BILAYER TABLET: A SUSTAIN RELEASE DRUG DELIVERY

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ABSTRACT

A bilayer tablet is a modified drug delivery or advanced dosage forms in market. Successful manufacturing of these ever more complex systems needs to overcome a series of challenges from formulation design to tablet press monitoring and control. This article provides an overview of the state-of-the-art of bilayer tablet technology, highlighting the main benefits of this type of oral dosage forms while providing a description of current challenges and advances toward improving manufacturing practices and product quality. Bilayer tablet includes mainly two separate layers name as Immediate release and Sustain release. A various section is also devoted to bilayer tablet characterization that present additional complexities associated with interfaces between layers. The available features of the manufacturing instruments for bilayer tablet production are also described indicating the different strategies for sensing and controls offered by bilayer tablet press manufacturers.

KEYWORDS: Bilayer Tablet, Sustain Release.

INTRODUCTION OF SUSTAIN RELEASE TABLET

Sustained Release

During the last two decades there has been remarkable increase in interest in sustain release drug delivery system. This has been due to various factor prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. These systems also provide slow release of drug over an extended period of time and also can provide some control. The system is successful at maintaining constant drug levels in the target tissue or cells.[1]
POTENTIAL ADVANTAGES AND DISADVANTAGES OF SUSTAIN RELEASE TABLET

Patient compliance

Lack of compliance is generally observed with long term treatment of chronic disease, as success of drug therapy depends upon the ability of patient to comply with the regimen. Patient compliance is affected by a combination of several factors, like awareness of disease process, patient faith in therapy, his understanding of the need to adhere to a strict treatment schedule.

Reduced ‘see-saw’ fluctuation

Administration of a drug in a conventional dosage form often results in ‘see-saw’ pattern of drug concentration in the systemic circulation and tissue compartments. The magnitude of these fluctuations depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The ‘see-saw’ pattern is more striking in case of drugs with biological half lives of less than four hours, since prescribe dosing intervals are rarely less than four hours. A well-designed sustained release drug delivery system can significantly reduce the frequency of drug dosing and also maintain a more steady drug concentration in blood circulation and target tissue cells.

Reduced total dose

Sustained release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.[1]

Improved efficiency in treatment

Optimal therapy of disease requires an efficient delivery of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A sustained release dosage forms leads to better management of the acute or chronic disease condition.
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DISADVANTAGES
Dose dumping
Dose dumping is a phenomenon where by relatively large quantities of a drug in a sustain release formulation is rapidly released, introducing potential toxic quantities of the drug into systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index.

Limited Choice of Selecting Desired Dose In The Unit
In conventional dosage forms, dose adjustments are much simpler. In case of sustain release tablet, this appears to be much more complicated. Sustain release property may get lost, if dosage form is fractured.

Poor in Vitro in Vivo Correlation
In sustained release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so called Absorption window becomes important and may give rise to unsatisfactory drug absorption in vivo despite excellent in-vitro release characteristics.[1]

Bilayer Tablet: A Sustain Release Drug Delivery
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 and gels. So use of bilayer tablet is a very different aspect for anti-inflammatory and analgesic. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustain release tablet in which one layer is immediate release as initial dose or loading dose and second layer that is sustain layer is maintenance dose. Bilayer tablet is improved beneficial technology to overcome the short coming of the single layer tablet.[2]
ADVANTAGES
1. Release of both drugs starts immediately.
2. Combination of different release profiles.
3. Immediate release and sustained release profile can be achieved in single table by forming.
4. IR layer and SR layer.
5. Combination of incompatible drugs.
6. Elegance to the tablet.

Disadvantages
1. Layer separation.
2. Order of layer sequence
3. Layer weight ratio.
4. Elastic mismatch of the adjacent layers.
5. Cross contamination between layers.\(^2\)

RELEASE MECHANISM

Normal Profile
Normally the drug release from hydrophilic swellable matrices depends on the polymer macromolecule coupling, relaxation and the drug diffusion 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 multilayer drug delivery design.

Bio-Model Profile
To design constant drug absorption, the dosage form should be able to release the drug in a varying manner, there by the release can compensate the change in the drug absorption in the
different part of gastrointestinal tract and provide a control release of drug. This kind of release pattern can be obtained with the help of bio-model release system.\textsuperscript{[5,6,7]}

**Formulation of Bilayer Tablet**

Bilayer tablets are the tablet which are formulated by compressing of two different granulation part into a die, one on top of another. Each layer contains individual weight control. One part is mostly smaller weight of granules than another. A modified release system suitable for bilayer tablet.\textsuperscript{[3]}

![Fig No. 2: Process of Bilayer Tablet.](image)

**Types of Bilayer Tablet Process**

- Single Sided Tablet Press
- Double Sided Tablet Press
- Bilayer Tablet Press with Displacement

**Single Sided Tablet Process**

Various types of Bilayer process 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 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.\textsuperscript{[8,9,10]}

**Limitations**

- No weight monitoring of the Individual layers.
- No distinct Visual separation between the two layers.
• Very difficult first layer tablet sampling and sample transport to a test unit for inline quality control and weight recalibration.

**Double Sided Tablet Process**

It offers an individual fill station, pre-compression and main compression of each layer. In fact the bilayer tablet will go through four compression stages before being ejected from the press. Most double sided tablet presses with automated production control use compression force to monitor and control tablet weight.

**Advantages**

- Displacement weight monitoring for accurate and independent weight control of the individual layer.
- Low compression force exerted on the first layer to avoid capping and separation of the individual layer.
- 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.
- A clear visual separation between two layers.[11]

**Bilayer Tablet with Displacement**

This 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 operation point. But depends on the applied pre-compression force. In fact the lower the pre-compression force, the more monitoring control system and this is ideal for good interlayer bonding of the bilayer tablet. The upper pre-compression roller is attached to an air piston which can moved up and down in air cylinder. The air pressure in the cylinder it set as a product parameter at initial product set-up and is kept at a constant value by the machine’s control system. This pressure multiplied by the piston surface is the constant force at which the piston and consequently the roller is pushed downwards against affixed stop.[10]

**Solubility**

Solubility is the property of a solid, liquid or gaseous chemical substances called solute to dissolve in a solid, liquid or gaseous solvent. The solubility of substance fundamentally depends on the physical and chemical properties of the solute and solvent as well as on
temperature, pressure and presence of other chemicals (including changes to pH) of the solution. Insolubility is the inability to dissolve in a solid, liquid or gaseous solvent.\[12\]

**Biopharmaceutical Classification System of Drug (Bcs)**

**Table No. 1: BCS Classification.**

<table>
<thead>
<tr>
<th>Class</th>
<th>Solubility</th>
<th>Permeability</th>
<th>Absorption Pattern</th>
<th>Rate limiting Step in Absorption</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High</td>
<td>High</td>
<td>Well absorbed</td>
<td>Gastric Emptying</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>II</td>
<td>Low</td>
<td>High</td>
<td>Variable</td>
<td>Dissolution</td>
<td>Etodolac</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>Low</td>
<td>Variable</td>
<td>Permeability</td>
<td>Insulin</td>
</tr>
<tr>
<td>IV</td>
<td>Low</td>
<td>Low</td>
<td>Poorly absorbed</td>
<td>Case by case</td>
<td>Taxol</td>
</tr>
</tbody>
</table>

**Permeability**

Permeability class boundaries are based indirectly on the extent of absorption of a drug substances in humans and directly on the measurement of rates of mass transfer across human intestinal membrane. Alternatively non-human systems capable of predicting drug absorption in humans can be used. A drug substances is considered highly permeable when the extent of absorption in humans determined to be 90% or more of the administered dose based on a mass-balance determination or in comparison to an intravenous dose.\[4\]

**Approximate Solubility**

**Table No. 2 Approximate Solubility.**

<table>
<thead>
<tr>
<th>Terms</th>
<th>Parts of Solvent required for 1 part of solute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Soluble</td>
<td>Less than 1</td>
</tr>
<tr>
<td>Freely Soluble</td>
<td>From 1 to 10</td>
</tr>
<tr>
<td>Soluble</td>
<td>From 10 to 30</td>
</tr>
<tr>
<td>Sparingly Soluble</td>
<td>From 30 to 100</td>
</tr>
<tr>
<td>Slightly Soluble</td>
<td>From 100 to 1000</td>
</tr>
<tr>
<td>Very Slightly Soluble</td>
<td>From 1000 to 10000</td>
</tr>
<tr>
<td>Insoluble</td>
<td>From 10000 and above</td>
</tr>
</tbody>
</table>

**Factors Affecting Solubility**

**Temperature**

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased. If the solution process release (Exothermic process) then solubility will decrease with increase in temperature. Organic compounds nearly always become soluble as temperature is raised in most of the solvents.
Pressure
Solids and liquid solutes that changes in pressure, have practically no effect on solubility. For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decreases in solubility.

Molecular Size
The larger the molecular size or higher its molecular weight the substance will be less soluble. Larger molecules are difficult to surround with solvent molecules in order to solvate the substances. As the particle size reduces the surface area of solute particle increases and the solute dissolves more rapidly.

Polarity
Generally polar solute molecules will dissolve in polar solvents and non-polar solute molecules will dissolve in non-polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then the positive ends of solvents molecules will attract negative ends of solute molecules. This is type of intermolecular force between as dipole-dipole interaction.

Effect of Salt Form
In the case of salts, those that increase the solubility is said to “salt in” the solute and those that decrease the solubility to “salt out” the solute. Both effects are described by empirically derived Setschenow equation: \( \log \frac{S_0}{S} = kM \).\(^{[12]}\)

CONCLUSION
This article provides an overview of the state-of-the-art of bilayer tablet technology, highlighting the main benefits of this type of oral dosage forms while providing a description of current challenges and advances toward improving manufacturing practices and product quality. Extended release systems include any drug delivery system that achieves slow release of drug over an extended period of time. The route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release systems is subject to several inter related variables of considerable importance such as the type of delivery system, the disease being treated.
REFERENCES