International Journal of Scientific Research in Engineering and Management (IJSREM)
Volume: 08 Issue: 07 | July - 2024 SJIF Rating: 8.448 ISSN: 2582-3930

Formulation and Evaluation of Paracetamol Tablet by Using Combination of Caffeine and Aceclofenac

Ms. Rohini More *1, Ms. Suchita Gadekar*2, Mr. Shravan Somani*3, Ms. Manisha Ghavte*4,

*1 Student, Pratibhatai Pawar College Of Pharmacy, Shrirampur *2,*3, 4, Asst. Professor, Pratibhatai Pawar College Of Pharmacy, Shrirampur, Maharashtra

Corresponding Author: Ms. Rohini More*1

Abstract

The aim of this study was to develop an effective pharmaceutical formulation of paracetamol tablets enriched with the combination of caffeine and aceclofenac. Paracetamol, a widely used analgesic and antipyretic drug, faces challenges in achieving optimal pain relief and improving therapeutic efficacy. Caffeine is well known for its adjunctive role in analgesic preparations, and aceclofenac, a potent nonsteroidal anti-inflammatory drug (NSAID), was selected as a potential enhancer of synergy with acetaminophen. The formulation process includes the selection of appropriate excipients to ensure the stability, bioavailability and compatibility of the active ingredients. Different ratios of paracetamol, caffeine, and aceclofenac were studied to achieve the desired pharmacokinetic profile and therapeutic effect. Tablets are prepared using conventional pharmaceutical techniques and tested for various parameters including physical properties, dissolution profile, drug content uniformity and stability. Preliminary results suggest that the combination of caffeine, aceclofenac, and acetaminophen increases analgesic efficacy and may accelerate onset of action. Furthermore, these tablets exhibited satisfactory physical properties and dissolution behavior, indicating their potential to effectively treat pain. Further studies are needed to evaluate the pharmacokinetic parameters, therapeutic efficacy, and safety of the developed formulations through preclinical and clinical studies.

Keywords Analgesic, Antipyretic Activity, Anti-Inflammatory Activity

Introduction

Medication is more than just a science; This is also an art. It's not a combination of pills and patches; It involves actual life processes that must be understood before they can be controlled. Pharmaceutical oral solid dosage forms have been widely used for decades, primarily because of their ease of administration and suitability for delivering drugs with systemic effects.

Tablets may be defined as solid pharmaceutical dosage forms containing the active ingredient, with or without appropriate diluents, and prepared by compression or molding processes.[1]

Defination

According to the Indian Pharmacopoeia, a pharmaceutical tablet is a solid, flat or biconvex shell in unit dosage form prepared by compression of a drug or a mixture of drugs (with or without diluent).

Tablets are described as compressed solid dosage forms containing drug with or without excipients. Depending on the amount of drug and intended route of administration, tablets may vary in shape and may vary significantly in size and weight

Advantages [2,3]

1) Tablets are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
2) They are easiest and cheapest to package and strip.
3) Low in cost.
4) Lighter and compact.
5) Having greatest chemical and microbial stability over all oral dosage forms.
6) Suitable for large scale production.
7) Easy to swallow with least tendency for hang-up.

Disadvantages

1. Difficult to swallow in case of children and unconscious patients.
2. Some drugs resist compression into dense compacts, owing to amorphous nature,low density character.
3. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
4. Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.

Fig No: 01Types Of Tablet

Paracetamol [4,5]

Paracetamol is a commonly used antipyretic and analgesic medication that comes in various pharmaceutical forms and doses. It was first synthesized in 1893 by Joseph von Mering through a reaction involving p-nitrophenol, tin, and glacial acetic acid.

In clinical practice, paracetamol is considered a safe alternative to acetoacetic acid and phenacetin. Its widespread use highlights the importance of accurately determining its dosage in pharmaceutical formulations, as excessive intake can lead to severe liver damage and other toxic effects. Paracetamol is widely available both over-the-counter

and with a prescription, and it is commonly used to alleviate pain and reduce fever. Its clinical pharmacological profile is characterized by potent analgesic and antipyretic properties, with minimal anti-inflammatory effects. Additionally, it has minor side effects on the gastrointestinal, renal, and vascular systems.Phenacetin initially exceeded paracetamol in popularity and was introduced to the market in 1887. However, due to the severe side effects associated with phenacetin, such as hemolytic anemia and methemoglobin formation, its clinical use declined. As a result, the focus shifted to paracetamol, which was launched in 1893.

Additionally, further research conducted on phenacetin during the 1940s revealed that paracetamol is a significant metabolite of the compound, leading to the conclusion that its pharmacological effects can be attributed to paracetamol.

Paracetamol has been readily available since the 1950s, making it the most commonly used non-narcotic analgesic that can be obtained without a prescription for managing mild to moderate pain and fever.

Caffeine

Caffeine, a stimulant drug, is known for its ability to increase activity in the central nervous system. While coffee and tea are natural sources of caffeine, it is also added to other products like sodas, energy drinks, and energy bars by manufacturers. The primary purpose of consuming caffeine is to combat fatigue and drowsiness, but it has various other uses as well.

Caffeine is primarily derived from coffee beans, but it can also be found naturally in certain types of tea and cacao beans. Additionally, it is used as an additive in soda and energy drinks. The consumption of caffeine activates noradrenaline neurons and appears to impact the local release of dopamine. The alerting effects of caffeine are believed to be related to its action on serotonin neurons. In animals, caffeine induces dose-response increases in locomotor activity, acting as a psychostimulant. However, its effects on humans are often subtle and not easily detectable.

The effects of caffeine on learning, memory, performance, and coordination are primarily associated with its impact on arousal, vigilance, and fatigue. It is worth noting that the effects of caffeine on anxiety and sleep can vary depending on individual sensitivity to the drug. However, children do not seem to be more sensitive to the effects of caffeine compared to adults. While the central nervous system does not develop a significant tolerance to caffeine, reports of dependence and withdrawal symptoms exist.

Aceclofenac

Aceclofenac, a phenyl acetic acid derivative nonsteroidal anti-inflammatory drug (NSAID), possesses significant anti-inflammatory and analgesic properties. It acts as a potent inhibitor of cyclooxygenase (COX), a crucial enzyme involved in the production of prostaglandins and thromboxanes, showing a preference for the COX-2 isoform over COX-1. Initially approved in the EU in 1990 and introduced in Spain in 1992, aceclofenac has gained approval for use in 69 countries globally, with an estimated exposure to approximately 171 million treated patients. While the authorized indications for aceclofenac may vary by country, it is generally recommended for managing inflammatory and painful conditions such as low back pain, dental pain, shoulder periarthritis, and extraarticular rheumatism, as well as for treating osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Aceclofenac, similar to diclofenac, exhibits anti-inflammatory and analgesic effects, with preclinical data suggesting a lower risk of gastrointestinal complications compared to diclofenac. Double-blind comparative trials have demonstrated that aceclofenac's efficacy is comparable to ketoprofen in rheumatoid arthritis patients, akin to indomethacin and diclofenac in osteoarthritis patients, and similar to tenoxicam, indomethacin, and naproxen in individuals with ankylosing spondylitis.

The analgesic efficacy of aceclofenac 100mg lasts longer than that of paracetamol (acetaminophen) 650mg. If the improved gastrointestinal tolerability of aceclofenac compared to diclofenac is confirmed through broader clinical experience, aceclofenac has the potential to become the preferred initial drug in a personalized NSAID regimen for patients with rheumatic disorders. Aceclofenac, manufactured by Almirall Prodesfarma SA, is an oral NSAID that effectively treats painful inflammatory diseases and has been administered to over 75 million patients worldwide. It has demonstrated comparable effectiveness to diclofenac, naproxen, and piroxicam in patients with osteoarthritis,

and to diclofenac, ketorolac, tenoxicam, and indomethacin in patients with rheumatoid arthritis. Additionally, it has shown similar efficacy to tenoxicam, naproxen, and indomethacin in patients with ankylosing spondylitis.

Material And Methods

Sr. No.	Ingredient	Category
1	Paracetamol	Analgesic, Antipyretic
2	Caffeine	CNS Stimulant
3	Aceclofenac	Analgesic,Anti Inflammatory
4	Starch	Binder
5	Magnessium Stearate	Lubricant
6	Lactose	Sweetening Agent
7	Water	Vehicle

Preparation Of Tablet

1) Depending on the tablets to be submitted calculate the working formula.
2) Preparation of granulating medium (10% W/V starch paste): Weight 10g starch and transfer in to a beaker (250ML). Add 50ml of water in to a beaker and prepare slurry by stirring with a glass rod. Add 25 ml of water in above beaker. Heat the slurry to obtain a thick paste Add remaning 25ml of water and stir well. Stop heating and cool the starch paste.
3) Sifting Of Powders: Weigh**t** required quantities of paracetamoland starch powder per the working formula. Pass these powders 60 mesh sieve.
4) Blending of powder: Mix sifted powder thoroughly in morter with peste until uniform powder blend is obtained.
5) Wet granulation (wet Screening): Take small quantity of granulating medium in to abeaker and weight (A g). From this transfer little quantity of granulating medium to the morter containing powders and triturate.

Formulation Table

Sr. No	Formulation	F1	F2	F3	F4	F5
1	Paracetamol	220 mg	220	210	210	220
2	Caffeine	90 mg	100	110	120	90
3	Aceclofenac	150 mg	140	140	130	150
4	Starch	5 g	5 g	5 g	5 g	5 g

5	Magnessium Stearate	4 g	4 g	4 g	4 g	4 g
6	Lactose	20 g	20 g	20 g	20 g	20 g
7	Water	q.s	q.s	q.s	q.s	q.s

Evaluation Test

- Size and Shape
- Appearance
- Organoleptic properties
- Uniformity Of Thickness
- Hardness
- Friability
- Weight Variation Test
- Content Consistency Test
- Tablet Disintegration
- Dissolution Time
- Disintegration Time

Size and Shape:

Tablet thickness ought to be controlled Inside a ±5% variety of standard worth. One of a kind recognizable proof checking These stamping use some type of emblazoning, Etching or printing. These markings incorporate Organization name or image, item code, item Name and so on.

Appearance:

Acceptance of the appearance of batches of the tablet has been done based on the measurement of the following factors like size, colour,
shape, presence or absence of odour, taste et.[28,29]

Organoleptic properties:

Variety conveyance should be uniform with no mottling. For visual variety examination think about the shade of Test against standard tone.

Uniformity of thickness:

To determine the uniformity of thickness random selection of tablets has to be done from each and every batch and need to measure its thickness independently.

Hardness Test:

Hardness Test is the most important feature for assessing tablet in the study it was found that Tablet passed the test of tablet crushing strength or hardness both these brand have acceptable crushing strength of Between 5kKg/Cm2 to 10kg/ Cm2 This test done from Pfizer Test machine

Drug Content & release Test of Weight Variation:

(U.S.P.) Take 20 tablets and weigh each one separately. Calculate Compare the individual tablet's average weight The average gets more weight.

Friability:

Tablets are placed in a plastic chamber which revolves at 25 rpm and they are subjected to fall from a height of 6 inches in

the friabilator for about 100 revolutions. Then measure the weight of the tablet (W final) and observe any weight difference before tablet and after the friabilator processing Limits: loss in weight less than 0.5 to 1% of the initial weight of the tablet should be considered as acceptable

Weight variation test :

Random selection of 20 tablets from each batch should be done and note down the weight of the tablet individually and check for any variation in its weight. According to US Pharmacopeias small

Content Consistency Test:

select 30 tablets. 10 of these testedSeparately. The Tablet breeze through the assessment if9 of the 10Tablets should contain at least 85% and not more.

Tablet disintegration :

It was performed using USP disintegrationdevice 6 tablets were placed in disintegration test apparatus. It was maintained at 37 + 0.20C containing simulated gastric fluid (0. 1N HCI). D) Noted down the time tablets to disintegrates. Tablet Dissolution: For this test U.S.P. Type- 1 (Basket), 6 Paddle Apparatus was used. Gastric Fluid as Dissolution Medium:

Dissolution Test :

A solitary tablet is put in a little wire network containerAppended to the lower part of the shaft associated with aVariable speed engine. The crate is drenched in aDisintegration medium (as determined in monograph)Contained in a 100ml flagon. The flagon is round and hollowWith a hemispherical base. The flagon isKept up with at 37±0. 50C by a consistent temperatureShower. The engine is changed in accordance with turn at the predefinedSpeed and test of the liquid are removed atStretches to decide how much medication .

Disintegration Time:

The U.S.P. gadget to test crumbling utilizes 6 glass Tubes that are 3”long; open at the top and 10 cross section Screens at the base end. To test for deterioration Time, one tablet is put in each cylinder and the crate Rack is situated in a 1-L measuring utencilof water, Reenacted gastric liquid or reproduced gastrointestinal liquid at 37 ± 20 C with the end goal that the tablet stay 2. 4 cm beneath The outer layer of fluid on their vertical development and Not nearer than 2. 4 cm from the lower part of the measuring glass In their descending development.

Result And Discussion

1) Organoleptic properties of tablet

Sr. No	Properties	F1	F2	F3	F4	F5
1	Appearance	Smooth	Smooth	Rough	Rough	Smooth
2	Odour	Odourless	Odourless	Odourless	Odourless	Odourless
3	Colour	Off White	Off White	Off White	Off White	Off White

2) Uniformity Of Thickness

F1	F2	F3	F4	F5
4.5 to 0.01	4.5 to 0.02	4.5 to 0.03	4.5 to 0.01	4.5 to 0.04

3) Hardness Test

F1	F2	F3	F4	F5
3.44 to 0.025	3.33 to 0.27	3.51 to 0.24	3.63 to 0.24	3.61 to 0.24

4) Friability Test

F1	F2	F3	F4	F5
0.3296	0.3788	0.2993	0.3427	0.3296

5) Disintegration Test

F1	F2	F3	F4	F5
5 Min	10 Min	6 Min	15 Min	12 Min

Conclusion

In conclusion, the formulation of paracetamol tablets using a combination of caffeine and aceclofenac presents a promising avenue for enhancing pain management outcomes. Through the synthesis of existing literature and our own research findings, several key conclusions can be drawn:

1. Synergistic Effects: The combination of paracetamol, caffeine, and aceclofenac offers synergistic effects in pain management, with each component contributing unique pharmacological properties. Paracetamol acts centrally to modulate pain perception, while caffeine enhances its absorption and adds mild analgesic effects. Aceclofenac provides potent anti-inflammatory action, complementing the analgesic effects of paracetamol and caffeine**.**

2. Optimized Formulation: Optimization of formulation parameters, including drug ratios and excipients, is essential for achieving the desired therapeutic effects while ensuring product stability and quality. Our formulation studies have demonstrated the feasibility of incorporating paracetamol, caffeine, and aceclofenac into tablet formulations with satisfactory physicochemical properties.

3. Enhanced Efficacy: Preclinical and clinical studies have consistently shown enhanced analgesic efficacy of the combination therapy compared to individual drug formulations. This suggests that the combination of paracetamol, caffeine, and aceclofenac may offer improved pain relief for patients with various pain conditions, potentially allowing for lower doses and reducing the risk of adverse effects associated with high-dose monotherapy.

4. Further Research Directions: While our research provides valuable insights into the formulation and efficacy of the combination tablet, further studies are warranted to elucidate the optimal dosing regimens, pharmacokinetics, and safety profile of this combination therapy. Long-term clinical trials in diverse patient populations are needed to assess the efficacy and tolerability of the combination tablet in real-world settings**.**

This conclusion summarizes the key findings and implications of the research on formulating paracetamol tablets using a combination of caffeine and aceclofenac, emphasizing the potential benefits and avenues for future investigation**.**

Reference

1) Leon Lachman, Herbert A. Lieberman, Joseph L. Kanig: The theory and Practice of Industrial Pharmacy, Varghese publication house, 3rd edition, 1990, 293-373.
2) G. Hymavathi, J. Adilakshmi, K. Dwarathi, M. Kavya, G. Pravallika. Review Article on In process Problems and Evaluation Tests of Tablet Manufacturing. International Journal of Research in Pharmaceutical and Nano Sciences. 2012, 3(7).

3) Moore R.A., Moore N. Paracetamol and pain: The kiloton problem. *Eur. J. Hosp. Pharm.* 2016;23:187–188. doi: 10.1136/ejhpharm-2016-000952.

4) O'Neil CK, Hanlon JT, Marcum ZA. Adverse effects of analgesics commonly used by older adults with osteoarthritis: focus on non-opioid and opioid analgesics. Am J Geriatr Pharmacother. 2012;10(6):331–342. doi:10.1016/j.amjopharm.2012.09.0048) K. Ashutosh, New Age International (P) limited, Publishers, New delhi, 2004, 83-89.

5) A Review on the Properties and Uses of Paracetamol. International Journal of Pharmacy and Chemistry. Vol. 5, No. 3, 2019, pp. 31-35. doi: 10.11648/j.ijpc.20190503.12

6) Nehlig A, Daval JL, Debry G. Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. Brain Res Brain Res Rev. 1992 May-Aug;17(2):139-70.

7) Kugelman A, Durand M. A comprehensive approach to the prevention of bronchopulmonary dysplasia. Pediatr Pulmonol. 2011 Dec; 46 (12):1153-65.

8) Almirall Ltd. PRESERVEX® (aceclofenac) 100 mg film-coated tablets: UK summary of prescribing characteristics; 2018. Available from:
https://www.medicines.org.uk/emc/product/6578/smpc. Accessed November 6, 2021.
9) Almirall SA. Airtal (aceclofenac) 100 mg film-coated tablets: summary of product characteristics; https://cima.aemps.es/cima/dochtml/ft/59024/FT_59024.html. Accessed November 6, 2021.

10) Valenta C, Kast CE, Harich I, Bernkop-Schnurch A. Development and In Vitro Evaluation of a Mucoadhesive Vaginal Delivery System for Progesterone. J Cont Release 2001, 77: 323-332.

11) Mullarney MP, Hancock BC, Carlson GT, Ladipo DD, Langdon BA. The powder flow and compact mechanical properties of sucrose and three high-intensity sweeteners used in chewable tablets. Int J Pharma 2003; 257: 227-236. https://doi.org/10.1016/S0378-5173(03)00144-3