

[3] Associate Professor, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

ABSTRACT

Oral route is the most popular route of drug delivery due to it is ease of administration patient compliance least sterility constraints and flexible design of dosage form. Bilayer tablet have some key advantages compared to conventional monolayer tablets. Such tablets commonly used to avoid chemical incompatibilities of formulation component by physical separation. bilayer tablets have enabled the Development of controlled delivery of active pharmaceutical ingredients with predetermined release profiles by combining layer with various release patterns or by combining slow release with immediate release layers. Bilayer tablets have some key advantages compared to conventional monolayer tablets For instance such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. In addition, bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with predetermined release profiles by combining layers with various release patterns, or by combining slow-release with Immediate-release layers. The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depend on the applied pre compression force.

KEY WORDS: bilayer tablets, paracetamolN-acetyl cysteine, drug products

INTRODUCTION

Oral route is the most popular route of drug delivery due to it is ease of administration patient compliance least sterility constraints and flexible design of dosage form. It is agreat scientific accomplishment of this age that a vast array of effective medicinal agents are available today as the knowledge of basic science increased and so did their application to pharmacy. But over the past few years, the fraction of new drug products with new chemical entities has steadily decreased which flectsre the tremendous cost required to bring new chemical entities to the market. Increased understanding of drug metabolic and toxico- logic factors, the genetic factors that may result in dramatic inter subject variability in metabolism, short-term versus long-term exposure toxicities and the potential for teratogenic, mutagenic and embryo- toxic effects has increased the scrutiny under which governmental agencies view the new chemical entity. This careful inspection is intended to minimize the possibility of toxic reaction and to demonstrate the safety and efficacy of new drug products.

Pain Management

Medication

The analgesic acetaminophen is the first line treatment for OA. However, a 2015 review found acetaminophen to only have a small short term benefit. For mild to moderate symptoms effectiveness is similar to non-steroidal anti-inflammatory drugs (NSAIDs),though for more severe symptoms NSAIDs may be more effective. NSAIDs such as naproxen while more effective in severe cases are associated with greater side effects such as gastrointestinal bleeding. Another class of NSAIDs, COX-2 selective inhibitors(such as celecoxib) are equally effective to NSAIDs with lower rates of adverse gastrointestinal effects but higher rates of cardiovascular disease such as myocardial infarction. They are also more expensive than non-specific NSAIDs.

Surgery:

If problems are significant and more conservative management is ineffective, joint replacement surgery or resurfacing may be recommended. Evidence supports joint replacement for both knees and hips as it is both clinically effective, and cost effective. Surgery to transfer articular cartilage from a non-weight-bearing area to the damaged area is one possible procedure that has some success but there are problems getting the transferred cartilage to integrate well with the existing cartilage at the transfer site.

**Corresponding author: Premanjali Divya /*

Tablet

Over 90% of the formulations manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction.

Overview on Type and Class of Tablets:

A) Oral Tablets for Ingestion:

These tablets are mean to be swallowed intact along with a sufficient quantity of potable water. Exceptions are chewable tablets and oral dispersible tablets. Standard compress tablet this class includes tablets like, multiple compress tablet, compression coated tablet, layered tablet and modified release tablet etc.

B) Tablet Used in Oral Cavity:

The tablet under this group are aim to release active pharmaceutical ingredient in the oral cavity or to provide local action in this region. The tablets under this category avoid first pass metabolism, decomposition of gastric environment, nauseatic sensation and give rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity.

C) Tablet administered by other route:

These tablets are administered by other route for the oral cavity and so the drugs avoided from passing through GIT. These tablets may be inserted into other body cavities or directly placed below the skin to absorb into systematic circulation from the site of application. This class include tablet like vaginal tablet or implants.

D) Tablets Used to Prepare Solution:

The tablets under this category are required to be dissolved 1st in water or other solvent before administration or application into body cavity. This solution may be for ingestion or parenteral application or for topical use depending upon type of medicament used. This class includes tablets like effervescent tablet and hypodermic tablet.

Bilayer Tablets:

Bilayer tablet have some key advantages compared to conventional monolayer tablets. Such tablets commonly used to avoid chemical incompatibilities of formulation component by physical separation. bilayer tablets have enabled the Development of controlled delivery of active pharmaceutical ingredients with predetermined release profiles by combining layer with various release patterns or by combining slow release with immediate release layers. Bi-layer tablets is suitable for sequential release of two drugs in combination, separate two incompatible substance and also for sustained release in which one layer is immediate release as initial dose and second layer is maintenance dose.

Need of Bilayer Tablets:

1. For the administration of fixed dose combinations of fixed APIs, prolong the drugproduct life cycle.

2. Controlling the delivery rate of either single or two different APIs

3. To modify the total surface area for APIs layer either sandwiched with one or twoinactive layers in order to swellable / erodible barrier for modified release.

4. To separate incompatible APIs from each other to control release of API from onelayer by utilising the functional property of the other layer.

Advantages of Bilayer Tablets:

1. Bilayer execution with optional single layer conversion kit.
2. Cost is lower to all other oral dosage form.
3. Greatest chemical and microbial stability of among all over oral dosage form.
4. Easy to swallow with least tendency to hang up.
5. Objectionable odour and bitter taste can be masked by coating membrane.
6. Suitable for large production.

Disadvantages of Bilyer Tablets:-

1. Difficult to swallow in case of child.
2. Bitter taste drug with objectionable odour drugs that are sensitive to oxygen may require encapsulation or coating.
3. Some drugs resist compression into dense compact due to their amorphous nature.

Characterstics of Bilayer Tablets:

- A bilayer tablet should have elegant product identity while free of defect like chip, break, contamination and discoloration.
- It should have sufficient strength to withstand mechanical shock during it production, packaging, shipping and dispensing.
- It should have chemical, physical stability to maintain its physical attributes over time.
- The bilayer tablet must be able to release a medicinal agent in predictable and reproducible manner.
- It must have a chemical stability self life so as not to follow alteration of medicinal agent.

Advantages of Bilayer Tablet over Convention Tablets:

Bilayer tablets have some key advantages compared to conventional monolayer tablets For instance such tablets are commonly used to avoid chemical incompatibilities of formulation components by physical separation. In addition, bilayer tablets have enabled the development of controlled delivery of active pharmaceutical ingredients with predetermined release profiles by combining layers with various release patterns, or by combining slow-release with Immediate-release layers. 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. Conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency

Ideal Properties for Bi-Layer Tablets Press:

• Preventing Capping and separation of the two individual layers that constitute the bi-layer tablet.

• Preventing cross contamination between two layers.

• Producing a clear visual separation between two layers.

• High yield and accurate and individual weight control of the two layers.

Types of Bi-Layer Tablet Press:

1. Single sided tablet press.
2. Double sided tablet press.
3. Bi-layer tablet press with displacement monitoring.

Bi-layer Tablet Press with Displacement:

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depend on the applied pre compression force.

Advantages:

• Weight monitoring/control for accurate and independent weight control of the individual layers.

• Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.

• Independence from machine stiffness.

• Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed.

• Maximum prevention of cross contamination between two layers.

• Clear visual separation between the two layers and maximized yield.

Fig.1: Bilayer Tablet Compression Machine

Sustained release drug delivery system:

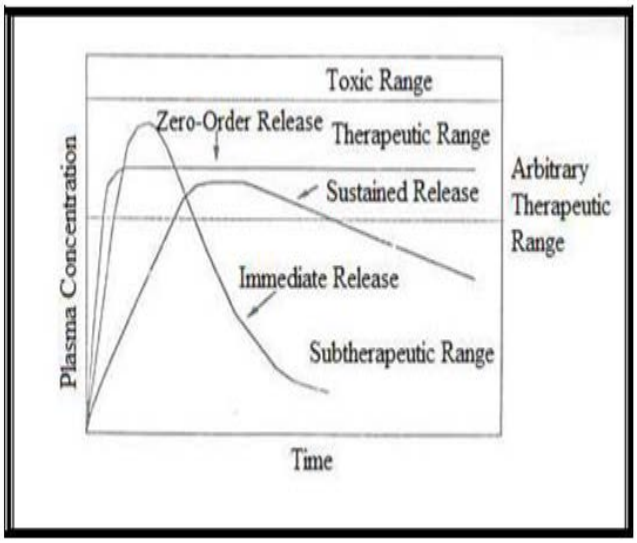

Fig.2: Sustained/ controlled release

The Major goal set in designing sustained or controlled delivery is to:

➢ Reduce the frequency of dosing or to increase effectiveness of the Paracetamol localization at the site of action, reducing the dose required, or providing the uniform drug delivery.

➢ It would be a single dose for the duration of treatment whether it is for days or weeks, as with infection, or for the life time of patient, as in hypertension or diabetes.

- It should deliver the active entity directly to the site of action, minimizing or eliminating side effects. This may necessitates delivery to specific receptors or to localization to the cells or to specific areas to the body.
- The safety margin of high potency drug can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.

Criteria to be met by drug proposed to be formulated in sustained release dosage forms:

a) Desirable half-life:

The half life of drug is an index of its residence time in the body. If the drug has short half life(less than 2 hrs, the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half-life of eight hours or more are sufficiently sustained in body, when administered in a conventional dosage form and controlled release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of three to four hours.

b) High therapeutic index:

Drug with low therapeutic index are unsuitable for incorporation in controlled release formulations. If the system fails in body, dose dumping may occur, leading to fatalities eg. Digitoxin.

c) Small dose:

If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release formulation would become too big to administer without difficulty.

d) Desirable absorption and solubility characteristics:

Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into controlled release formulation is therefore unrealistic and may reduce overall absorption efficiency.

e) Desirable absorption window:

Certain drugs when administered orally are absorbed only from a specific part of GIT. This part is referred to as the absorption 'window'. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as controlled release dosage form are unsuitable.

f) First pass clearance:

Delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release forms.

DRUG RELEASE MECHANISM:

Release of medicament can follow various mechanisms;

A) Diffusion:

Diffusion is a rate limiting step for the release of drug. Diffusion is the driving force where the movement of drug molecules occurs from high concentration in the tablet to lower concentration in the gastrointestinal fluids. This movement depends on surface area exposed to gastric fluid, diffusion pathway, drug concentration gradient and diffusion coefficient of the system.

In practice, we can follow either of two methods,

1. The drug is formulated in an insoluble matrix. The gastric fluid penetrates the dosage form and dissolves the medicament and release the drug through diffusion.

2. The drug particles are coated with polymer of defined thickness so as the proportion drug slowly diffuse through the polymer to maintain constant drug level in blood.

B) Dissolution:

Dissolution is a rate limiting step for the release of drug. The drug with poor water solubility (BCS class 2 and 4) are inherently sustained release forms. While for water soluble drugs, it's possible to incorporate a water insoluble carrier to reduce dissolution of the drug particles are coated with this type of materials e.g. polyethylene Glycol.

C) Osmotic pressure:

Osmotic pressure is a rate limiting step for the release of drug. Osmosis is a phenomenon in which the flow of liquid occurs from lower concentration to higher through a semi permeable membrane which allows transfer of liquid only. The whole drug is coated with a semi permeable membrane with a hole on one end of tablet made by a laser beam. The gastric fluid penetrates through the membrane, solubilizes the N-Acetyl Cysteinend increases the internal pressure which pumps the drug solution out of the aperture and releases the drug in gastric environment. The delivery rate is constant provided that the excess of drug present inside the tablet. But it declines to zero once the concentration drop below saturation.

D) Release controlled by ion exchange:

Ion exchangers are water insoluble resinous materials containing salt forming anionic or cationic groups. While manufacturing, the drug solution is mixed with resin and dried to form beads which are tablet. The drug release

depends upon high concentration of charged ions in gastro intestinal tract where, the drug molecules are exchanged and diffused out of the resin into the surrounding fluid. This mechanism relies upon the ionic environment of resin and not PH or enzyme on absorption site.

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