



## A REVIEW OF FORMULATION AND EVALUATION OF ANTIPIRETTIC TABLET OR CAPSULE USING DIFFERENT PLANT EXTRACT

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### 1. INTRODUCTION

An antipyretic (derived from the words anti- "against" and pyretic "feverish") is a chemical that reduces fever.<sup>[1]</sup> Antipyretics cause the hypothalamus to override a prostaglandin- induced increase in temperature.<sup>[1][2]</sup> The body then works to lower the temperature, which results in a reduction in fever.

Most antipyretic medications have other purposes. The most common antipyretics in the US are usually ibuprofen and aspirin, which are nonsteroidal anti-inflammatory drugs (NSAIDs) used primarily as anti-inflammatories and analgesics (pain relievers), but which also have antipyretic properties; and paracetamol (acetaminophen), an analgesic without anti-inflammatory properties.<sup>[3]</sup>

There is some debate over the appropriate use of such medications, since fever is part of the body's immune response to infection.<sup>[4][5]</sup> A study published by the Royal Society claims that fever suppression causes at least 1% more influenza deaths in the United States, or 700 extra deaths per year.<sup>[6]</sup>

#### Non-pharmacological treatment

Bathing or sponging with lukewarm or cool water can effectively reduce body temperature in those with heat illness, but not usually in those with fever.<sup>[7]</sup> The use of alcohol baths is not an appropriate cooling method, because there have been reported adverse events associated with systemic absorption of alcohol.<sup>[8]</sup>

#### Medications

The list of medications with antipyretic effects includes many common drugs that also have analgesic and anti-inflammatory activity, several of which are commonly sold over the counter (OTC).

- NSAIDs (non-steroidal anti-inflammatory drugs), a broad class of medications that in addition to their defining effect of reducing inflammation, also tend to be potent analgesics and antipyretics. The majority work by inhibiting the activity of the

cyclooxygenase (COX) family of enzymes in the body.

- Nonselective COX enzyme inhibitors like ibuprofen and naproxen.<sup>[9]</sup>
- Salicylates, including aspirin (acetylsalicylic acid), magnesium salicylate, and sodium salicylate. These are also primarily nonselective COX inhibitors but also work through other mechanisms including activating AMP-activated protein kinase.<sup>[10]</sup>
- COX inhibitors that are relatively selective for the COX-1 enzyme, such as ketoprofen and flurbiprofen.<sup>[9]</sup>
- Conversely, COX inhibitors that are relatively selective for COX-2, including nimesulide, diclofenac and celecoxib.<sup>[9]</sup>
- Phenazone-like drugs (pyrazolones), many of which have been largely phased out of use owing to safety concerns in most countries (including metamizole (the "Mexican aspirin"), banned in over 30 countries for causing agranulocytosis), but remain available in some locations or for specific purposes such as for treating otitis media in the form of ear drops.
- Paracetamol (acetaminophen) class antipyretics, which have negligible anti-inflammatory activity. Apart from paracetamol itself, the medications in

this class are mainly previously marketed drugs which were withdrawn owing to safety concerns, one example of this being phenacetin.

- A few other medications have antipyretic effects of varying strength. While these medications tend to have too weak fever reducing effects or too many adverse effects to use primarily as antipyretics, their antipyretic effect may occasionally be useful. For example, there are theoretical reasons to believe,<sup>[11]</sup> as well as slight evidence from one human trial,<sup>[12]</sup> that  $\alpha$ 2-adrenergic agonists, and particularly clonidine (a common drug used to treat high blood pressure, ADHD, spasticity and several other conditions), may have antipyretic effects, which if verified could potentially be useful in patients with septic shock or acute respiratory distress syndrome.<sup>[13]</sup>

#### Use in children

The U.S. Food and Drug Administration (FDA) notes that improper dosing is one of the biggest problems in giving acetaminophen (paracetamol) to children.<sup>[14]</sup> The effectiveness of acetaminophen alone as an antipyretic in children is uncertain, with some evidence showing it is no better than physical methods.<sup>[15]</sup> Therapies involving alternating doses of acetaminophen and ibuprofen have shown greater antipyretic effect than either drug alone.<sup>[16]</sup> One meta-analysis indicated that ibuprofen is more effective than acetaminophen in children at similar doses when both are given alone.<sup>[17]</sup>

Due to concerns about Reye syndrome, it is recommended that aspirin and combination products that contain aspirin not be given to children or teenagers during episodes of fever-causing illnesses.<sup>[18][19]</sup>

#### Traditional medicine

Traditional use of vascular plants with antipyretic properties is a common worldwide feature of many ethnobotanical cultures. In ethnobotany, a plant with naturally occurring antipyretic properties is commonly referred to as a *febrifuge*.<sup>[20]</sup>

Since ancient times, herbal therapy has been used to treat and prevent a wide range of illnesses. Many physiologically active substances with therapeutic qualities can be found in medicinal plants. Because herbal formulations are safer, more effective, less expensive, and have less adverse effects than synthetic medications, interest in them has grown in recent years. Herbal medicine delivery systems are made to efficiently introduce plant-based active ingredients into the body in appropriate dose forms, including tablets, capsules, syrups, lotions, and powders.<sup>[21]</sup>

According to estimates from the World Health Organization (WHO), around 80% of people worldwide rely on herbal remedies for their basic medical requirements. Pharmaceutical researchers have been motivated to create standardized herbal formulations

with better therapeutic efficacy and patient compliance due to the growing demand for herbal medicines.<sup>[22]</sup>

Because they offer precise dosing, superior stability, ease of administration, portability, and increased patient acceptance, tablets and capsules are the most used oral dosage forms.

#### 1.1 Fever and Antipyretic Agents

A brief rise in body temperature over the typical physiological range brought on by an infection, inflammation, or illness is called a fever, sometimes referred to as pyrexia. The average body temperature is roughly 37°C, or 98.6°F. Pyrogenic chemicals cause the hypothalamus to raise body temperature, which results in fever.

#### Pyrogens can be classified as:

1. Exogenous pyrogens, such as viruses, fungi, and bacterial toxins
2. Endogenous pyrogens, which include cytokines such as tumor necrosis factor and interleukins.<sup>[23]</sup>

Fever is typically thought of as the body's defence mechanism against infection. On the other hand, discomfort, dehydration, weakness, and serious problems might result from a prolonged high temperature.

Antipyretic medications work on the hypothalamus thermoregulatory center to lower high body temperatures. These substances assist return the body's temperature to normal by preventing prostaglandin formation.<sup>[24]</sup>

#### Common synthetic antipyretic drugs include

- Paracetamol
- Aspirin
- Ibuprofen
- Diclofenac

#### Although effective, long-term use of synthetic antipyretics may produce adverse effects such as

- Gastric irritation
- Hepatotoxicity
- Kidney damage
- Allergic reactions
- Gastrointestinal bleeding

Due to these limitations, attention has shifted toward herbal antipyretic agents that are safer and possess additional pharmacological activities.<sup>[25]</sup>

#### The Most Common Antipyretics

Nearly all antipyretics fall into two categories: acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). They lower fever through the same general pathway, but they differ in important ways.

**Acetaminophen** (sold as Tylenol and many store brands) is the most widely used antipyretic worldwide. It reduces fever and relieves pain but has minimal anti-inflammatory effects. Its primary risk is liver damage, which can occur

if you exceed 4,000 milligrams in 24 hours, take it alongside other products that contain acetaminophen, or drink three or more alcoholic beverages a day while using it. Some formulations, like Tylenol Extra Strength, set a lower ceiling of 3,000 milligrams per day.

**Ibuprofen** (Advil, Motrin) and **naproxen** (Aleve) are NSAIDs. They reduce fever, pain, and inflammation.

Their main risk involves stomach bleeding, which is more likely if you're over 60, have a history of ulcers, take blood thinners or steroid medications, or use them for longer than directed. NSAIDs can also affect kidney function, so people with kidney disease, high blood pressure, or heart disease should check with a doctor first.<sup>[26]</sup>

Common Name	Biological Name	Family	Major Constituents
Tulsi	Ocimum sanctum	Lamiaceae	Eugenol, flavonoids
Neem	Azadirachta indica	Meliaceae	Nimbidin, azadirachtin
Guduchi	Tinospora cordifolia	Menispermaceae	Alkaloids, diterpenoids
Ginger	Zingiber officinale	Zingiberaceae	Gingerol, shogaol
Turmeric	Curcuma longa	Zingiberaceae	Curcumin
Papaya leaf	Carica papaya	Caricaceae	Alkaloids, flavonoids
Andrographis	Andrographis paniculata	Acanthaceae	Andrographolide

## 1.2 Herbal Antipyretic Drugs

Examples of medicinal plants with antipyretic activity include:

These medicinal plants exhibit antipyretic, anti-inflammatory, antioxidant, antimicrobial and immunomodulatory activities.<sup>[27]</sup>

## 1.3 Advantages of Herbal Antipyretic Formulations

Herbal formulations have various advantages over manufactured medications:

1. Reduced side effects.
2. Improved patient tolerance.
3. Cost effectiveness.
4. Easy access to raw materials
5. Eco-friendly nature
6. Improved therapeutic effects by synergistic action.
7. Improve compatibility with bodily systems.
8. Effective in chronic treatment.

Because of these advantages, pharmaceutical companies are increasingly turning to herbal dosage forms.<sup>[28]</sup>

## 1.4 Oral Dosage Forms

Oral drug delivery is the most common and convenient route of drug administration. Tablets and capsules are widely accepted oral dosage forms.

### Tablets

Tablets are solid dosage forms prepared by compression of powders or granules containing active pharmaceutical ingredients and excipients.

### Advantages of Tablets

- Accurate dose administration
- Ease of handling
- Stability
- Portability
- Economical manufacturing
- Better patient compliance

### Disadvantages

- Difficulty in swallowing by pediatric and geriatric

- patients
- Slow onset in some cases<sup>[29]</sup>

### Capsules

Capsules are solid dosage forms in which active ingredients are enclosed in hard or soft gelatin shells.

### Advantages of Capsules

- Elegant appearance
- Easy swallowing
- Tasteless administration
- Faster drug release
- Suitable for herbal powders

### Disadvantages

- Sensitive to humidity
- Higher manufacturing cost than tablets<sup>[30]</sup>

## 1.5 Phytochemical Constituents Responsible for Antipyretic Activity

Medicinal plants contain several bioactive compounds responsible for fever reduction.

### Flavonoids

Flavonoids inhibit cyclooxygenase and prostaglandin synthesis. They also possess antioxidant and anti-inflammatory activities.

### Alkaloids

Alkaloids exert pharmacological effects on the central nervous system and inflammatory mediators.

### Tannins

Tannins possess antimicrobial and anti-inflammatory properties.

### Terpenoids

Terpenoids reduce inflammation and fever by inhibiting inflammatory mediators.

**Phenolic Compounds**

Phenolics act as antioxidants and reduce oxidative stress associated with fever.<sup>[31]</sup>

**1.6 Preformulation Studies**

Preformulation studies help determine the physicochemical properties of powders before formulation.

**Angle of Repose**

Measures flow properties of powder.

**Bulk Density**

Indicates packing characteristics.

**Tapped Density**

Determines compressibility.

**Carr's Index**

Indicates flowability of powder.

**Hausner Ratio**

Measures interparticle friction.

These studies are essential for successful tablet and capsule manufacturing.<sup>[32]</sup>

**1.7 Formulation of Herbal Tablets**

Tablets can be prepared using Wet granulation

1. Dry granulation
2. Direct compression

**Wet Granulation Method**

1. Mixing of plant extracts and excipients
2. Preparation of binder solution
3. Formation of wet mass
4. Granulation
5. Drying
6. Lubrication
7. Compression into tablets

**Excipients Used**

- Diluent – lactose
- Binder – starch paste
- Lubricant – magnesium stearate
- Glidant – talc
- Disintegrant – sodium starch glycolate<sup>[33]</sup>

**1.8 Formulation of Herbal Capsules**

The powdered extract is blended uniformly with excipients and filled into hard gelatin capsules.

**Materials Used**

- Herbal extract
- Lactose
- Talc
- Magnesium stearate
- Gelatin capsule shells

Capsules are suitable for moisture-sensitive and bitter herbal extracts.<sup>[34]</sup>

**1.9 Evaluation of Herbal Tablets General Appearance**

Tablets are evaluated for color, odor, shape, and texture.

**Thickness**

Measured using vernier calipers.

**Hardness Test**

Determines mechanical strength.

**Friability Test**

Measures resistance to abrasion.

**Weight Variation Test** Ensures uniformity of dosage.

**Disintegration Test**

Determines time required for tablet breakdown.

**Dissolution Test**

Measures drug release profile.

**Stability Studies**

Performed to determine stability under different storage conditions.<sup>[35]</sup>

**1.10 Evaluation of Herbal Capsules Parameters Evaluated**

1. Capsule appearance
2. Weight variation
3. Disintegration time
4. Dissolution profile
5. Moisture content
6. Content uniformity

**1.11 Antipyretic Activity Evaluation**

Antipyretic activity is commonly evaluated using experimental animal models.

**Brewer's Yeast-Induced Pyrexia Method**

This method is widely used to evaluate antipyretic activity.

**Procedure**

1. Fever is induced using Brewer's yeast.
2. Elevated temperature is recorded.
3. Herbal formulation is administered.
4. Rectal temperature is measured periodically.
5. Reduction in temperature indicates antipyretic activity.

The activity is compared with standard drugs such as paracetamol.<sup>[36]</sup>

**1.12 Mechanism of Antipyretic Action of Herbal Drugs**

Herbal antipyretic agents act mainly through:

- Inhibition of prostaglandin synthesis
- Suppression of inflammatory cytokines
- Antioxidant activity
- Regulation of hypothalamic temperature center<sup>[37]</sup>

## 2. A REVIEW OF FORMULATION AND EVALUATION OF ANTIPYRETIC TABLET OR CAPSULE USING DIFFERENT PLANT EXTRACT

### 1. FORMULATION AND EVALUATION OF EFFERVESCENT TABLETS OF PARACETAMOL<sup>[38]</sup>

The oral dosage forms are the most popular way of taking medication despite having some disadvantages like slow absorption and thus onset of action is prolonged. This can be overcome by administering the drug in liquid form but, many APIs have limited level of stability in liquid form. So, Effervescent Tablets acts as an alternative dosage form. The tablet is added into a glass of water just before administration and the drug solution or dispersion is to be drunk immediately. The tablet is quickly broken apart by internal liberation of CO<sub>2</sub> in water due to interaction between tartaric acid and citric acid with alkali metal carbonates or bicarbonates in presence of water. Due to liberation in CO<sub>2</sub> gas, the dissolution of API in water as well as taste masking effect is enhanced. The advantages of effervescent tablets compared with other oral dosage forms includes an opportunity for formulator to improve taste, a more gentle action on patient's stomach and marketing aspects. In present work an attempt has been made to formulate an effervescent tablet containing immediate release of paracetamol using various acids and bases. In present work we are used different acids and bases in different concentration. In the preformulation study, compatibility evaluation was performed which implies that drug, acids, bases and other excipient are compatible with each other. The formulation of tablets was done by using wet granulation as well as dry granulation in that technique wet granulation which was found acceptable. The total nine placebo tablets were prepared and evaluated for hardness, disintegration time, weight variation and solubility. All the formulation shows hardness and weight variation within limit but the combination of citric acid (12.56%), tartaric acid (25.17%), sodium bicarbonate (38.20%), sodium carbonate (6.41%), binding agent PVP-K-30 (2.94%) and sodium benzoate (0.52%). for the final formulation, (F7) Because these ingredients show the good effervescent reaction and has no problem in capping and sticking like other formulation.

### 2. EVALUATION OF BIOPHARMACEUTICAL AND PHARMACOLOGICAL PROPERTIES OF COMBINED TERNARY COMPONENTIAL ANALGESIC TABLETS<sup>[39]</sup>

This study aimed to investigate the biopharmaceutical and the pharmacological features of the recommended combined tablets using in vivo and in vitro methodology. We previously developed technology obtaining combined ternary tablets with a potential analgesic effect. In vitro experimental analyses were performed on a Rotating Basket instrument included in the State Pharmacopoeia XI (SPh XI). Based on the results of studying the effect of pH on the dissolution rate of the recommended tablets, the use of a neutral medium -

purified water is recommended for further studies. From a biopharmaceutical point of view, the basket rotation speed is 100 turnover per minutes. The acute toxicity of the compared drugs was studied by the generally accepted method described in the literature, a single administration with the determination of the toxicity class. The analgesic effect of the drug was studied on white outbred mice, in the amount of 18 animals, weighing 20-23 grams. A specific pain reaction - "cramps" (characteristic movements of animals, including contractions of the abdominal muscles, alternating with their relaxation, stretching of the hind limbs and flexing of the back) were caused by intraperitoneal administration of 0.75% acetic acid (0.1ml/10g body weight). The antipyretic effect of the drugs was evaluated in rats weighing 180-200 g. Body temperature excited by intravenous administration of Pyrogenal. The experimental study of the indicators of acute toxicity, and specific activity of the recommended combined tablets performed in comparison with the tablets Metamizole Sodium 500 mg tablets (under brand name "Analgin"). Key words--Analgesic; Combined ternary componential (CTC) tablets; Metamizole sodium.

### 3. IN VIVO EVALUATION OF ANTIMICROBIAL, ANTIPYRETIC, ANALGESIC, AND ANTI-INFLAMMATORY ACTIVITIES OF NILAVEMBU KUDINEER CAPSULE IN COMPARISON WITH SIDDHA CLASSICAL NILAVEMBU KUDINEER<sup>[40]</sup>

Background: The classical Siddha formulation Nilavembu Kudineer (NVK) is more effective in treating fever, infection, pain, and inflammation, but it is a liquid, is bitter in taste, is in a non-palatable form, and hence it was converted into a portable and palatable NVK capsule with increased shelf-life to comply with the needs of patients. The present study aimed to evaluate the effectiveness of the NVK capsule in comparison with the classical NVK by using animal models.

Materials and Methods: NVK and NVK capsules were processed as per the standard operating procedures, and the extracts were prepared for oral administration. The antibacterial and antifungal activities of the drug in comparative assay with the standards – ciprofloxacin and fluconazole – were evaluated by the agar diffusion method. Analgesic activity of NVK and NVK Capsule was studied in Swiss albino mice of either sex (n=4), compared with positive control group; Antipyretic and anti-inflammatory activity was studied in Wistar rats of either sex (n=4), compared with the positive control of Paracetamol and Indomethacin respectively...

Results: The zone of inhibition in antimicrobial assay revealed that NVK capsule is more effective than the extract of NVK. The NVK capsule at 200 mg/kg has equal and consistent efficacy

#### 4. ANTIPYRETIC EFFECT OF A POLYHERBAL AYURVEDIC FORMULATION: A RANDOMIZED CONTROLLED CLINICAL STUDY<sup>[41]</sup>

The ancient ayurvedic text *Aṣṭāṅgahr̥daya* of Vāgbhaṭa (7th Century A.D.) prescribes a specific formulation of four plants having antipyretic properties with minimal side-effects. This polyherbal ayurvedic formulation contains whole plant of *Solanum surratense*, rhizomes of *Zingiber officinale*, stem of *Tinospora cordifolia* and fruits with bracts of *Piper longum*, exhibited significant antipyretic-analgesic properties during rodent experiments without any toxicity may be due to flavonoidic phenolic compounds in it. Present randomized controlled clinical study in sixty-eight patients was conducted with this polyherbal ayurvedic formulation using aspirin as standard drug for comparison. The primary outcome measured was reduction in body temperature, while the secondary outcomes measured were assessment of associated symptoms of fever and routine haematological parameters. A representative sample of patients was also studied for reduction in the level of prostaglandin (PGE<sub>2</sub>). The clinical study showed that fever was rapidly and substantially reduced after oral administration of the test drug and this antipyretic effect was significant (p) when compared to placebo and more sustained in comparison to aspirin. Many associated symptoms of fever also exhibited significant reductions with this test drug. Prostaglandin levels also registered a substantial decrease during treatment with this polyherbal ayurvedic formulation.

Keywords: Ayurveda, Antipyretic, *Solanum surratense*, *Zingiber officinale*, *Tinospora cordifolia*, *Piper longum*.

#### 5. DESIGN, FORMULATION AND PHYSICOCHEMICAL EVALUATION OF ACETAMINOPHEN EFFERVESCENT TABLETS<sup>[42]</sup>

The main objective of this study was to design, formulate and evaluate the physicochemical properties of 500 mg acetaminophen effervescent tablets, in order to accelerate its analgesic and antipyretic effects in patients with pill swallowing problems. Formulations with 500 mg of acetaminophen were prepared with effervescent bases including tartaric acid, citric acid, sodium bicarbonate, and PEG6000. Flowability of powders and granules was determined by measurement of bulk and tapped density, compressibility index and Hausner's ratio. Three methods were applied to prepare tablets: direct compression, wet granulation and fusion. The effervescence time, hardness, pH, thickness, CO<sub>2</sub> content, water content, weight variation, and content uniformity of the prepared tablets were investigated. In order to overcome the bitter taste of acetaminophen, different sweeteners and fruity essences such as orange, lemon, and cherry flavors were applied. Panel taste was performed using 20 volunteers. The physicochemical characteristics of three different methods of preparing tablets were pretty similar. Wet granulated formulations had higher hardness and better

flowability while direct compressed tablets had stable effervescence time and better solubility. According to the panel taste, orange flavor was more acceptable. Wet granulated tablets which were prepared using alcohol and PVP had higher hardness and variable effervescence time in comparison to direct compressed tablets. Flowability of wet granulated formulations was better than the one with direct compressed formulations.

#### 6. FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF VALDECOXIB<sup>[43]</sup>

**ABSTRACT:** Valdecoxib is a selective COX- II inhibitor with anti – inflammatory, analgesic and antipyretic properties. The poor aqueous solubility of the drug leads to variable dissolution rates. In the present study an attempt has been made to prepare fast dissolving tablets of Valdecoxib in the oral cavity with enhanced dissolution rate. The fast-dissolving tablets of Valdecoxib was prepared with some carriers (polymers) and super disintegrants such as Polyvinyl Pyrrolidone (PVP), Sodium Carboxy Methyl Cellulose (SCMC), Crospovidone NF and  $\beta$  – Cyclodextrin. The above mentioned all carriers and super disintegrants were taken in different proportions of 5, 10, and 15%.

All the formulations of the fast-dissolving tablets of Valdecoxib were prepared by direct compression technique. The blend was examined for Angle of repose, Bulk density, Compressibility index and Hausner's ratio. The prepared tablets were evaluated for hardness, drug content uniformity, friability, disintegration time and dissolution rate. An effective pleasant testing formulation released 99.88% drug within 10 minutes. The prepared formulations drug release was found to be comparable with the marketed dispersible tablets.

**Keywords:** Fast dissolving tablets, Super disintegrants, Valdecoxib, Crospovidone, Sodium carboxy methyl cellulose.

#### 7. QUALITY ASSESSMENT ON GENERIC ANTIPYRETIC TABLETS AND THEIR STABILITY WITHSTANDING UNFAVOURABLE ENVIRONMENTS<sup>[44]</sup>

Paracetamol is an antipyretic drug that is commonly used to lower body temperature. It is classified as an over-the-counter medicine and safe to be consumed with proper guidance. Paracetamol comes in many dosage forms, most commonly in tablet form. In this research, a comparison of two different brands of generic paracetamol tablets with a significant difference in selling price difference was evaluated. Two brands were tested, namely brand A and brand B, which passed the quality tests set by British Pharmacopoeia and United State Pharmacopoeia in terms of the weight variation, friability, hardness test, disintegration, uniformity of thickness and dissolution. It was suggested that the cheaper paracetamol tablets (brand A) exhibited better quality as per the required standard. A stability study on the cheaper tablets (brand A) was also performed by manipulating the storage temperature of the

tablet for a period of 30 days. The study revealed there were no significant quality changes when there was a change in storage temperatures. Overall, the study suggested that cheaper medication especially in tablet dosage form possessed excellent quality and appeared stable in different storage conditions. The present finding indirectly debunks the stigma that expensive medications are far better in terms of quality than the cheaper ones. Simultaneously, this will help in reducing the economic burden of patients from low- or middle-class income in finding suitable medication. Keywords: Tablet dosage form, paracetamol, quality control, pharmacy, pharmaceutical technology.

### 8. FORMULATION AND EVALUATION OF BILAYER TABLETS OF METOCLOPRAMIDE HYDROCHLORIDE AND DICLOFENAC SODIUM<sup>[45]</sup>

#### Abstract

The main objective of the present research work was to develop a bilayer tablet of metoclopramide hydrochloride (MTH) and diclofenac sodium (DS) in separate layers to avoid incompatibility and thus to maximize the efficacy of both drugs in combination for the effective treatment of migraine headaches. MTH and DS were formulated as immediate and sustained release layers respectively. In vitro dissolution kinetic studies of an optimized (D10) batch of DS in both sustained release layer and bilayer tablet forms show good linearity of regression coefficient 0.9773 (first order equation). The results reveal that an optimized immediate release layer (M5) of MTH and a sustained release layer (D10) of DS might be suitable for the treatment of migraine by sequential release of the two drugs in a bilayer tablet.

*LAY ABSTRACT:* Migraine is a type of recurring headache of moderate to severe intensity associated with gastrointestinal, neurological, and autonomic symptoms. In migraine, a combination of pretreatment with antiemetics is required for symptomatic treatment, when nausea and vomiting are severe. In our present research, we have selected the metoclopramide hydrochloride (MTH) active ingredient for study because it has an antiemetic effect and is a prokinetic agent. MTH is more effective to counteract gastric stasis associated with migraine, and it enhances the rate of absorption of non-steroidal anti-inflammatory drugs (NSAIDs). In the present investigation we combine MTH and a second active ingredient, diclofenac sodium, as a formulated bilayer tablet to prevent degradation of MTH.

### 9. PREPARATION OF ANTIPYRETIC ANALGESIC BY DIRECT COMPRESSION AND ITS EVALUATION<sup>[46]</sup>

Direct compression is able to produce tablets at a lower cost than wet granulation and tableting method, due to fewer items of process validation. In this study, acetaminophen was used as a medicine with various granular diameters to formulate tablets by direct compression, thus evaluating their physical properties.

Consequently, direct compression was found effective in formulating tablets with excellent physical properties, with the granular diameter taken into account. It was confirmed that tablets produced by direct compression were similar in physical properties in tablets produced by wet granulation and tableting method. Further, it was suggested that use of a dry-type binder would make it possible to provide a tablet having higher content of the medicine with excellent physical properties.

Keywords: direct compression; acetaminophen; medicine content; antipyretic analgesic; tablet hardness

### 10. PHARMACOKINETIC-PHARMACODYNAMIC MODELLING OF THE ANTIPYRETIC EFFECT OF TWO ORAL FORMULATIONS OF IBUPROFEN<sup>[47]</sup>

Objective: To analyse the population pharmacokinetic-pharmacodynamic relationships of racemic ibuprofen administered in suspension or as effervescent granules with the aim of exploring the effect of formulation on the relevant pharmacodynamic parameters. Design: The pharmacokinetic model was developed from a randomised, cross over bioequivalence study of the 2 formulations in healthy adults. The pharmacodynamic model was developed from a randomised, multicentre, single dose efficacy and safety study of the 2 formulations in febrile children. Patients and participants: Pharmacokinetics were studied in 18 healthy volunteers aged 18 to 45 years, and pharmacodynamics were studied in 103 febrile children aged between 4 and 16 years with bodyweight  $\geq 25$ kg. Methods: The pharmacokinetic study consisted of two 1-day study occasions, each separated by a 1-week washout period. On each occasion ibuprofen 400mg was administered orally as suspension or granules. The time course of the anti-pyretic effect was evaluated in febrile children receiving a single oral dose of 7 mg/kg in suspension or 200 or 400mg as effervescent granules. During the pharmacodynamic analysis, the predicted typical pharmacokinetic profile (based on the pharmacokinetic model previously developed) was used. Results: The disposition of ibuprofen was described by a 2-compartment model. No statistical differences ( $p > 0.05$ ) were found between the 2 formulations in the distribution and elimination parameters. Absorption of ibuprofen from suspension was adequately described by a first-order process; however, a model with 2 parallel first-order input sites was used for the drug given as effervescent granules, leading to time to reach maximum drug concentration ( $t_{max}$ ) values of 0.9 and 1.9 hours for suspension and granules, respectively. The time course of the antipyretic effect was best described using an indirect response model. The estimates (with percentage coefficients of variation in parentheses) of  $E_{max}$  (maximum inhibition of the zero-order synthesis rate of the factor causing fever),  $EC_{50}$  (plasma concentration eliciting half of  $E_{max}$ ),  $n$  (slope parameter) and  $k_{out}$  (first order rate constant of degradation) were 0.055 (10), 6.16 (14) mg/L, 2.71 (18) and 1.17 (23)  $h^{-1}$ , respectively, where  $T_0$  is the estimate of the basal

temperature, 38.8 (1) °C. No significant ( $p > 0.05$ ) covariate effects (including pharmaceutical formulation) were detected in any of the pharmacodynamic parameters. Conclusions: Because of the indirect nature of the effect exerted by ibuprofen, the implications of differences found in the plasma drug concentration profiles between suspension and effervescent granules are less apparent in the therapeutic response.

#### 11. FORMULATION AND EVALUATION OF BI-LAYER TABLET OF METOCLOPRAMIDE HYDROCHLORIDE AND IBUPROFEN<sup>[48]</sup>

##### Abstract

The aim of this study was to prepare bi-layer tablet of Metoclopramide Hydrochloride (MTH) and Ibuprofen (IB) for the effective treatment of migraine. MTH and IB were formulated as immediate and sustained release layer respectively. MTH was formulated as immediate release layer by using various disintegrants like Ac-Di-Sol, Polyplasdone XL, Explotab, Agar and Gellan Gum. Treated form of gellan gum and agar was prepared and compared for their disintegrant efficiency with other disintegrants. IB was formulated as sustained release layer using hydrophilic matrix (hydroxypropylmethylcellulose [HPMC K4M]). The effect of concentration of hydrophilic matrix (HPMC K4M), binder (polyvinylpyrrolidone [PVP K30]) and buffer (sodium bicarbonate) on IB release was studied. The dissolution study of sustained release layer showed that an increasing amount of HPMC or PVP K30 results in reduced IB release. The inclusion of buffer (sodium bicarbonate) enhanced the release of IB from sustained release layer. The rationale for formulation of bi-layer tablet of these two drugs in combination was (1) MTH increases the absorption of acidic non-steroidal anti-inflammatory drug (NSAID) by increasing gastric motility. So sequential release of MTH (as immediate release) and IB (as sustained release) was suitable for treatment of migraine. (2) MTH was degraded when prolonged contact with acidic NSAID. Bi-layer tablet was suitable for preventing direct contact of these two drugs and thus to maximize the efficacy of combination of two drugs for migraine.

**KEYWORDS:** bi-layer tablet; gellan gum; ibuprofen; metoclopramide hydrochloride.

#### 12. FORMULATION AND EVALUATION OF DICLOFENAC SODIUM EFFERVESCENT TABLET<sup>[49]</sup>

Ten different formulations were prepared (F1-F10) that contain citric acid, sodium bicarbonate and sodium carbonate, PVP K 30, PEG 6000, different flavors by wet granulation method with an objective to minimize the side effects of diclofenac sodium on gastric mucosa by preparing the diclofenac tablet using effervescent techniques. The prepared tablets were evaluated for various pre and post compression characteristics as per official and non-officials' procedures. Among all the formulations, batch F10 showed that maximum drug

release upto 94.86 % within 3 min. Selected as optimized batch kept for accelerated stability study for 90 days. The result of stability study indicates no significant difference between the parameters tested before and after stability studies. FTIR Spectroscopy of formulation F10 did not show any additional peaks for new functional groups indicating no chemical interaction between drug and excipient used in formulation.

**Keywords:** Effervescent tablet, diclofenac Sodium, FTIR, PVP-K 30, wet granulation.

#### 13. ANALGESIC AND ANTIPYRETIC ACTIVITIES OF ETHYL ACETATE FRACTION TABLET OF ANDROGRAPHIS PANICULATA IN ANIMAL MODELS<sup>[50]</sup>

**Objectives.** To determine the analgesic and antipyretic activities of a tablet derived from *Andrographis paniculata* ethyl acetate fraction (AS201-01) in animal models. **Methods.** The tablet derived from AS201-01 contains an equivalent of 35mg andrographolide per tablet. Analgesic activity was determined using an acetic acid-induced writhing test on adult male mice. A writhing was recorded by a stopwatch and was defined as the stretching of the abdomen and/or stretching of at least one hind limb. For the determination of antipyretic activity, pyrexia was induced by subcutaneous injection of 15% w/v Brewer's yeast into adult male rats. Rectal temperature was monitored at 1, 2, 3, and 4 hours after treatment. **Results.** The results showed that the AS201-01 tablet had analgesic and antipyretic activity. In the acetic acid-induced writhing model, AS201-01 tablet exhibited significant analgesic effect with a 66.73% reduction in writhing response at a dose of 50mg andrographolide/kg body weight compared to the negative control group. The tablet also showed a significant antipyretic effect. The maximum antipyretic effect was observed after the third hour of administration of the AS201-01 tablet at a dose of 100mg andrographolide/kg body weight. **Conclusion.** Tablet of *Andrographis paniculata* ethyl acetate fraction (AS201-01) exhibited analgesic and antipyretic activities.

#### 14. FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF NIMESULIDE AND PARACETAMOL<sup>[51]</sup>

Clinical efficacy is the most important criterion for any novel drug administration. A novel fast dissolving drug formulation has been developed for a combination of Nimesulide and Paracetamol by using a direct compression technique. Nimesulide and paracetamol have an antipyretic as well as analgesic activity. The combination of both these drugs favours the combined effect and also reduces the multiple dosing. Hence, the aim of the current work was to design and evaluate the quick disintegrating tablets of Nimesulide and Paracetamol combo via two super disintegrants termed Croscarmellose sodium (CCS) and Sodium Starch Glycolate (SSG), which occur in a different proportion to reduce disintegration time and increase the onset of action of the formulation. In this current study, there are five

formulations prepared by utilizing two diverse super disintegrants. The selected formulation batch (F5) which has a 1:1 ratio of two diverse super disintegrants named Croscarmellose sodium (CCS) and Sodium Starch Glycolate (SSG) shows the best dissolution time (only 60 min) while other formulation shows more than 60 min for the complete release. At last, the accelerated stability study was conducted for the optimized formulation (F5) at 45 °C /75%RH (as per the ICH guideline) for 30 days indicated no significant change occur before or after keeping the formulation in an excessively stressed condition. Thus, the prepared formulation (F5) shows rapid absorption, increasing bioavailability, and reducing multiple dosing than the conventional dosage form.

**Keywords:** Croscarmellose sodium (CCS); Drug delivery; Sodium starch glycolate (SSG); Solid dispersions; Oral drug delivery.

### 15. FORMULATION AND EVALUATION OF ENTERIC COATED TABLET OF ACECLOFENAC<sup>[52]</sup>

Aceclofenac is an analgesic, antipyretic as well as nonsteroidal anti-inflammatory drug. The Enteric coated tablets of Aceclofenac are designed with the aim to protect the ulceration and prevent the drug release into stomach. The purpose of this research is to create an enteric coated tablets containing Aceclofenac that will help to overcome GI associated problem, minimize frequency of dose, patient compliance as well as duration of pharmacological action. Various post-compression parameters like Appearance, Weight variation, Hardness, Thickness, content uniformity, Friability, disintegration test and In-vitro release studies were evaluated. Aceclofenac tabs. were evaluated and found within parameters as in IP limit.

**KeyWords:** Analgesic, enteric coated tablet, disintegration test.

### 3. CONCLUSION

The present review on the formulation and evaluation of antipyretic tablets or capsules using different plant extracts emphasizes the growing importance of herbal medicines in modern healthcare systems. Fever is one of the most common clinical symptoms associated with infections and inflammatory disorders, and although synthetic antipyretic drugs such as paracetamol and aspirin are widely used, their prolonged administration may produce adverse effects including gastric irritation, liver toxicity, kidney damage, and hypersensitivity reactions. Due to these limitations, there has been increasing interest in the development of herbal antipyretic formulations that are safer, economical, and therapeutically effective.

Medicinal plants have been used since ancient times in traditional systems of medicine such as Ayurveda, Siddha, Unani, and Traditional Chinese Medicine for the treatment of fever and associated illnesses. Numerous

plants contain phytochemical constituents including flavonoids, tannins, alkaloids, terpenoids, steroids, glycosides, phenolic compounds, and saponins, which possess significant antipyretic, anti-inflammatory, antioxidant, and analgesic properties. These bioactive compounds act by inhibiting the synthesis of prostaglandins and inflammatory mediators responsible for elevated body temperature.

The review also demonstrates that different herbal extracts such as *Ocimum sanctum* (Tulsi), *Azadirachta indica* (Neem), *Tinospora cordifolia* (Guduchi), *Andrographis paniculata*, *Zingiber officinale* (Ginger), *Curcuma longa* (Turmeric), and *Moringa oleifera* have shown promising antipyretic activity in various experimental and preclinical studies. The extraction process, solvent selection, drying method, and phytochemical composition significantly influence the therapeutic efficacy of the plant extract. Ethanolic and aqueous extracts are commonly preferred because of their ability to extract a wide range of active constituents.

Formulation of herbal antipyretic tablets and capsules requires proper selection of excipients and optimization of manufacturing techniques to achieve acceptable pharmaceutical properties. Excipients such as binders, diluents, lubricants, glidants, disintegrants, and coating agents play an important role in maintaining the stability, appearance, and performance of the dosage form. Techniques such as wet granulation, direct compression, and capsule filling are commonly employed for the preparation of these formulations. Among these, tablets are widely preferred due to their convenience, ease of administration, accurate dosing, low production cost, and better patient compliance, whereas capsules provide advantages such as rapid drug release and masking of unpleasant taste and odor.

Evaluation parameters are essential to determine the quality, safety, and effectiveness of the developed formulations. The prepared tablets and capsules are evaluated for physical characteristics such as hardness, thickness, friability, weight variation, disintegration time, dissolution rate, moisture content, drug content uniformity, and stability under different environmental conditions. These quality control tests ensure that the formulation complies with pharmacopeial standards and delivers consistent therapeutic action. In addition, phytochemical screening and compatibility studies help in identifying active constituents and detecting any interaction between herbal extracts and excipients.

The review further indicates that herbal antipyretic formulations possess additional pharmacological benefits such as antioxidant, antimicrobial, immunomodulatory, and anti-inflammatory activities, which may enhance the overall therapeutic outcome. Herbal medicines are generally considered safer due to their natural origin and lower incidence of side effects. They are also cost-effective and easily accessible, especially in rural and

developing regions where traditional medicine continues to play a major role in healthcare.

Despite these advantages, several challenges remain in the development of herbal antipyretic formulations. Variability in plant sources, seasonal changes, geographical conditions, harvesting methods, extraction procedures, and storage conditions can affect the quality and consistency of herbal products. Lack of proper standardization, insufficient clinical trials, limited regulatory guidelines, and difficulties in large-scale production are major obstacles for the commercialization of herbal medicines. Therefore, strict quality control measures, standardization protocols, advanced analytical techniques, and scientific validation are necessary to ensure the reproducibility and reliability of herbal formulations.

Future research should focus on isolation and characterization of active phytoconstituents, development of novel herbal drug delivery systems, improvement in bioavailability, and detailed pharmacological and toxicological studies. Clinical investigations involving human subjects are also essential to establish the safety, efficacy, and therapeutic dosage of herbal antipyretic formulations. Furthermore, integration of traditional medicinal knowledge with modern pharmaceutical technology can lead to the discovery of innovative and effective herbal medicines with global acceptance.

In conclusion, the formulation and evaluation of antipyretic tablets or capsules using different plant extracts represent a promising and rapidly developing field in pharmaceutical and herbal research. Herbal formulations offer an effective alternative to conventional synthetic drugs with reduced side effects and multiple therapeutic benefits. With proper standardization, quality assurance, and scientific validation, herbal antipyretic dosage forms have the potential to become safe, effective, affordable, and widely accepted therapeutic agents for the management of fever and related conditions.

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