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Formulation and Evaluation of Paracetamol and Diclofenac Sodium Bilayer Tablet as per QBD Approach

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ABSTRACT

The paper intends to enlighten the readers about the challenges of making dual-layer tablets and some possible solutions. In an effort to improve patient convenience and effectiveness, pharmaceutical companies over the years have been concentrating on blending multiple APIs in one drug as well as scrutinizing studies on the deployment of quality by design (Qbd) concepts in paracetamol and diclofenac sodium bilayered tablet formulation. This ranges from appraisal of critical material attributes (CMA) and critical process parameters (CPP) concerning critical quality attributes (CQA) in the process and finished product of the bilayer tablet. In order to control the drug release and maintain its concentration, the recent study deals with formulation and evaluation of bilayer tablet of Paracetamol and Diclofenac Sodium. By using a wet granulation process, the primary ingredients for both Diclofenac sodium and Paracetamol granules were made. Wet mass passed through sieve no. 10 while dry granules passed through sieve no. 22. Their percent friability, hardness, thickness, disintegration and in vitro drug release were evaluated after their preparation as bilayer tablets. Paracetamol showed 86.18% drug release while diclofenac sodium released 51.27% drugs.

Keywords: *Bilayer Tablets, Paracetamol, Diclofenac Sodium*

1. INTRODUCTION

Two-layer medicine is superior to the current use case. It works well for the combination and release of two drugs. Additionally, it can separate two different types of medication and use it with continuous tablets that have two layers: an immediate-release layer for the first dose and a layer for further continuous injection. Bilayer tablet have the one layer is immediate release and second layer is extended release. There is a super disintegrate to accelerate the release of the first dose and ensure its use as soon as possible. Another time to do this is the loading dose. The second layer, called extended-release (medication), releases the drug slowly over time. [1-4]

Rationale to designing of bilayer tablet

- To obtain a synergistic effect.
- Reducing the frequency of dose.
- To prevent drug interaction.
- Therapeutic support and reduce pill burden.

To device new drug delivery systems: Buckle system,HDBS (Hydro dynamically Balanced System).

Characteristics of bilayer tablet

- Chip must be product specification free fromdefectssuch as cracks, staining and contamination.
- Chemical Stability must have a shelf life to avoid trace changes in the drug.
- The physical and chemical stability maintain over time.

It needs to be strong enough to resist mechanical shocks during production, packaging, shipping, and distribution. [5-8]

Challenges in bilayer tablet manufacturing

Material Compatibility: It is crucial to ensure that the materials in each layer are compatible to prevent negative interactions among different APIs, excipients, and coatings.

Layer Adhesion: Proper adhesion between the two layers is essential to prevent separation during handling or use.

Compression Challenges: The compression process involved in bilayer tablet manufacturing poses challenges, especially when dealing with layers that have different physical properties. Ensuring uniform tablet hardness, thickness, and weight can be demanding, particularly with materials that exhibit varying compression behaviours.

Uniformity of Dosage: Maintaining consistent dosage levels between the two layers is paramount for ensuring the drug's therapeutic efficacy and safety. [9-14]

Manufacturing Equipment Challenges: Bilayer tablet manufacturing often necessitates specialized equipment capable of handling the intricacies of two-layer compression. [15-16]

Quality by Design:

A strategic development approach based on quality research and risk management, starting with the prioritization of goals and addressing product, process understanding and process management.

A reliable drug quality system is key to customer satisfaction with high quality medicine. Such a system has the following characteristics:

1.Complies with Current Good Manufacturing Practices (cGMP) requirements.

2. Based on science and risk.

3. Comprehensive.

4. Hardworking and responsible. [17-22]

Why Qbd is important

- Increase the manufacturing efficiency
- Increase the product efficiency.
- Reduction in product rejects and recalls.
- Increase the company reputation.
- Prevent from error during manufacturing. [22-25]

Elements of Qbd

- Quality Target Product Profile
- Critical Quality Attributes
- Quality Risk Management
- Critical Process Parameters
- Design Space
- Control Strategy

Materials

Paracetamol, Lactose, Starch, Magnesium Stearate, Diclofenac Sodium, HPMC and Distilled water, Sodium Hydroxide, Potassium Dihydrogen Orthophosphate.

Method of Preparation

Wet granulation or wet granulation is the most traditional, versatile and widely used process in the production of compressed tablets, as it transfers all physical energy to the granules. This technology differs from other granulation methods in that it uses liquid as solid material. [26-29]

Preparation of Immediate Release Layer (Paracetamol)

- Weigh the 27 gm. of API powders (PCM) and transfer into the Mortar pestle.
- Then again weigh 1.95 gm. of Lactose and transfer it into the mortar pestle.

- Weigh the 0.75 gm. of starch and again it transfers into a mortar pestle.
- Now add 5% of starch slurry to make the daw and pass through sieve no. 10.
- Now put granules into the Hot air oven for drying at 55 ℃ for 1hrs.
- Then again pass through sieve no.22.

Now add 0.30 gm. Magnesium Stearate into the dried granules again to check the flow properties of granules. [30-32]

Preparation of Sustained Release Layer (Diclofenac Sodium)

- Weigh the 2.4 gm. of Diclofenac Sodium and transfer into the Mortar pestle.
- Then again weigh 2.14 gm. of Hydroxypropyl methyl cellulose and transfer it into the mortar pestle.
- Weigh the 2.10 gm. of starch and again it transfers into a mortar pestle.
- Now add sufficient quantity of water to make the dough and pass through sieve no. 10.
- Now put granules into the Hot air oven for drying at 55 ℃ for 1hrs.
- Then again pass through sieve no.22.
- Now add the Magnesium Stearate into the dried granules again to check the flow properties of granules. [33-35]

Preparation of Phosphate Buffer 7.4

- Weigh 20.4 gm of Potassium Dihydrogen Orthophosphate.
- Then add 4.68 gm of NaOH
- Now add the 2.7 liter of distilled water.
- Now adjust the desired pH using HCL or NaOH.
- Make up the volume up to 3 lit. [33-35]

Formulation of bilayer tablets

- Firstly, take the lower punch, the upper punch, and die.
- Now set the lower punch and die cavity.
- Then fill the powder of layer 1 (PCM) into the die cavity, and then place the upper punch.
- Now apply the force with the help of a hammer to the upper punch and formulate the layer 1 tablet.
- Then again, remove the upper punch and fill the powder.
- Now apply the force with the help of a hammer to the upper punch and formulate the bilayer tablet. [33-35]

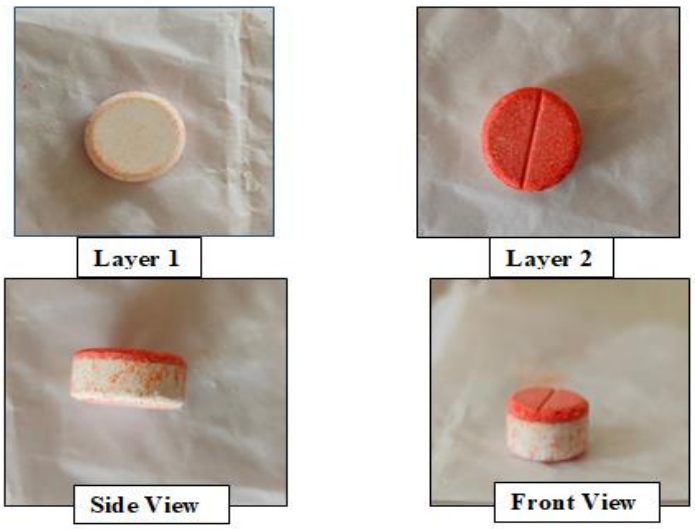

Figure 1: Formulation of Bilayer Tablet

Evaluation Parameter [36-40]

Physical appearance

The bilayer tablets were visually examination for any tablet.

Weight Variation Test

20 tablets to be weighed individually. The mean weight needs computation and the weight variance is determined using the subsequent equation, expressed as a percentage. Weight variation (%)= $\frac{I-Aw}{Aw} x\ 100$

Hardness

The hardness can be determined by Pfizer.

Thickness

Thickness can be measured by the Vernier Caliper

Friability

Friability testing can be conducted using a Roche

friability tester, where 10 tablets are placed inside and rotated at 25 rpm for 4 minutes. The initial and final weights of the tablets are then recorded, and the friability is determined using the provided formula.

F = 100 × (1-w/w0)

In Vitro Dissolution Study

Place the 900 ml 7.5 pH Phosphate buffer in the vessel. Equilibrate the dissolution medium at 37.5 ºC. Put one tablet in the apparatus, taking care to exclude bubbles from the tablet surface. Starting from zero time withdraw the sample. Start withdrawing the sample in each 5 minutes time interval. Filter the sample solution with membrane filter disc. Calculate the amount of dissolved active ingredient in solution as a percentage of the stated amount.

Formula

Table 1: Composition of Paracetamol Tablet

S. No.	Ingredients	Quantity for 1 Tablet (mg)	Quantity for 50 Tablets (gm)	Category
1.	Paracetamol	540	27	API
2.	Lactose	39	1.95	Diluent
3.	Starch	15	0.75	Binder
4.	Magnesium stearate	6	0.30	Talc
5.	Distilled Water	Q.S.	Q.S.	Vehicle

Table 2: Composition of Diclofenac Sodium

S. No.	Ingredients	Quantity for 1 Tablet (mg)	Quantity for 50 Tablets (gm)	Category
1.	Diclofenac Sodium	48	2.4	API
2.	HPMC	43	2.14	Polymer
3.	Starch	42	2.10	Binder
4.	Magnesium stearate	17	0.85	Talc
5.	Distilled Water	Q.S.	Q.S.	Vehicle

Table 3: Composition of Phosphate Buffer

S. No.	Ingredients	Quantity for 1 Liter	Quantity for 3 Liter
1.	Potassium Dihydrogen Orthophosphate	6.8 gm	20.4 gm
2.	Sodium Hydroxide	1.56 gm	4.68 gm

2. RESULTS

The result of flow properties of both the powders such as Bulk Density, Tapped Density, Angle of Repose, Hausner's Ratio, Carr`s Index and the evaluation parameters such as the Physical Appearance, Weight Variation, Hardness, Thickness, Friability and In Vitro drug release study.

Table 4: Flow Properties of PCM Powders

S. No.	Bulk Density	Tapped Density	Hausner's Ratio	Carr`s Index	Angle of Repose
1.	0.5	0.90	1.8	44.44%	26.16º

Table 5: Flow Properties after Granules Formed

S. No.	Bulk Density	Tapped Density	Hausner's Ratio	Carr`s Index	Angle of Repose
1.	0.5	0.66	1.32	24.24%	29.16º

Table 6: Flow Properties of Diclofenac Sodium Powders

S. No.	Bulk Density	Tapped Density	Hausner's Ratio	Carr`s Index	Angle of Repose
1.	0.4	0.50	1.25	20%	25.68º

Table 7: Flow Properties of Diclofenac Sodium Powders after Granules Formed

S. No.	Bulk Density	Tapped Density	Hausner's Ratio	Carr`s Index	Angle of Repose
1.	0.5	0.62	1.24	19.24%	31.38º

Table 8: Evaluation Parameters of Bilayer Tablets

S.No.	Evaluation Parameters	Observed Results
1.	Physical Appearance: Dosage Form Colour	Solid Dosage Form White and red colour
2.	Weight Variation	698.67- 772.22
3.	Hardness	2.3 kg
4.	Thickness	5.03 mm
5.	Friability	9.8 %
6.	In Vitro Dissolution Study of PCM	86.18 % Drug release in 45 min.
7.	In Vitro Dissolution Study of Diclofenac Sodium	51.27 % Drug release in 2.5 hr.

In Vitro Dissolution Study of Paracetamol at 243nm

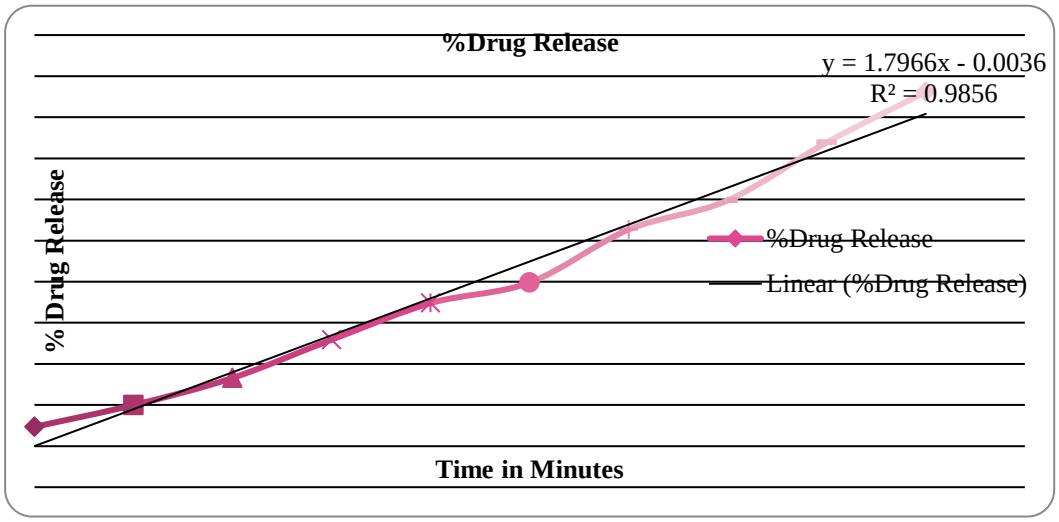

Figure 2: In Vitro Dissolution Study of Paracetamol

In Vitro Dissolution Study of Diclofenac Sodium at 276nm

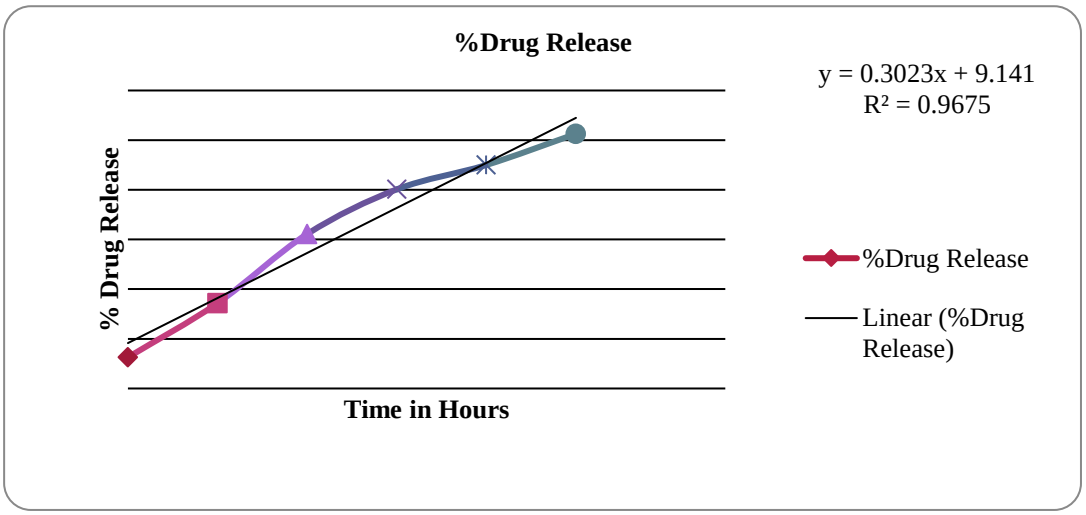

Figure 3: In Vitro Dissolution Study of Diclofenac Sodium

QbD Elements

Table 8: Qbd Elements

S. No.	Qbd Parameters	Target	Observation
1.	QTPP: Dosage Form	Bilayer Tablet	Bilayer Tablet
	Dosage Design	Immediate Release and Extended Release	Immediate Release and Extended Release
	Route of Administration	Oral	Oral

2.	CQA	Physical Attributes, Weight Variation, Hardness, Thickness, Disintegration, Dissolution	P.A- Red and White Color Weight Variation- 712.5 - 787.5 mg Hardness- 2.3 kg Thickness- 5.03 mm Disintegration- 0.50 min. – 10 min Dissolution-Paracetamol 86.18% in 45 min Diclofenac Sodium 51.27% in 2.5 hr
4.	CPP	1st and 2nd Compression forces, Mixing time, Hardness, 1st and 2nd Feeder Speed	Maintain forces by manual NA NA

3. DISCUSSION

We have done the formulation and evaluation of Paracetamol and Diclofenac Sodium BilayerTablet tablets as per Qbd Approach by wet granulation methods mentioned in the literature review. Firstly, we collect the all ingredients that are required for formulation of Paracetamol and Diclofenac Sodium Bilayer Tablet. Firstly prepared the first layer i.e. Paracetamol and the second layer i.e. Diclofenac sodium granules by using wet granulation method and performed various evaluation parameters of Bilayered Tablet as per Indian Pharmacopeia. Firstly Formulation of Bilayer Tablet by hand manual method by using lower punch, upper punch, dies cavity and hammer. Absorbance was measured by UV-visible spectroscopy (SHIMADZU-1900) at an interval of interval of 0, 5,10,15,30,45,60 minute and 0, 30, 60, 90, 120, 150 minutes and the concentration of drug release were noted.

4. CONCLUSION

Although all the tablets released approximately 80% of the drug within 45 minutes as required by the pharmacopoeia, there were some differences in their release characteristics. The drug concentration of bilayer tablets of was within the Pharmacopeia limit. We concluded from the data that the selected tablets used for evaluation of their quality assessment to ensure efficacy and potency yielded diverse results. It may be concluded that the Paracetamol are the immediate release and Diclofenac Sodium is Extended Release. The paracetamol drug release within 45 minutes is 86.18% and Diclofenac Sodium drugs release within 2.5 hours is 51.27%.

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