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Research Article

Formulation Development and Evaluation of Paracetamol and Ibuprofen Bilayer Tablet

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ABSTRACT

In order to maximize pain treatment through different release profiles, the study describes the creation and assessment of bilayer tablets that combine sustained-release ibuprofen and immediate-release paracetamol. The physical properties of several formulations, including their total density, pressed density, angle of repose, Carr's index, and Hausner ratio, were generated and assessed using wet granulation for paracetamol and dry granulation for ibuprofen. Compression was followed by evaluations of tablet toughness, thickness, weight deviation, friability, disintegration time, and in vitro dissolution tests. The findings showed that formulation F6, which included sodium starch glycolate for paracetamol and HPMC K4M with sodium alginate for ibuprofen, met dissolving criteria and had the best release characteristics. This formulation approach highlights the potential of bilayer tablets in improving therapeutic outcomes in pain management by efficiently utilizing the synergistic effects of both medications, offering a quick onset of pain relief together with a prolonged anti-inflammatory action.

INTRODUCTION

A single tablet having two separate layers that are each intended to release the active pharmaceutical ingredients (APIs) at varying rates or times is the basis of the bilayer tablet concept. When mixing drugs with distinct release patterns, such instant release (IR) and sustained release (SR) formulations, this formulation technique is especially helpful. One example of a formulation intended to offer both immediate and long-term pain and inflammation relief is a bilayer tablet that contains sustained-release ibuprofen and instant release paracetamol (acetaminophen). A popular analgesic and antipyretic, paracetamol provides quick pain relief but has a brief half-life. On the other hand, ibuprofen, a medicine called non-steroidal (NSAID), is effective at controlling discomfort and reducing swelling. It has a prolonged duration of action due to its sustained-

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release mechanism. The formulation aims to maximize the therapeutic benefits of both medications by combining them in a bilayer tablet: ibuprofen's long-lasting anti-inflammatory effects and paracetamol's quick onset of pain relief. The development of bilayer tablets has emerged as a promising strategy to address challenges related to drug release profiles, dosing convenience, and patient compliance in combination therapy. This innovative drug delivery system allows for the incorporation of two different drugs or two forms of the same drug with varied release kinetics into a single dosage form. As demonstrated in the treatment of pain and inflammation, it is particularly helpful in situations that call for a combination of rapid and long-term therapeutic activity.[1]

MATERIALS

Table 1: List of ingredients

Sr. No.	Name of the material	Grade	Source
1	Paracetamol	LR	Modern Industries, Nashik Pvt Ltd
2	Ibuprofen	LR	Researchlab Fine Industries, Mumbai
3	Lactose	LR	Researchlab Fine Industries, Mumbai
4	HPMC K_4M	LR	Modern Industries, Nashik Pvt Ltd
5	Maize Starch	LR	Modern Industries, Nashik Pvt Ltd
6	Starch	LR	Modern Industries, Nashik Pvt Ltd
7	Magnesium Stearate	LR	Modern Industries, Nashik Pvt Ltd
8	Talc	LR	Modern Industries, Nashik Pvt Ltd

METHODS

Wet granulation for Paracetamol

One of the most used techniques in pharmaceutical manufacturing for creating granules that may be compacted into tablets is wet granulation. This approach creates a wet mass by combining a liquid binder with a powdered mixture of excipients and active pharmaceutical ingredients (APIs). The wet mass is then dried and sieved to create granules that may be compressed into tablets. When formulating a tablet containing paracetamol as the active ingredient, the wet granulation method ensures uniformity of the drug and helps achieve the desired tablet characteristics such as hardness, dissolution, and content uniformity.[2]

Ingredient: Paracetamol (as the active pharmaceutical ingredient) Excipients like binders (like starch powder), disintegrants (like maize starch), and diluents (like lactose), and lubricants (e.g., Talc). Weigh all ingredients accurately according to the formulation requirements.

Dry granulation for Ibuprofen

The preparation of dry granules for ibuprofen typically involves a process called dry granulation, which can be used when the drug (ibuprofen) is sensitive to moisture or heat.

Below is a general method for preparing dry granules for ibuprofen, though specific formulations might vary based on desired tablet characteristics.

Ingredients: Ibuprofen (Active Pharmaceutical Ingredient - API) Excipients: Binders: (e.g., HPMC K4M, Sodium Alginate) Fillers, such as lactose Lubricating agents: (e.g., magnesium stearate, Talc) [3]

EVALUTION OF GRANULES

Bulk density: The mass of a powder or granular substance per unit volume, including the spaces between particles, is known as its bulk density.

Formula: Bulk Density = Powder Mass / Total Powder Volume

Tapped density: After a powder or granular material has been vibrated or tapped to remove air pockets and settle the particles, the density of the material is referred to as "tapped density."

Formula: Tapped Density = Mass of powder / Tapped volume of powder [4]

Angle of repose: The greatest angle at which a pile of granular or powdered material may stay stable without collapsing or moving is known as the angle of repose.[4]

Formula = Tan θ h/r

Carr's Index

A powder's compressibility is gauged by Carr's Index, sometimes referred to as the Compressibility Index.[5]

Formula: Carr's index : ((Pressed Density - Bulk Density) / Pressed Density) x 100.

Hausner ratio

The Hausner Ratio assesses the powder's ability to flow and pack efficiently.

Formula: Hausner ratio : Pressed Density / Total Density

FORMULATION OF BILAYER TABLET

Formulating a bilayer tablet involves creating a tablet that consists of two distinct layers. These layers can serve different purposes, such as controlling the release of the active pharmaceutical ingredients (APIs) in a specific sequence (e.g., immediate release followed by sustained release) or combining different types of drugs in one tablet. [6,7] Active Pharmaceutical Ingredients (APIs):

1. Layer 1 API (e.g., immediate-release drug, such as Paracetamol)

2. Layer 2 API (e.g., sustained-release drug, such as ibuprofen)

Formulations with Paracetamol Rapid Release Layer (in milligrams)

Table 2: Formulation of Paracetamol

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Paracetamol	500	500	500	500	500	500
Starch Powder	25	25	25	25	25	25
Maize Starch (10%)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Lactose	45	45	35	45	45	45
Talc	10	10	10	10	10	10
Sodium Starch Glycolate	-	-	10	-	-	10

Formulations with Ibuprofen Sustained Release Layer (in milligrams)

Table 3: Formulation of Ibuprofen

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Ibuprofen	125	125	125	125	125	125
HPMC K4M	25	50	50	75	100	75
Lactose	158.68	133.68	133.68	108.68	83.68	58.68
Magnesium Stearate	1.25	1.25	1.25	1.25	1.25	1.25
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Sodium Alginate	-	-	-	-	-	50

Figure 1: Paracetamol and Ibuprofen Bilayer tablets

Post-Compression Evaluation (Tablet Evaluation)

Tablet Hardness: In a test apparatus that produces a bending or tension stress, "tablet hardness" is a measurement of the force needed to shatter a tablet. The total effectiveness and performance of a tablet are greatly influenced by its hardness, particularly in relation to consumer use, wrapping, and transportation. It is also an essential part of tablet quality control. Several tools are employed to complete this task: The Monsanto tester was created half a century ago. In this design, "a barrel containing a compressible spring held between 2 plungers" is the main component. After positioning the tablet on the bottom plunger, the higher plunger is lowered upon it.

Tablet Thickness: Tablet thickness, which is commonly expressed in millimeters or inches, is the distance through a tablet. In the food and pharmaceutical industries, this measurement is essential for figuring out dissolving rates, packaging specifications, and general quality control

Place between two arms of Vernier caliper, the tablet thickness was measured. [8]

Weight Variation: A crucial quality control test for ensuring dosage unit homogeneity in tablet formulations, particularly bilayer tablets, is weight variation. The weight variation test is used to evaluate the consistency of the weight of individual units in the case of bilayer tablets in order to guarantee that the active pharmaceutical ingredients (APIs) are distributed uniformly throughout both layers.

Friability: When exposed to mechanical stress, such as handling or vibration, a solid material, like a tablet, has the propensity to fracture or crumble into smaller pieces. This phenomenon is known as friability. Roche Friability Test measures tablet friability, assessing their resistance to wear, tear and breakage. Developed by Hoffmann-La Roche, it's widely used in pharmaceutical industries [9].

Disintegration: The tablet's disintegration time was calculated using the tablet disintegration test tool. There were 6 tablets in tube of the tablet disintegration testing equipment. In order to track how long it took for the full tablet to dissolve, the medium was kept at 37 ± 2°C. A tablet or capsule's in vitro disintegration time is a measurement of how long it takes for it to dissolve in a laboratory environment that replicates physiological fluids. [10,11]

In Vitro dissolution: In vitro dissolution analysis is a controlled laboratory procedure used to determine the rate and extent of drug release from a dosage form (tablet, capsule, or injection).

Test Procedure:

1. Place the sample: Fill each basket with one dose unit.
2. Turn on the device: Start the timer and agitation. (RPM of 50)
3. Collect samples: Withdraw the paracetamol samples at predetermined intervals. (15,30,45,60,)
4. Then discard the sample solution and add phosphate Buffer (PH 6.8) then Withdraw the sample at predetermined intervals. (1hr, 2hr, 3hr, 6hr, 8hr, 9hr, 11hr, 12hr.)
5. Examine samples: Use UV spectrophotometry and dissolved drug concentration measurement
6. Data recording: Record the dissolution profile (drug release percentage versus time) [12].

Formula:

Drug release quantity (mg/ml) is calculated as follows: concentration × dissolving medium volume × dilution factor / 1000%

Drug release: Drug release amount divided by total drug formulation amount (mg) × 100

RESULT & DISCUSSION:

Pre-compression parameter of paracetamol granules.

Table 4: Paracetamol's pre-compression parameter

Formulation code	Angle of repose	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner's ratio
F1	29.45	0.435	0.536	18.84	1.23
F2	28.79	0.382	0.520	26.53	1.36
F3	29.50	0.395	0.502	21.31	1.27
F4	31.25	0.381	0.515	26.01	1.35
F5	30.25	0.395	0.522	24.32	1.32
F6	28.6	0.451	0.545	16.66	1.20

Angle of repose: The granules of F1–F6 had an angle of repose of 28.6–31.25, indicates good flow properties.

Carr's index: The paracetamol granules of F1–F6 had a Carr's index of 16.66–26.53%, indicating good and fair flowing qualities.

Hausner ratio: The paracetamol granules of F1–F6 had a Hausner ratio of 1.20–1.36, which suggests that their flow characteristics are satisfactory and acceptable.

Pre-compression parameter of Ibuprofen granules:

Table 5: Pre-compression Parameter of Ibuprofen

Formulation Code	Angle of repose (θ)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index (%)	Hausner's ratio
F1	30.45	0.534	0.736	27.44	1.37
F2	29.79	0.682	0.720	26.53	1.05
F3	28.50	0.569	0.715	20.41	1.25
F4	30.25	0.510	0.700	27.14	1.37
F5	29.21	0.559	0.722	22.57	1.29
F6	28.75	0.615	0.741	17.00	1.20

Angle of repose: The granules of F1–F6 had an angle of repose of 28.21–30.45, indicating good flow properties.

Carr's index: The Ibuprofen granules of F1–F6 had a Carr's index of 17.00–26.53%, indicating good and fair flowing qualities.

Hausner ratio: Ibuprofen granules of F1–F6 had a Hausner ratio of 1.20–1.37, which suggests that the granules have good and acceptable flow characteristics.

Post compression evaluation study:

Table 6: Post-compression evaluation study

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)
F1	7	6.8	0.22	911
F2	7	6.21	0.22	922.5
F3	6.9	7.10	0.21	879.5
F4	7	7.51	0.21	936.4
F5	7	7.95	0.22	916.05
F6	7	8	0.22	928.9

The thickness of tablet was found in the range of 6.9-7. The hardness of tablet was found to be 6.21 to 8. The friability of bilayer tablet was found to be 0.21 to 0.22 % which is less than 1% means it passed the friability test. The thickness of tablet was found in the range of 6.9-7. The hardness of tablet was found to be 6.21 to 8. The friability of bilayer tablet was found to be 0.21 to 0.22 % which is less than 1% means it passed the friability test.

Disintegration time:

Table 7: Disintegration time

Formulation code	Disintegration time of Paracetamol (min)
F1	0.56
F2	1.4
F3	3.20
F4	0.55
F5	1
F6	2.15

Disintegration time for Paracetamol immediate layer For F1-F6 was found 0.56-3.20 min and for Ibuprofen sustained release was not disintegrate and lumps were formed.

In -Vitro dissolution drug release profile of batch F1 to F5

Table 8: Profile of drug release for batches F1 to F5

Time	Cumulative % drug release									
	Paracetamol					Ibuprofen				
	F1	F2	F3	F4	F5	F1	F2	F3	F4	F5
0	0	0	0	0	0	0	0	0	0	0
15	57.99	56.99	58.29	61.29	58.21	28.54	23.54	23.47	22.24	2.07
30	77.4	76.42	75.42	78.24	73.24	61.78	52.78	35.07	37.76	5.47
45	93.64	92.64	91.64	95.24	89.99	89.6	68.92	41.22	42.21	10.13
60	98.58	97.58	97.68	98.28	97.58	92.58	79.27	55.71	54.77	20.12
120	-	-	-	-	-	98.27	87.42	61.27	69.72	30.27
180	-	-	-	-	-	-	95.07	75.88	76.84	45.63
240	-	-	-	-	-	-	-	89.42	87.24	58.34
300	-	-	-	-	-	-	-	93.47	92.57	69.78
360	-	-	-	-	-	-	-	98.68	96.28	75.42
420	-	-	-	-	-	-	-	-	-	85.22
480	-	-	-	-	-	-	-	-	-	96.72

To assess the release behaviors of paracetamol and ibuprofen over time, the in-vitro dissolution profiles of formulations F1 through F5 were examined. All formulations of paracetamol demonstrated quick release, with over 90% of the medication being delivered in less than 45 minutes. Among the formulations, F4 exhibited the highest release rate (95.24% at 45 minutes and 98.28% at 60 minutes), suggesting an optimized formulation for immediate drug availability.[18] In contrast, ibuprofen demonstrated a markedly slower and sustained release profile. Formulation F1 exhibited the fastest release with 92.58% drug release at 60 minutes and 98.27% at 120 minutes, whereas formulation F5 had the slowest release profile, reaching only 96.72% at 480 minutes. The gradual release in formulations F3, F4, and F5 indicates their potential for extended or controlled-release applications.

The differing release patterns between paracetamol and ibuprofen can be attributed to their physicochemical properties and interactions with excipients within each formulation. The immediate release of paracetamol suggests that its formulation matrix allows for rapid dissolution, whereas the sustained release of ibuprofen, particularly in F5, may be due to a more hydrophobic matrix or controlled-release polymer incorporation.[19]

In – vitro dissolution drug release profile of Batch F6:

Table 9: The drug release profile of the F6 batch

Time	Sq. root of time	Log of time	Cumulative % Drug Release		log	
			Paracetamol	Ibuprofen	Paracetamol	Ibuprofen

0	0	0	0	0	0	0
1	1	0	98.58	21.06	1.99	1.33
2	1.41	0.149219113	98.58	25.12	1.99	1.4
3	1.73	0.238046103	-	29.47	-	1.46
6	2.44	0.387389826	-	35.63	-	1.55
8	2.82	0.450249108	-	61.78	-	1.79
9	3	0.477121255	-	77.66	-	1.89
12	3.46	0.539076099	-	98.17	-	1.99

Drug release profile of batch F6:

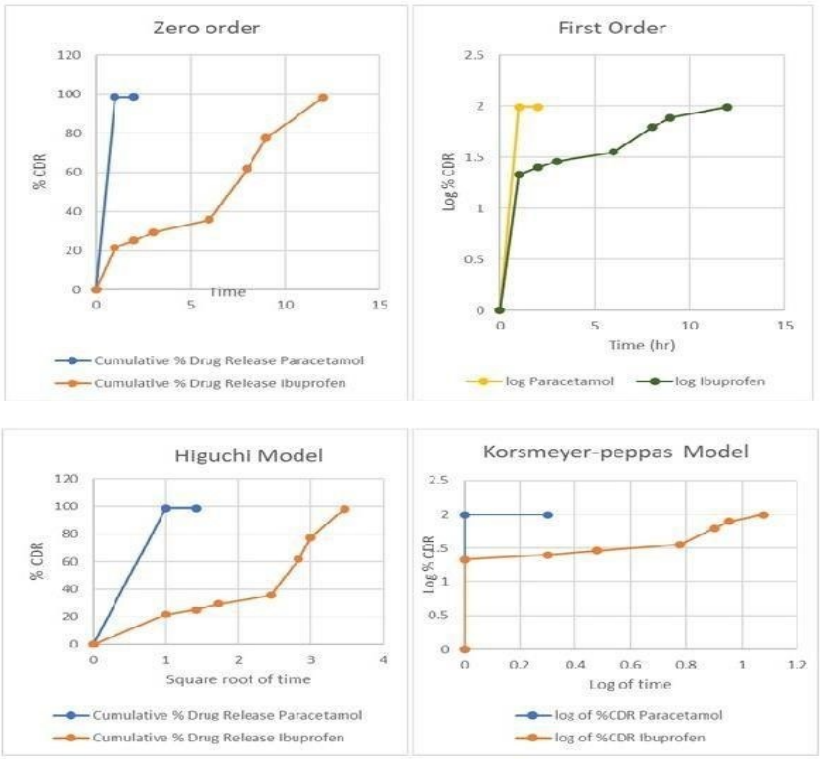

Figure 2: Drug release profile of F6

The data presents the cumulative percentage drug release of Paracetamol and Ibuprofen over a 12-hour period, including calculated square root and logarithmic values of time.

Paracetamol exhibited a rapid release profile, reaching approximately 98.58% cumulative release within just 1 hour and maintaining that release level throughout the observed time frame. This suggests that Paracetamol is released almost instantaneously, likely indicating a fast-release formulation. The logarithmic value for Paracetamol remains constant at approximately 1.99 once released, signifying a saturation level being achieved early in the dissolution profile.

In contrast, Ibuprofen demonstrated a sustained release behavior. At the 1-hour mark, only 21.06% of the drug had been released, with a gradual increase over time, reaching 98.17% at the 12-hour

point. The logarithmic values for Ibuprofen increased steadily from 1.33 to 1.99, consistent with its progressive release. This sustained release is ideal for prolonged therapeutic effects and aligns with formulations designed for extended drug availability.

The differing release patterns highlight the contrast between immediate-release (Paracetamol) and sustained-release (Ibuprofen) drug delivery systems. Such comparisons are crucial in pharmacokinetics for tailoring drug formulations to desired therapeutic outcomes.[20]

CONCLUSION

The study's objective was to develop bilayer pills containing sustained-release (SR) ibuprofen and immediate-release (IR) paracetamol. The formulation of the pills contained excipients such lactose, magnesium stearate, and HPMC K4M. Formulation F6 showed promising results, meeting the solubility requirements for ibuprofen release with HPMC K4M and sodium alginate and paracetamol release with sodium starch glycolate (SSG). We looked at the tablets' in vitro drug release, weight fluctuation, hardness, and friability.

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