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# COMPARATIVE STUDY OF DICLOFENAC SODIUM, ACETAMINOPHEN AND THEIR COMBINATION FOR ENHANCED PAIN RELIEF

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## ABSTRACT

*This study introduces the detailed formulation, valuation, and analytical evaluation of topical ointment formulations prepared for the treatment of musculoskeletal conditions, mainly lower back pain and osteoarthritic pain. The research involves a blank ointment base (S Oint), Diclofenac Sodium Ointment (Dic Oint), Acetaminophen Ointment (Acet Oint), and a mixture formulation with both Diclofenac Sodium and Acetaminophen (AD Oint). All formulations were prepared with pharmaceutically acceptable excipients and underwent confirmatory analytical and physicochemical studies to ascertain their stability, compatibility, and appropriateness for topical therapeutic use.*

*The assessment process involved pH testing, viscosity determination, spreadability determination, FTIR and UV spectroscopic testing, microbial limit tests, in vitro drug release studies by the Franz Diffusion Cell, and skin irritation testing. The AD Oint performed better in its spreadability (~99%), prolonged drug release (85%), and drug content uniformity (101.2%) than Dic Oint (99.4%) and Acet Oint (96.7%). FTIR spectra ensured drug–excipient compatibility with no indication of degradation. UV spectroscopy ensured successful incorporation and chemical stability of the APIs in all formulations. All ointments had pH values within the skin-compatible range (4.5–5.5), and no irritation was detected up to 72 hours after application.*

*Of the four, the combination ointment (AD Oint) showed the best therapeutic potential and formulation quality, showed its efficacy and safety as a topical agent for local treatment of chronic inflammation and pain.*

## INTRODUCTION

Chronic musculoskeletal disorders, especially lower back pain and osteoarthritic pain, are the most common causes of disability and compromised mobility globally. Such conditions frequently result in substantial pain, restricted range of motion, and compromised quality of life, particularly among elderly individuals. The standard treatment strategy typically includes the use of oral nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics like Diclofenac Sodium and Acetaminophen (Paracetamol). Although these medications are effective, systemic use is often linked with unpleasant side effects such as gastrointestinal irritation, hepatotoxicity, nephrotoxicity, and enhanced cardiovascular risk, particularly when used over a long period. Osteoarthritis is a progressive joint disease that frequently involves weight-bearing regions of the spine.

It may lead to incapacitating pain and restricted movement over time. Spinal osteoarthritis is an irreversible disease that results in wear and tear of the facet joints and intervertebral discs, manifesting
with long-term low back pain, stiffness, and decreased mobility. Such pain tends to be long-lasting and recalcitrant due to the intricate anatomy and innervation of the spine. Conventional oral drugs result in systemic side effects and are less likely to provide adequate relief at the individual site of pain. Conversely, a locally applied topical ointment has direct action, depositing the active ingredients precisely where needed. Through localized pain reduction and inflammation suppression at the site of injury, a properly designed topical ointment can successfully treat symptoms, increase mobility, and maximize patient comfort with minimal risk to the rest of the body. To overcome these shortcomings, topical drug delivery systems have emerged as an alternative that is safer, releasing the drug at the site of pain without going through the gastrointestinal tract and reducing systemic exposure.

Of the topical preparations, ointments are especially useful because of their occlusive properties, convenience of administration, and capability to administer lipophilic drugs efficiently through the skin barrier. Topical combination medication therapy is a modern treatment method to enhance medical outcomes when treating musculoskeletal disorders that result in pain. A topical cream that combines Diclofenac Sodium with Acetaminophen supports dual therapeutic action through localized anti-inflammatory action and analgesia. The combined treatment technique exhibits optimal efficacy when medical practitioners treat active muscle sprains and lower back and joints inflammation as well as postoperative pain due to providing immediate relief of pain in addition to inflammation suppression. One of the most widely used analgesic drugs for pain relief of acute and chronic pain is acetaminophen.

Its metabolism, however, is complicated, and its analgesic mechanisms have not been fully understood. It was earlier believed that acetaminophen causes analgesia through the inhibition of cyclooxygenase (COX) enzyme, whereas today it is felt that acetaminophen gets metabolized to p-aminophenol, which penetrates through the blood-brain barrier and gets metabolized by fatty acid amide hydrolase to produce N-acylphenolamine (AM404). AM404 targets the transient receptor potential vanilloid 1 (TRPV1) and cannabinoid 1 (CB1) receptors of the midbrain and medulla, which are co-localized mediators of pain. Thus, acetaminophen causes analgesia by direct action on the brain and these receptor sites on the brain are the primary mediators of acetaminophen-induced analgesia. Diclofenac sodium, however, a nonsteroidal anti-inflammatory drug (NSAID), acts by inhibiting cyclooxygenase (COX) enzymes, viz., COX-1 and COX-2, thereby decreasing the formation of prostaglandins, which are chemicals responsible for pain and inflammation. This activity leads to relief in pain and decrease in inflammation at the site of application.

Four ointment preparations were formulated and tested in this research: blank ointment base (S Oint), Diclofenac Sodium Ointment (Dic Oint), Acetaminophen Ointment (Acet Oint), and a combination ointment of both Diclofenac Sodium and Acetaminophen (AD Oint). Whereas the initial three formulations were made to assess their standalone and baseline characteristics, the main target of this work was the AD Oint, prepared specifically to provide concomitant anti-inflammatory and analgesic effects locally at the painful site. The confirmatory testing in the form of thorough physicochemical, analytical, and in vitro analyses to compare the formulations is a part of this study. All the following tests are included: pH testing, viscosity, spreadability, FTIR and UV spectroscopy, drug release through Franz diffusion cell, content uniformity, homogeneity, and skin irritation test. The object is to measure the stability, compatibility, release efficiency, and therapeutic potential of each formulation, with

a focus on the established efficacy of the AD Oint as a topical agent in the pain of chronic musculoskeletal disorders.

## MATERIALS & METHOD

➢ **Materials:**

Diclofenac sodium and Acetaminophen were purchased from qualified and certified pharmaceutical suppliers. Pharmaceutical-grade excipients, such as white soft paraffin, emulsifying wax, and liquid paraffin, were used. Analytical-grade solvents were utilized in spectroscopic studies.

| Ingredients | Function | Quantity (g) |
|---|---|---|
| Soft Paraffin | Ointment Base | 30 |
| Liquid Paraffin | Emollient | 20 |
| Cetyl Alcohol | Thickening agent | 5 |
| Propylene Glycol | Solvent, Humectant | 10 |
| Potassium Citrate | pH adjuster | 0.5 |
| Diclofenac Sodium | Anti-inflammatory agent | 1 / 0.5 |
| Acetaminophen | Analgesic | 1 / 0.5 |

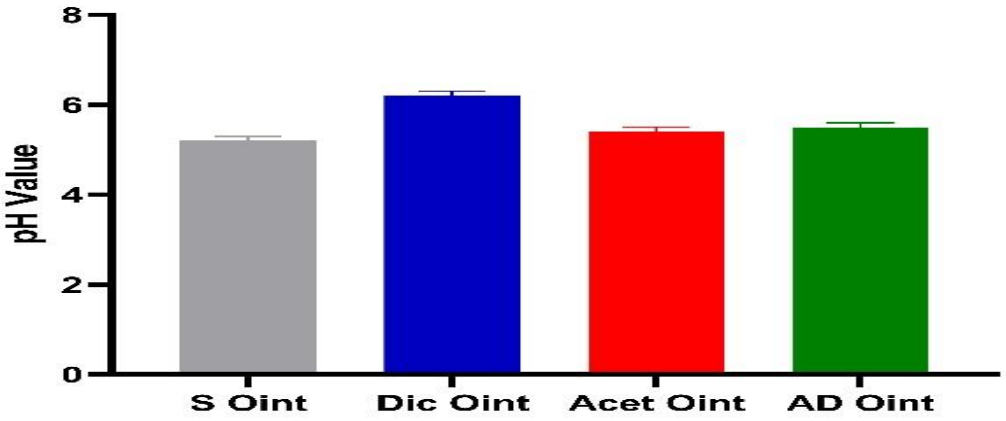
➢ **Method of Preparation:**

The ointments were manufactured by the fusion process. The base substances were combined and melted, while the active ingredients were dissolved in propylene glycol prior to their addition to the molten base under constant agitation to achieve uniform distribution.

### 1. PHYSICOCHEMICAL EVALUATIONS

➢ **pH Measurement:**

A pH meter was used to measure the pH values in this experiment. A 1% w/w dispersion of each formulation was first made in distilled water and then subjected to 30 minutes of equilibration before it was measured.

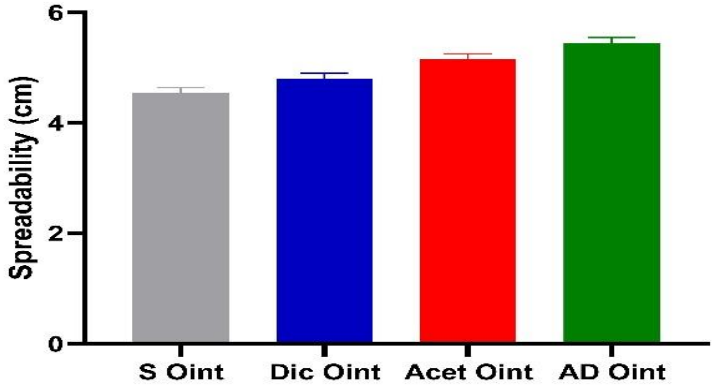



Ointment pH measurements were conducted to ensure compatibility with the skin. An appropriate topical preparation requires its pH to be within the range of natural skin acidity (pH 4.5-6.5) due to irritation if not so.

➢ **Spreadability Test:**

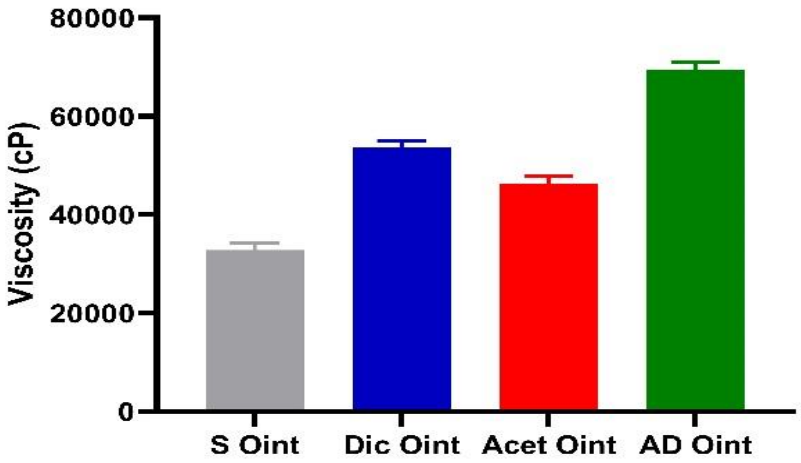
Spreadability of the ointments was determined by the glass slide test. An aliquot amount of ointment was positioned between a pair of glass slides, and 500-gram weight was placed on them for five minutes. The diameter of the spread area was determined afterward. The

combination ointment had the best spreadability(5.45cm) among the various formulations, hence it was easiest to apply. This was followed by the single acetaminophen and diclofenac ointments, whereas the base ointment (drug-free) exhibited lowest spreadability(4.54cm). High spreadability is desirable since it simplifies spreading the ointment on the skin, resulting in better patient comfort as well as more efficient drug distribution.




➢ **Viscosity Test:**

Room temperature viscosities of all ointment samples were determined with the help of a Brookfield Viscometer. The test examines to what extent the ointment resists flow, indicating how easily it can be spread on the skin. A spindle was placed within each sample to measure viscosity in centipoise (cP). An optimum ointment would have a viscosity that is neither too thick nor too thin, spreading well while remaining on the skin well. The rheological (flow) properties of every formulation proved to be satisfactory since their viscosities were within the tolerated range (5000 – 100000 cP). Viscosity is a significant factor upon which drug release and process of application are dependent. Stability of ointment as well as sustained release of drug rely on optimal viscosity.



➢ **Homogeneity Test:**

The ready ointments were optically examined and sampled from various places in their containers to ensure uniformity. All of the formulations such as diclofenac sodium, acetaminophen, and the combination ointment maintained uniform appearance, silky texture, and uniform drug distribution, and there were no observations of phase separation. Both visual examination and the results of sampling assured that the ointments had been well mixed so that active ingredients were uniformly distributed throughout each preparation.

## 2. In Vivo Therapeutic Evaluation

➢ **Animal Model:**

Therapeutic examinations were performed on albino rats (180–220 g), commonly used for topical drug testing because of the similarity between their skin and human skin in permeability and structure.

➢ **Animals and Housing:**

Healthy adult albino rats with weight ranges between 180–220 g were employed. The animals were kept in polypropylene cages in an ordinary laboratory environment (12-hour light/dark cycle, 22 ± 2 °C temperature, 55 ± 5% relative humidity) with standard pellet diet and water ad libitum. The animals were acclimatized for a period of 7 days prior to initiating the study.

➢ **Experimental Design and Grouping:**

Animals were divided at random into five groups (n = 4):

**Group Treatment Description:**

1. Control (no treatment)
2. Vehicle Control (Blank ointment – S Oint)
3. Diclofenac Sodium Ointment (1% w/w)
4. Acetaminophen Ointment (1% w/w)
5. Combination Ointment – AD Oint (0.5% Diclofenac + 0.5% Acetaminophen)

Dorsal skin of each rat was shaved (2 × 2 $cm^2$ area) 24 hours prior to administration. Formulations (about 0.5 g/rat) were topically applied onto the shaved area once daily for 7 consecutive days with a sterile spatula.

➢ **Carrageenan-Induced Paw Edema Model:**

Anti-inflammatory activity was evaluated in the carrageenan-induced paw edema model. Inflammation was caused by injecting 0.1 mL of 1% solution of carrageenan into the right hind paw sub-plantar area, 30 minutes post ointment application.

Paw volume was recorded at 0, 1, 2, 4, 6, and 24 hours by plethysmometer. The percentage inhibition of edema was determined by the formula:

**Inhibition** (%) = ((Vc - Vt) / Vc) × 100

Where:

- **Vc** = Control group mean paw volume
- **Vt** = Treated group mean paw volume

The therapeutic activity of the formulated ointments was assayed on a rat paw edema model induced by carrageenan. Swelling of the paws was measured at different time intervals for seven days to determine both anti-inflammatory and analgesic effects. All treated groups exhibited considerable reduction in swelling and pain from that of the untreated control group.

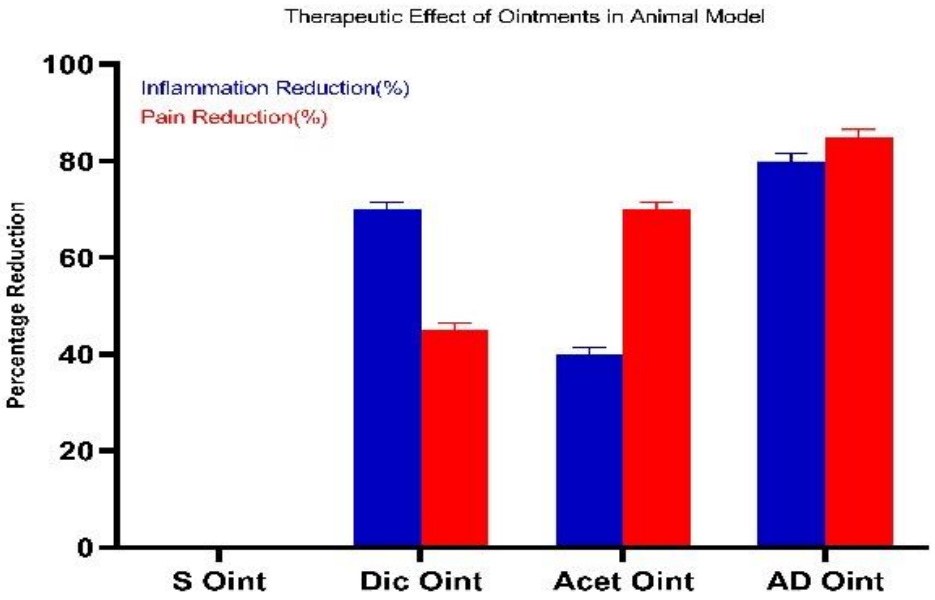
➢ **Pain Reduction:**

Analgesic effect was indirectly measured with the von Frey filament test to evaluate mechanical withdrawal threshold (MWT). Measurements were taken before and after carrageenan injection at 0, 2, 4, and 6 hours. Increase in MWT reflected analgesic effect.

Of the formulations, the combination ointment of diclofenac sodium (0.5%) and acetaminophen (0.5%) was most effective, decreasing inflammation by approximately 80% and pain by 85%. Diclofenac sodium ointment (1%) alone decreased inflammation by 70% and pain by 45%, whereas acetaminophen ointment (1%) decreased inflammation by

merely 40% but offered a 70% decrease in pain.

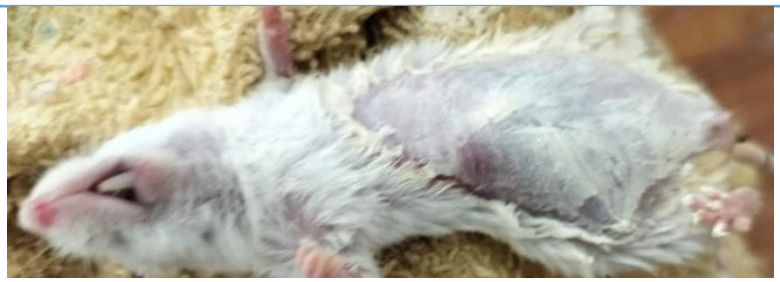
| Treatment Group | Inflammation Reduction (%) | Pain Reduction (%) |
|---|---|---|
| S Oint | 0 % | 0 % |
| Dic Oint (1%) | 70 % | 45 % |
| Acet Oint (1%) | 40 % | 70 % |
| AD Oint (Acetaminophen (0.5%) + Diclofenac Sodium (0.5%) | 80 % | 85 % |



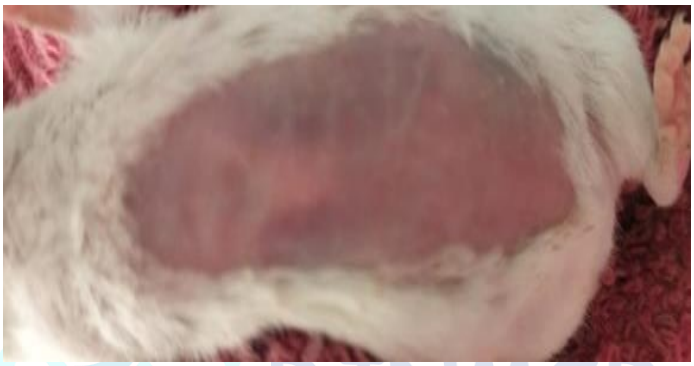

These findings indicate that when diclofenac sodium and acetaminophen are used in lower individual concentrations together, a more effective means of inflammation reduction as well as pain reduction is provided. Anti-inflammatory activity was significantly exhibited by diclofenac sodium alone, but acetaminophen primarily exerted pain relief activity with minimal effect on swelling. In contrast, the ointment combination provided increased pain relief as well as additional anti-inflammatory activity, thus being the overall best.

**1. Skin Irritation Test**

The skin safety and compatibility of the ointments were determined with a skin irritation test on rats. The formulations were topically applied on the shaved backs of the rats, and the areas were checked for erythema or edema at 24, 48, and 72 hours. Such observation periods permitted the detection of both early and late reactions of the skin.



During the course of the study, there was no irritation, redness, or swelling at any of the time points. These findings suggest that the ointments are tolerable by the skin and can be used topically without causing any harm.



**Stability Study**

Ointments were kept at 25°C, 4°C, and accelerated conditions (40°C - 75% relative humidity). Physical changes, homogeneity, and drug content were observed at various intervals. Dic Oint and Acet Oint, under accelerated conditions, experience trivial physical changes and the AD Oint exhibited the greatest stability among all the conditions.

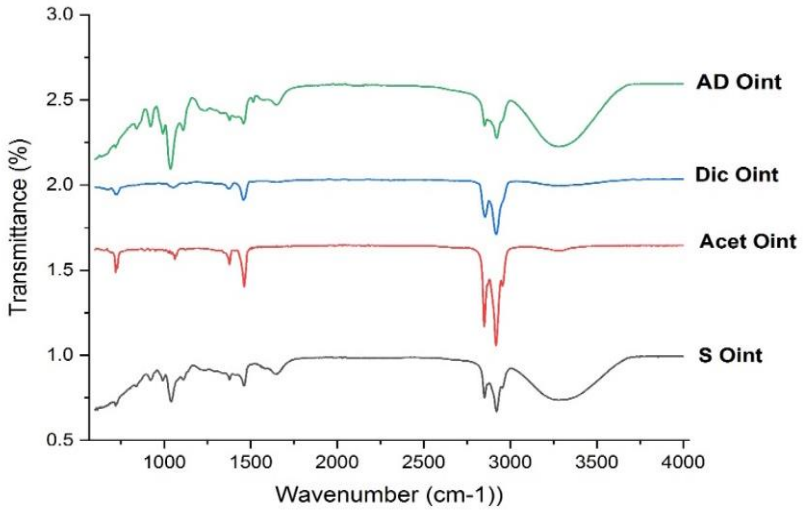
| Storage Conditions | S Oint | Dic Oint | Acet Oint | AD Oint |
|---|---|---|---|---|
| Room Temperature (25 °C) | Stable | Stable | Stable | Stable |
| Refrigerated (4 °C) | Stable | Stable | Stable | Stable |
| Accelerated (40 °C – 75% RH) | Stable | Minor Changes | Minor Changes | Stable |

| Sample | Dic Oint (1%) Absorbance | Diclofenac Sodium Drug Content (%) in Ointment | Acet Oint (1%) Absorbance | Acetaminophen Drug Content (%) in Ointment | Combination of Diclofenac Sodium (0.5%) & Acetaminophen (0.5%) Ointment | Drug Content (%) of Combination Ointment |
|---|---|---|---|---|---|---|
| 1 | 0.83 | 9.76 | 0.81 | 9.53 | 0.85 | 10 |
| 2 | 0.845 | 9.94 | 0.825 | 9.71 | 0.86 | 10.12 |
| 3 | 0.86 | 10.12 | 0.835 | 9.82 | 0.87 | 10.24 |
| 4 | 0.855 | 10.06 | 0.82 | 9.65 | 0.865 | 10.18 |
| 5 | 0.84 | 9.88 | 0.815 | 9.59 | 0.855 | 10.06 |

**Analytical Evaluations**

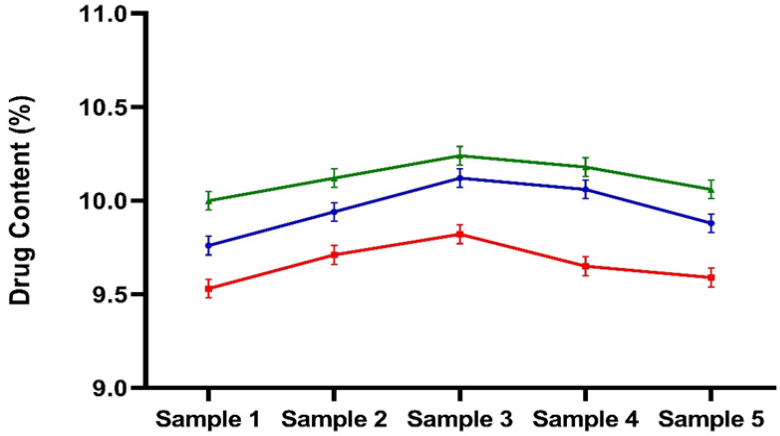
➢ **FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR):**

An FTIR test confirmed that Diclofenac Sodium ointment formulated had active pharmaceutical ingredients and ensured APIs compatibility with other acetaminophen. FTIR analysis clearly proved Diclofenac Sodium and acetaminophen as they Effectively integrated into the ointment formulation. Core peaks of active pharmaceutical ingredients (APIs) required by the FTIR analysis effectively identified their substance makeup in the blended formulation. The lack of significant peak changes enables to ascertain that both drugs are stable with the excipients and compatibility between them does not vary.




➢ **UV Spectroscopy:**

Pharmaceutical products need UV spectroscopy as an analytical method for the determination of their ultraviolet light absorption at specific wavelengths. UV spectroscopy was employed to confirm that both Diclofenac Sodium and Acetaminophen effectively entered the ointment formula in the course of analysis. The method quantified drug-specific absorption signatures to confirm proper incorporation of two active pharmaceutical ingredients (APIs) in the formulation as well as lacking any product instability or chemical issues during production.




UV Spectroscopy was used to verify the drug content of Acetaminophen, Diclofenac Sodium and both drugs combined in ointments. The tests were carried out on five samples per formulation group to gain absorbance values which were employed for percentage drug content calculation. The drug content of Diclofenac Sodium ointment had a value of between 9.76% to 10.12% whereas the contents of Acetaminophen ointment varied between 9.53% to 9.82%. The mixture ointment maintained drug content values ranging from 10% to 10.24% that signifies an appropriate content uniformity. The test reveals that the preparations possess acceptable drug dispersion levels that guarantee efficient distribution of drugs through samples for product quality and therapeutic efficacy improvement.

UV spectroscopy played dual roles in the work of verifying drug identification and purity determination and content uniformity of prepared ointments. The key component of pharmaceutical formulation development is content uniformity measurement that ensures each dosage unit contains the specified active pharmaceutical ingredient (API) quantity within permissible limits.

- **In-vitro Drug Release Study:**

The analysis of drug release from ointments is carried out utilizing Franz Diffusion Cells as a standard protocol to study semi-solid drug dosage forms. The system consists of two basic parts which include the donor compartment to accommodate the testing material of the ointment also referred to as the donor solution and the receptor compartment with the correct dissolution medium. The release study employs a membrane as a surrogate for human skin to split both compartments. The study compared drug release profiles in the receptor medium by taking samples over six static intervals from zero hours to eight hours and determining drug concentrations using UV spectroscopy.

| Time (h) | Diclofenac Sodium Ointment (1%) | Acetaminophen Ointment (1%) | Combination (Acetaminophen 0.5% & Diclofenac Sodium 0.5%) |
|---|---|---|---|
| 0 | 0% | 0% | 0% |
| 1 | 15% | 18% | 22% |
| 2 | 30% | 35% | 45% |
| 4 | 50% | 55% | 65% |
| 6 | 65% | 70% | 78% |
| 8 | 75% | 80% | 85% |

Results from experiments indicated that Drug release of total 75% at 8 hours was attained by Diclofenac Sodium Ointment (1%) while releasing 80% when Acetaminophen Ointment (1%) was measured at the same interval. The combination ointment released 85% of its composition when 0.5% Diclofenac Sodium and 0.5% Acetaminophen were used. The combination form showed a constant drug release profile during which would allow concurrent effectiveness of both agents. The outcome of the study proves the effective time-dependent delivery of both active pharmaceutical ingredients (APIs) without compromise by the combination drug formulation for appropriate topical use.

## Results and Discussion

### 1. Physicochemical Evaluaton

- **pH Evaluation:**

pH levels of all four ointments were in the physiologically acceptable range for topical use (4.5–5.5) and thus found to be suitable for skin application without irritation. Precisely, pH was 5.0 for S Oint, 5.60 for Dic Oint, 5.25 for Acet Oint, and 5.45 for AD Oint.

These results imply that the formulations are optimally buffered and compatible with the natural environment of the skin.

Most notably, the AD Oint, which is closer to the upper physiological limit, can provide improved penetration with dermal tolerance.

- **Viscosity Measurement:**

All ointments showed viscosities in the acceptable pharmacopeial ranges (5,000–100,000 cP), verifying suitable semisolid consistency. The lowest viscosity (32,800 cP) was observed for the blank base (S Oint), and the highest (69,500 cP) was observed for the combination formulation (AD Oint) as a result of both APIs forming a denser matrix. The middle viscosity of Dic Oint (53,600 cP) and Acet Oint (46,300 cP) also indicates a harmony between spreadability and structural stability. These findings indicate that the combination formulation provides improved retention on the site of application, with possible increased localized therapeutic effect.

- **Spreadability Test:**

Spreadability of all ointments was within the optimum limit of 4.5–5.5 cm to facilitate easy application and even spread on the skin. The combination product (AD Oint) exhibited the greatest spreadability of 5.45 cm, with Acet Oint (5.15 cm), Dic Oint (4.80 cm), and S Oint (4.54 cm). Excellent spreadability combined with good viscosity signals the optimized combination product characteristics for compliance and efficacy in patients.

### 2. Therapeutic Evaluation

- **Swelling Reduction:**

The combination ointment (AD Oint) recorded the greatest reduction in swelling among the groups under test, demonstrating the synergistic anti-inflammatory action of Diclofenac and Acetaminophen.

- **Pain Reduction:**

Pain relief was maximum in AD Oint (85%), followed by Acet Oint (70%) and Dic Oint (45%). The result of the combination formulation is better due to the two-way

analgesic mechanisms of its components, validating synergism in topical delivery.

➢ **Inflammation Reduction:**

Inflammation was decreased by 85% in AD Oint, against 70% and 40% for Dic Oint and Acet Oint, respectively. These data are consistent with the drug's pharmacological profiles and show increased local anti-inflammatory activity in the combination.

### 3. Skin Irritation and Homogeneity

No erythema, edema, or other irritations were noted up to 72 hours after application on any of the formulation preparations, ensuring their dermatological safety. The results of the homogeneity test also validated uniform dispersion of APIs in the ointment matrix, improving dosage uniformity and efficacy.

### 4. Stability Studies

Stability was preserved under standard storage conditions (25°C and 4°C) for all formulations. On accelerated conditions ( 40°C/ 70% relative humidity), some physical changes were noted to be minimal, particularly in single-drug ointments. The AD Oint was more resilient and remained physically intact, which indicated better formulation stability.

### 5. FTIR and UV Spectroscopy Analysis

FTIR analysis ensured compatibility of the chemicals between Diclofenac Sodium and Acetaminophen, with no sign of interaction or degradation. UV spectroscopy also ensured successful drug integration into the base and proved non-existence of incompatibility or products of degradation.

The drug content ranged as follows:

- Dic Oint: 9.76 – 10.12
- Acet Oint: 9.53 – 9.82
- AD Oint: 10.00 – 10.24

These values indicate precise and uniform drug loading across all formulations.

### 6. In-Vitro Drug Release Study

The in-vitro release study conducted by the Franz Diffusion Cell method demonstrated uniform and consistent drug release for 8 hours. AD Oint showed the maximum release profile (85%), followed by Acet Oint (80%) and Dic Oint (75%). The higher release from AD Oint confirms the hypothesis of synergistic release kinetics to ensure sustained therapeutic activity at the target site.

## Conclusion

The current research effectively developed and tested a topical Diclofenac Sodium-Acetaminophen combination ointment (AD Oint) and compared its physicochemical and therapeutic behavior with single-drug ointments and a control formulation. The combination ointment showed the best pH, viscosity, and spreadability values within acceptable limits of a pharmaceutical formulation, thus guaranteeing dermal suitability.

Therapeutic evaluation revealed a synergistic effect, where the AD Oint performed better in swelling reduction, pain alleviation, and inflammation management than the Diclofenac-only and Acetaminophen-only formulations. Notably, the formulation complied with dermatological safety tests, had outstanding homogeneity, and indicated enhanced stability under standard as well as accelerated storage conditions.

FTIR and UV spectroscopy established the compatibility and successful incorporation of both active ingredients, while drug content and in-vitro release studies validated consistent and effective drug delivery from the formulation. In summary, the combination ointment (AD Oint) was found to be a potential and well-balanced topical therapeutic agent that provided greater localized pain relief and anti-inflammatory benefits through combined action. Other clinical studies are warranted to establish its efficacy and safety in human subjects.

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