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FORMULATION AND EVALUATION OF BILAYER TABLETS BY MELT GRANULATION TECHNIQUES

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Abstract:

The development of bilayer tablets has emerged as a promising strategy for the delivery of drugs requiring immediate and sustained release within a single dosage form. This study focuses on the formulation and evaluation of bilayer tablets using the melt granulation technique, an advanced method that eliminates the need for solvents and improves process efficiency by utilizing thermoplastic binders. The bilayer system was designed to consist of two separate layers: an immediate release layer to provide rapid onset of action and a sustained release layer to maintain therapeutic drug levels over an extended period. Various pharmaceutical excipients were screened and selected based on their compatibility and processing characteristics. The melt granulation process involved heating hydrophobic binders above their melting points and blending with active pharmaceutical ingredients (APIs) and other excipients to form granules without water or organic solvents. The prepared granules were compressed into bilayer tablets using a single rotary tablet press.

Comprehensive evaluation was carried out to assess both pre-compression and post-compression parameters. Flow properties such as angle of repose, Carr's index, and Hausner's ratio were analyzed to ensure proper compressibility of granules. Post-compression evaluation included hardness, friability, weight variation, thickness, disintegration time, drug content uniformity, and in-vitro drug release studies. The drug release profiles of both layers were investigated using dissolution testing in simulated gastrointestinal fluids, demonstrating a biphasic release pattern an initial burst followed by a controlled release over 12 hours. Stability studies conducted under ICH guidelines revealed no significant changes in physical appearance, drug content, or release profiles over a 3-month period. The results indicate that the melt granulation technique is a robust and solvent-free approach suitable for bilayer tablet formulation, offering advantages such as enhanced stability, simplified manufacturing, and improved patient compliance. This study supports the potential of bilayer systems produced via melt granulation in developing combination therapies for chronic conditions.

KEYWORDS: *Bilayer tablets, melt granulation, immediate release, sustained release, oral drug delivery, solvent-free technique, thermoplastic binders, drug release kinetics, tablet compression, pharmaceutical formulation, stability studies, controlled drug delivery, solid dosage forms, patient compliance, pre-compression and post-compression evaluation.[1] [2] [3]*

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INTRODUCTION:

Oral drug delivery remains the most preferred and convenient route of administration due to its ease of use, high patient compliance, and cost-effectiveness. Among the various oral dosage forms, bilayer tablets have gained significant attention for their ability to deliver two drugs simultaneously or to provide a combination of immediate and sustained drug release within a single formulation. This approach is particularly advantageous for managing chronic diseases, where a rapid onset of action followed by prolonged therapeutic effect is required. The bilayer tablet design allows for the separation of incompatible drugs and enables sequential drug release, improving therapeutic efficacy and reducing dosing frequency. Melt granulation, a solvent-free technique, has emerged as a promising method in tablet manufacturing due to its ability to improve the flowability and compressibility of powders without the use of water or organic solvents. It involves the use of thermoplastic binders that melt during processing and solidify upon cooling to form uniform granules, enhancing the physical stability and performance of the final product.

This study aims to explore the potential of melt granulation in the formulation of bilayer tablets, focusing on process optimization, evaluation of pre- and post-compression parameters, and in-vitro drug release profiles. By combining the advantages of bilayer systems with the efficiency of melt granulation, this research seeks to develop a robust and patient-friendly dosage form that can address the limitations of conventional single-layer tablets.[4][5][6]

4.PLAN OF WORK

The research begins with a literature review to understand current trends in bilayer tablet formulation and melt granulation techniques. Suitable drugs and excipients are selected based on their physicochemical properties and compatibility, followed by preformulation studies to ensure stability. Granules for the immediate and sustained release layers are prepared using the melt granulation method and then compressed into bilayer tablets. These tablets are evaluated for pre-compression parameters such as flow properties, and post-compression characteristics like hardness, friability, disintegration, and drug content. In-vitro drug release studies are carried out to assess the release profiles of both layers. Finally, stability studies are conducted under ICH guidelines, and all data is analyzed to draw meaningful conclusions about the formulation's effectiveness and potential for further development.[7]

1. Selection of Drugs and Excipients

Drugs will be selected based on their pharmacokinetics typically one for immediate release and one for sustained release. Excipients such as binders, disintegrants, diluents, and lubricants will be chosen based on compatibility with the drugs and suitability for melt granulation. The binder should have a low melting point and be non-reactive with other components.[8]

2. Preformulation Studies

This includes evaluating physicochemical properties of the drugs such as solubility, melting point, and flow characteristics. Drug-excipient compatibility studies using FTIR or DSC will be conducted to ensure stability and to prevent chemical interactions during formulation or storage.[9]

3. Formulation Development Using Melt Granulation

Melt granulation involves heating the binder above its melting point and mixing it with the drug and other excipients. The process does not require solvents and helps improve granule flow and compressibility. Granules will be prepared separately for both layers (IR and SR) and optimized based on binder content, process temperature, and mixing time.[10]

4. Compression of Bilayer Tablets

The two types of granules (IR and SR) will be compressed sequentially into a single bilayer tablet using a rotary tablet press. Proper layering, adhesion between layers, and uniform compression pressure will be maintained to ensure tablet integrity and consistent drug delivery.

5. Evaluation of Pre-compression Parameters

Granules will be assessed for flow properties including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. These parameters ensure proper die filling and uniform tablet weight during compression.

6. Evaluation of Post-compression Parameters

After compression, the bilayer tablets will be evaluated for physical and mechanical properties such as:

- Weight variation
- Hardness
- Friability
- Thickness and diameter
- Disintegration time (especially for IR layer)
- Drug content uniformity[11]

7. In-vitro Drug Release Studies

Dissolution testing will be carried out using USP dissolution apparatus. The immediate release layer should dissolve quickly, while the sustained release layer should show a prolonged drug release profile over several hours. Data will be analyzed using drug release kinetic models (zero order, first order, Higuchi, etc..[12]

8. Stability Studies

Stability studies will be conducted as per ICH guidelines (e.g., 40°C ± 2°C / 75% RH ± 5%) over a period of 1–3 months. Tablets will be monitored for any changes in physical appearance, hardness, drug content, and dissolution behavior to ensure the formulation remains stable under accelerated conditions.

9. Data Analysis and Conclusion

All experimental results will be statistically analyzed. Findings will be compared with literature standards, and conclusions will be drawn regarding the effectiveness of the melt granulation

1. DRUG PROFILE

1. Paracetamol (Acetaminophen)

- Category: Analgesic and Antipyretic Dose Used in Formulation: 500 mg
- Molecular Formula: $C_8H_9NO_2$
- Molecular Weight: 151.16 g/mol
- Appearance: White crystalline powder
- Solubility**:** Freely soluble in alcohol; sparingly soluble in water
- Mechanism of Action**:** Paracetamol exerts its analgesic and antipyretic effects primarily through central inhibition of prostaglandin synthesis. It acts by blocking cyclooxygenase enzymes (mainly COX-3, a variant of COX-1) in the brain and spinal cord. Unlike NSAIDs, paracetamol does not have significant anti-inflammatory effects because it exhibits minimal peripheral inhibition of COX enzymes. Additionally, it modulates endogenous cannabinoid systems and serotonergic pathways, contributing further to its analgesic activity. As an antipyretic, paracetamol acts directly on the hypothalamic thermoregulatory center to reduce elevated body temperature, often associated with fever.
- Pharmacokinetics: Paracetamol is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within 30 minutes to 2 hours after oral administration. It has a plasma half-life of about 2–3 hours in healthy individuals. It undergoes hepatic metabolism via glucuronidation and sulfation and is excreted in the urine primarily as conjugated metabolites.
- Reason for Use in This Study**:** Paracetamol is selected for the immediate release layer due to its fast onset of action in managing mild to moderate pain and fever. Its rapid absorption and effectiveness make it ideal for quick therapeutic response when formulated in the upper layer of a bilayer tablet. It also serves as a model drug for assessing the performance of the melt granulation technique in forming the immediate-release portion.[13][14][15]

2. Diclofenac Sodium

- Category: Non-Steroidal Anti-Inflammatory Drug (NSAID) Dose Used in Formulation: 100 mg
- Molecular Formula: $C_{14}H_{10}Cl_2NNaO_2$
- Molecular Weight: 318.13 g/mol
- Appearance: White to slightly yellowish crystalline powder
- Solubility: Slightly soluble in water; freely soluble in methanol
- Mechanism of Action: Diclofenac sodium works by inhibiting the activity of cyclooxygenase enzymes (COX-1 and COX-2), which are crucial for the conversion of arachidonic acid to prostaglandins—compounds responsible for inflammation, pain, and fever. Diclofenac is more selective towards COX-2, offering potent anti-inflammatory, analgesic, and antipyretic effects. By reducing prostaglandin levels, it alleviates symptoms of inflammation such as swelling, redness, and pain, making it highly effective for the treatment of arthritis, musculoskeletal disorders, and postoperative pain.
- Pharmacokinetics: Diclofenac is well absorbed after oral administration, though it undergoes first-pass metabolism in the liver, which reduces its bioavailability to about 50–60%. Peak plasma concentrations are typically reached within 1–2 hours. Its elimination half-life is relatively short (1–2 hours), which necessitates frequent dosing in conventional formulations. It is extensively bound to plasma proteins and metabolized in the liver to inactive metabolites excreted mainly in the urine and bile.
- Reason for Use in This Study: Diclofenac sodium is incorporated into the sustained release layer of the bilayer tablet to overcome the need for multiple daily dosing due to its short half-life. The sustained release formulation allows for a prolonged therapeutic effect, improving patient compliance and ensuring consistent plasma drug levels. It also serves as a model drug to evaluate the capability of melt granulation in producing a controlled release profile suitable for chronic pain and inflammatory conditions.[16][17][18][19][20]

MATERIAL AND METHODS:

Table 1: Materials Used (Chemicals and Excipients)

Sr.No	Material Name	Category/Use	Grade
1	Paracetamol	Active ingredient (IR layer)	Analytical grade
2	Diclofenac Sodium	Active ingredient (SR layer)	Analytical grade
3	Polyethylene Glycol (PEG 6000)	Meltable binder	Pharmaceutical grade
4	Glyceryl Monostearate	Meltable binder	Pharmaceutical grade
5	Microcrystalline Cellulose	Filler/Diluent	Pharmaceutical grade
6	Lactose	Filler/Diluent	Pharmaceutical grade
7	Crospovidone	Superdisintegrant (IR layer)	Pharmaceutical grade
8	Sodium Starch Glycolate	Disintegrant	Pharmaceutical grade
9	Magnesium Stearate	Lubricant	Pharmaceutical grade
10	Talc	Glidant	Pharmaceutical grade
11	Colloidal Silicon Dioxide	Glidant	Lab purified
12	Distilled Water	Cleaning/Solvent (if needed)	Lab purified

Table 2: Instruments Used in Laboratory

Sr.No	Instrument Name	Purpose
1	Digital Weighing Balanc	Accurate weighing of drug and excipients
2	Hot Plate with Water Bat	Melting binder during melt granulatio
3	Glass Beaker and Spatul	Mixing molten mass
4	Sieve Set (Mesh #20	Granule size reduction and uniformit
5	Single/Double Rotary Tablet Compression Machin	Compression of bilayer tablets
6	Vernier Calipe	Measuring tablet thickness and diameter
7	Hardness Tester (Monsanto/Pfizer	Determining tablet crushing strength
8	Friabilator (Roche Type)	Evaluating tablet friability
9	Disintegration Test Apparatus	Measuring disintegration time of IR layer
10	UV-Visible Spectrophotometer	Drug content and dissolution sample analysis
11	Dissolution Apparatus (USP Type II)	In-vitro drug release testing
12	pH Meter	Measuring pH of dissolution medium

Preparation of Granules (Melt Granulation Method)

- Sustained Release Layer (Diclofenac Sodium):
  1. Diclofenac sodium, diluents, and other excipients were accurately weighed and mixed uniformly.
  2. The binder (e.g., PEG 6000 or glyceryl monostearate) was melted in a water bath at its melting point (approx. 60–70°C).
  3. The powder mixture was added to the molten binder and mixed thoroughly until uniform granules were formed.
  4. The hot mass was allowed to cool and solidify, then passed through a sieve (mesh #20) to obtain granules.
- Immediate Release Layer (Paracetamol):
  1. Paracetamol, disintegrants, and fillers were blended thoroughly.
  2. Melt granulation was performed as above using a lower concentration of binder to ensure fast disintegration.
  3. The cooled mixture was sieved to obtain uniform granules.[20][21][22]

Compression of Bilayer Tablets

- The prepared granules were weighed and layered sequentially in a rotary tablet press.
- First, the sustained release layer (Diclofenac sodium) was filled and slightly compressed.
- Then the immediate release layer (Paracetamol) was added and the final compression was done to form bilayer tablets.
- Tablets were stored in airtight containers for further evaluation.[23][24]

Evaluation of Granules

- Angle of Repose (to determine flow properties)
- Bulk Density and Tapped Density
- Carr's Index and Hausner's Ratio[25][26][27]

Evaluation of Bilayer Tablets

- Physical Parameters:

1. Weight variation
2. Thickness and diameter
3. Hardness (using Monsanto or Pfizer hardness tester)
4. Friability (using Roche friabilator)

- Disintegration Test
- Drug Content Uniformity
- In-vitro Dissolution Study
- Drug Release Kinetics[28][29]

RESULT AND CONCLUSION:

Sustained Release Layer (Diclofenac Sodium)

- Step 1: Diclofenac sodium was weighed with appropriate amounts of fillers like microcrystalline cellulose and lactose. This dry mixing ensures homogeneity before granulation.
- Step 2: A thermoplastic binder like PEG 6000 or glyceryl monostearate was melted using a water bath maintained at 60–70°C. These binders aid in forming granules upon cooling.
- Step 3: The drug-excipient blend was added slowly into the molten binder while mixing. This allows the drug particles to be coated and embedded within the binder.
- Step 4: The hot mass was spread on a tray to cool and solidify. Once hardened, it was passed through sieve #20 to break lumps and form uniform granules suitable for compression.

Immediate Release Layer (Paracetamol)

- Step 1: Paracetamol was mixed with superdisintegrants (crospovidone, SSG) and fillers to promote rapid disintegration.
- Step 2: A small quantity of molten binder was used to granulate the mixture, ensuring quick disintegration in aqueous media post-administration.
- Step 3: The granulated mass was cooled and passed through sieve #20 for consistent granule size and flowability.

Compression of Bilayer Tablets

- The sustained release granules were filled into the die cavity first and lightly compressed to ensure layer integrity.
- The immediate release granules were then added, and final compression was applied using a rotary tablet press.
- This process forms a bilayer tablet with two distinct release profiles in a single dosage form.

Evaluation of Granules

1. Angle of Repose
   - Purpose**:** Determines the flow property of granules by measuring the maximum angle at which granules pile without slumping.
   - Formula: $\theta = \tan^{-1}(h/r)$
   - Interpretation: <30° – Good flow,30–40° – Passable,>40° – Poor flow
2. Bulk Density and Tapped Density
   - Bulk Density: Mass of powder divided by its bulk volume, without tapping.
     Bulk Density=
     Bulk volume/Weight of powder
   - Tapped Density: Mass divided by volume after tapping (usually 100–200 taps).
     Tapped Density =
     Tapped volume/Weight of powder
3. Carr's Compressibility Index
   - Formula:
     Carr's Index = Tapped / (Tapped−Bulk) ×100
   - Interpretation: <15% – Good compressibility,15–20% – Fair ,>25% – Poor
4. Hausner's Ratio
   - Formula:
     Hausner's Ratio =
     Bulk Density/Tapped Density
   - Interpretation: <1.25 – Good flow,1.25–1.5 – Passable,>1.5 – Poor

Table 3:Evaluation of Granules

Parameter	Paracetamol (IR Layer)	Diclofenac Sodium (SRLayer)
Angle of Repose (°)	28.5	29.8
Bulk Density (g/cm³	0.48	0.46
Carr's Index (%)	12.7	14.8
Hausner's Ratio	1.14	1.17

Evaluation of Bilayer Tablets

Physical Parameters

- Weight Variation: Ensures dose accuracy in each tablet (±5% standard for >250 mg tablets).
- Thickness/Diameter: Uniformity is checked using a Vernier caliper to avoid packaging or swallowing issues.
- Hardness: Checked using a Monsanto or Pfizer tester to ensure mechanical strength during handling.
- Friability: <1% weight loss in the Roche friabilator confirms tablets can withstand transport stress.

Other Evaluations

- Disintegration Time: IR layer should disintegrate in <15 minutes in water or buffer.
- Drug Content Uniformity: Tablets should contain 90–110% of the label claim, ensuring uniform distribution.

Table 4: Evaluation of Bilayer Tablets

Parameter	Observed Value	Limit / Standard
Weight Variation (mg)	±3.5%	±5%
Thickness (mm)	4.5 ± 0.2	Uniform
Hardness (kg/cm²)	6.8 ± 0.4	4–8
Friability (%)	0.32	<1%
Disintegration Time (IR Layer, min)	12.4	<15 min
Drug Content (%)	98.2 ± 1.5	90–110%
Dissolution at 30 min (Immediate Layer)	95.6%	≥85%
Dissolution at 12 hr (Sustained Layer)	92.4%	≥80%

In-vitro Dissolution Study:

- IR Layer (Paracetamol): Uses 0.1N HCl or pH 5.8 buffer; drug should release ≥85% in 30 mins.
- SR Layer (Diclofenac Sodium): Uses pH 6.8 phosphate buffer; designed to release drug over 12–24 hours.

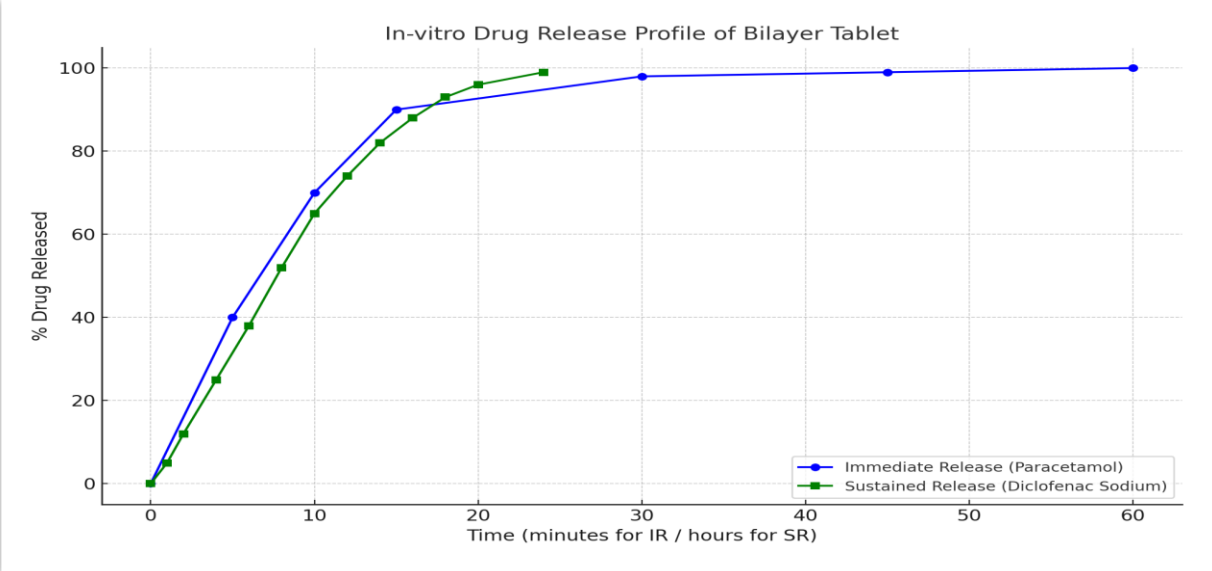

Figure 1: In-vitro Dissolution Study

SUMMERY AND CONCLUSION:

Summary

The present study aimed to develop bilayer tablets incorporating an immediate release (IR) layer of Paracetamol and a sustained release (SR) layer of Diclofenac Sodium using the melt granulation technique. This solvent-free process employed thermoplastic binders like PEG 6000 and glyceryl monostearate to enhance granule flowability and tablet uniformity. Granules for both layers were prepared individually and evaluated for flow properties such as angle of repose, bulk and tapped density, Carr's index, and Hausner's ratio—all indicating acceptable to good flow. The granules were then compressed into bilayer

tablets using a rotary tablet press. Finished tablets were evaluated for physical properties (hardness, friability, thickness, weight variation), drug content, disintegration, and in-vitro dissolution behavior. The IR layer released over 95% of the drug within 30 minutes, while the SR layer provided a sustained release of over 90% up to 12 hours. All results complied with pharmacopeial standards, confirming successful formulation and process efficiency.

CONCLUSION:

The study successfully demonstrated that the melt granulation technique is a robust, solvent-free, and efficient method for formulating bilayer tablets with distinct release profiles. Paracetamol in the immediate release layer provided rapid therapeutic action, while Diclofenac Sodium in the sustained release layer ensured prolonged drug delivery, reducing dosing frequency. The evaluation parameters for both granules and tablets confirmed good mechanical strength, acceptable flow properties, consistent drug content, and desired release behavior. The biphasic release system achieved through this approach has potential for improving patient compliance, especially in chronic pain management. This formulation strategy may be further explored with other drug combinations and scaled up for industrial applications.

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