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Formulations Aspect and Evaluation of Antipyretic Syrup

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ABSTRACT
Acetaminophen is a common analgesic and antipyretic used to treat fever and mild to moderate pain in infants and children, and is considered the first-line treatment for the management of both, according to international guidelines and recommendations. The mechanism of action of paracetamol is complex and multifactorial, and several aspects of pharmacology influence its clinical use, especially in choosing the right dose of analgesics and antipyretics. A systematic literature review was conductedaccording to the procedures for transparent reporting of systematic reviews and meta-analyses. In order to maximize effectiveness and avoid delays in action, it is essential to use the appropriate dose of paracetamol. Older clinical trials of paracetamol at sub-therapeutic doses of ≤ 10 mg/kg generally show that it is less effective than non-steroidal anti-inflammatory drugs (NSAIDs).However; recent evidence shows that acetaminophen at a dose of 15 mg/kg is significantly more effective than placebo and at least as effective as NSAIDs in controlling fever and pain. Paracetamol 15 mg/kg has a similar tolerability profile to placebo and NSAIDs such as ibuprofen and ketoprofen, which are used for the short-term treatment of fever. However, when used in repeated doses on consecutive days, paracetamol shows a lower risk of adverse events compared to NSAIDs. Also, unlike NSAIDs, paracetamol is indicated for use in children of all ages. In general, clinical evidence qualifies acetaminophen 15, mg/kg as a safe and effective option for treating pain and fever in children.

Keywords:antipyretic, child, fever, pain, paracetamol and safety.

I. INTRODUCTION

Fever and pain occur frequently in infants and children [1]. Management of fever tends to be characterized by over-treatment, because of the parents anxiety and fever phobia [2–6], whereas management of pain is characterized by under-treatment, particularly in very young children with acute painful injuries [7, 8]. Paracetamol is a common analgesic and antipyretic drug for management of fever and mild-to-moderate pain in pediatric patients. It is the first-line choice for the treatment of both fever and pain according to national and international guidelines and recommendations and it is also included in the List of Essential Medicines for Children of the World Health Organization (WHO) [9–20].the syrup is primarily composed of a mixture of sugars, water, and minerals. In addition to these three components, maple syrup will contain minor amounts of various other organic compounds such as organic acids, amino acids, proteins, phenol compounds and even a few vitamins. Variation in the levels of these various components gives syrup the broad spectrum of flavors experienced with syrup from different producers and from different sap runs at the same location When making any syrup has a good flavor as most of the flavors will only be further concentrated resulting in poor tasting products.Appropriate doses should be used to ensure optimal paracetamol efficacy and safety [18]. Given the wide range of body weights in children of different ages, pain management guidelines emphasize the importance of administering the correct dose according to body weight, hence the use of milligrams per kilogram (mg/kg) dosage.)[10, 12, 14, 15, 18]. Pediatric patients, especially if they have fever or pain, may feel very uncomfortable, anxious, and less cooperative than usual [21]. Flexible formulations should ensure ease of administration and aid dosing accuracy. Special oral formulations of paracetamol, such as syrup and drops, should be recommended because of their ease of administration and because they allow selection of the appropriate mg/kg dose.The recommended doses of paracetamol range from 10 to 15 mg/kg every 4 to 6 hours (up to 60 mg/kg/day) [9, 14, 18, 22]. A common problem is the variability of dosages for the treatment of fever and pain in clinical practice, where paracetamol doses range from 5 to 20 mg/kg [9, 23-25]. Studies have shown that dose variability can depend on the specialty of the prescribing physician, with

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pediatricians prescribing more appropriate doses than primary care physicians or otolaryngologists [23].

Antipyretic syrup

Paracetamol is one of the most popular and widely used analgesics and antipyretics worldwide, available in both mono-component and multi-component preparations without a prescription [4]. It is the drug of choice in patients who cannot be treated with nonsteroidalanti-inflammatory drugs (NSAIDs), such as It is recommended as a first-line treatment for pain associated with osteoarthritis. The mechanism of action is complex and includes the effects of both peripheral COX (COX inhibition) and central COX [5 Paracetamol is one of the most popular and widely used analgesics and antipyretics worldwide, available in both mono-component and multi-component preparations without a prescription[4]. It is the drug of choice in patients who cannot be treated with nonsteroidalanti-inflammatory drugs (NSAIDs), such as it is recommended as a first-line treatment for pain associated with osteoarthritis. The mechanism of action is complex and includes the effects of both peripheral COX (COX inhibition) and central COX [5]

Formulation development of syrups

Based on solubility determination studies, acetaminophen syrups (containing 6% w/v or 5% w/v acetaminophen) were prepared using the solubilizer blends. The required amounts of all solubilizes were transferred to a volumetric flask (100 mL capacity) containing 50 mL of distilled water and the flask shaken to completely dissolve the solubilizes. Then the required amount of paracetamol drug was added and the flask was shaken to completely dissolve the drug. The required amount of sucrose was added and the flask again shaken to dissolve. It was then made up to the mark with distilled water and the syrup was filtered through filter paper.The first few mL of syrup were discarded and the filtered syrup stored in an airtight container.[7]

Paracetamol syrup formulation for 250mg/10ml

Ingredients	Weight	Function
Part I		
Paracetamol	1.25g	Active ingredient
Polyethylene glycol 6000 (PEG 6000)	5.0 g	Solubilizer
Glycerin	1.25 g	Diluent and sweetener
D.M. Water	15.0 ml	Diluent
Part II		
Sucrose	15.0 g	Sweetening agent
D.M Water	10.0 g	Diluent
Propylene glycol	.002 g	Preservative
Citric acid monohydrate	0.030 g	pH modifier

Excipients in the formulation: This productcontains:

• Methyl and propyl hydroxybenzoates. These may cause (possibly delayed) allergic reactions.

• Sucrose (3 g per 5 ml dose). Patients with rare hereditary problems of fructose intolerance, glucose-galactosemalabsorption or sucrose-isomaltase deficiency should not take this medicine. [2]

• Sorbitol.This medicine contains 782.25 mg per 5 ml dose. The additive effect of concomitantly administered sorbitol (or fructose) containing products and dietary intake of sorbitol (or fructose) should be considered.[7]

The sorbitol content of oral medicinal products may affect the bioavailability of other co-administered oral medicinal products. Sorbitol can cause gastrointestinal problems and has a mild laxative effect.It has a calorific value of 2.6 kcal/g sorbitol.

Patients with hereditary fructose intolerance (HIF) should not take or receive this medicine.

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• Propylene Glycol. This medicinal product contains 144.8 mg propylene glycol per 5 ml dose. Concomitant administration with alcohol dehydrogenase substrates such as ethanol may cause adverse effects in children under 5 years of age.[9]

Although propylene glycol has not been shown to have reproductive or developmental toxicity in animals or humans, it can reach the fetus and has been found in milk. Therefore, administration of propylene glycol to pregnant or lactating patients should be considered on a case-by-casebasis. Medical supervision is required in patients with renal or hepatic impairment as severaladverse reactions attributable to propylene glycol have been reported, including renal dysfunction (acute tubular necrosis), acute renal failure and hepatic dysfunction.[11]

6.1 List of excipients

- Propylene glycol
- Methyl hydroxybenzoate
- Propyl hydroxybenzoate
- Xanthan gum
- Sorbitol solution 70%
- Sucrose
- Mango flavour
- Purified wate[7-15]

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Paracetamol (g)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
COM (g)	1	1.5	2	2.5	3	-	-	-	-	-
Acacia (g)	-	-	-	-	-	1	1.5	2	2.5	3
Glycerin (mL)	10	10	10	10	10	10	10	10	10	10
Methyl paraben (g)	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Propyl paraben (g)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Amaranth solution (mL)	2	2	2	2	2	2	2	2	2	2
Raspberry syrup (mL)	2	2	2	2	2	2	2	2	2	2
Chloroform water B.P (mL)	25	25	25	25	25	25	25	25	25	25
Distilled water to (mL)	100	100	100	100	100	100	100	100	100	100

Interaction with other medicinal products and other forms of interaction

ADRs are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available or 2) when incidence is unavailable, frequency category is listed as Not known.[16]

System Organ Class (SOC)	Frequency	Adverse Drug Reaction (Preferred Term)
Blood and lymphatic system disorders	Not known	Blood disorder (including thrombocytopenia and agranulocytosis) [1]
Immune System Disorders	Very rare Very rare	Anaphylactic reaction Hypersensitivity
Hepatobiliary disorders	Not known	Liver injury[2]
Skin and Subcutaneous Tissue disorders	Very rare	Rash
	Not known	Fixed eruption
	Not known	Rash pruritic
	Not known	Urticaria
Renal and urinary disorders	Uncommon	Nephropathy toxic

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	Not known	Renal papillary necrosis[3]
Investigations	Not known	Transaminases increased[4]

Reported after use of paracetamol, but not necessarily causally related to the drug
• Chronic liver necrosis was reported in one patient who took therapeutic doses of paracetamol daily for approximately one year [50]
• Reported after prolonged us
Low elevations of Transaminases may occur in some patients taking therapeutic doses of paracetamol; These elevations are not associated with hepatic failure and generally resolve with continued treatment or discontinuation of paracetamol.
• Very rare cases of serious skin reactions have been reported. [8]
• Chronic liver necrosis has been reported in one patient who took daily therapeutic doses of paracetamol for approximately one year, and liver damage has been reported after ingestion of excessive daily amounts for shorter periods. A review of a group of patients with chronic active hepatitis showed no differences in liver function abnormalities in patients who usedparacetamol for a long time, or improved disease control after paracetamol discontinuation.[41-43]

Preparation of Syrups
Syrups are prepared by one of the following four general methods, depending on the physical and chemical properties of the ingredients:[49-54]
1. Dissolution of ingredients using heat
2.Dissolution of ingredients by stirring without the use of heat
3.Addition of sucrose to a prepared medicinal liquid or flavored liquid
4. Percolation of the source of medicinal substance or sucrose

solution with the aid of heat
This method is used when the active components are neither volatile nor thermolabile.Procedure:
• Heavy sucrose is placed in a beaker.
• Purified water is added.
• Heat in a water bath (less than 70°C) until a solution is obtained.
• The product is filtered.
• The volume is filled up toq.yes

Dissolution of ingredients by stirring without application of heat
Procedure for thermolabile ingredients
• Sucrose and other ingredients are weighed correctly.
• Dissolved in purified water.
• Store in a bottle with approximately twice the volume of the syrup, followed by constant stirring.
• The amount of syrup prepared is filled up to q.Yes
Adding Sucrose to a Prepared Medicinal Liquid or Flavored Liquid
This procedure is used when liquid extracts, tinctures or other liquids are added to the syrup.
• Alcohol is added to dissolve resinous or oily substances.
• Alcohol also acts as a preservative.

Drug percolation or source of sucrose
• Sucrose is placed in a percolator.• Water slowly passes through sucrose.
• The neck of the coffee maker is stuffed with cotton.
• The percolation rate controls the rate of dissolution.
• After complete dissolution, the final volume is q.s.

Evaluation of Paracetamol Syrup
Physical property [48-56]
Appearance: clear and transparent
Determination of pH [9]

pH usually represents the acidity or alkalinity of an aqueous solution. The pH value of a solution was determined potentiometricallyusing the glass electrode. A digital pH meter was allowed to stabilize. The pH meter was then standardized with buffer tablets. Suspension Formulationwas added to the pH meter.The reading was noted when there were no fluctuations in the pH meter.

Determination of weight per ml [10]
A previously weighed 50 ml volumetric flask was removed and the oral syrup was added to the mark. The net volume was noted. He then weighed the top of the flask to determine the weight per ml.

freeze-thaw studies [11]
freeze-thaw studies were performed by alternating exposure of the final formulation (F1) to 8°C.Accelerated stability study [12]

Syrup F1 was packaged in a 100ml PET bottle. The

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packaged bottles were placed in a stability chamber maintained at 28°C and 25°C for 2 weeks. The analyzes included chemical testing of quantifiable parameters that could potentially change during storage, such as pH.

Paracetamol Syrup Assay [13]

High performance liquid chromatography using a stainless steel column (25 cm x 4.6 mm) packed with octasilyl silica gel (5 µm).Mobile phase preparation method Prepare a solvent mixture consisting of 0.4 volumes of formic acid, 15 volumes of methanol, and 85 volumes of water. Use a filtered and degassed solution of 0.01 M sodium butanesulfonate in the solvent mixture above as the mobile phase.Operationwith flow rate 1.0 ml per minute.Use a UV spectrophotometer set to a wavelength of 243 nm as the detector.

Prepare the Assay solutions

1. Shake the oral suspension container to resuspend any settled material. Shake out an accurately weighed amount of oral syrup containing the equivalent of Filter a portion of this solution through a 0.45 µm filter, and discard the first few mL of the filtrate.

2. Accurately weigh approximately 250 mg of paracetamol and dissolve in a solvent mixture. Dilute this solution to 5 mL of the 100 mL solvent mixture. Dilute 10 mL of the resulting solution in 50 mL of the solvent mixture. Filter a portion of this solution through a 0.45-µm filter and discard the first few mL of filtrate.

3.Dissolve 10.1812 g paracetamol syrup solution in approximately 5 ml solvent mixture and 1000 ml solvent mixture. And 5ml of the resulting solution to 100ml of mixed solvent. Filter a portion of this solution through a 0.45 µm filter and discard the first few mL of the filtrate. Separately inject 20 µL of each of solutions (1), (2), (3), (4), and (5) and record standard paracetamol chromatograms and take two chromatograms of laboratory-made paracetamol syrup on. In the chromatogram obtained with a solution, the following peak elutes with the following relative retention with respect to paracetamol. Measure the areas of the peak responses in the chromatograms obtained with solutions.

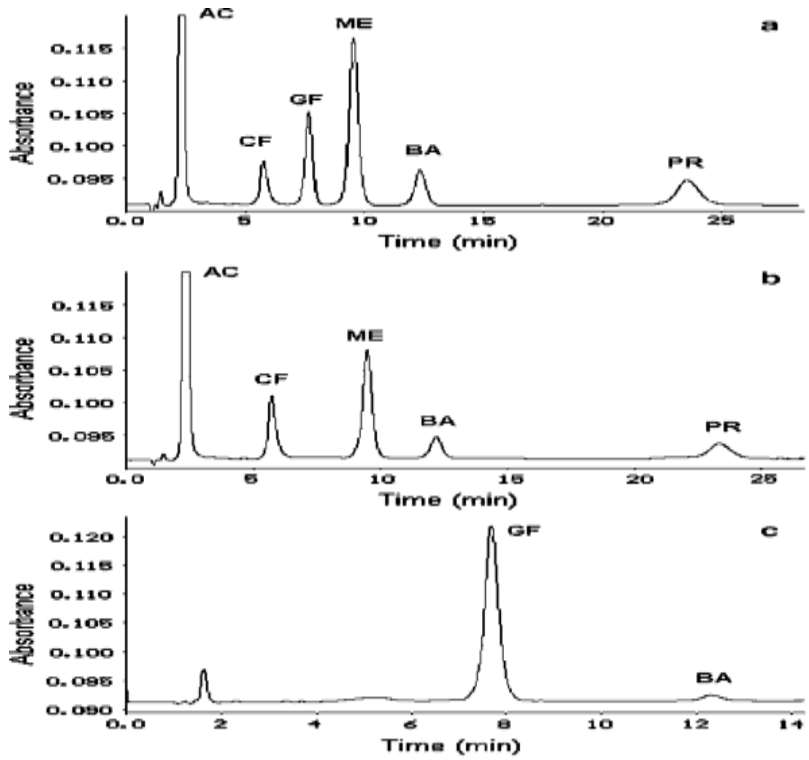

Fig-Chromatography of syrup

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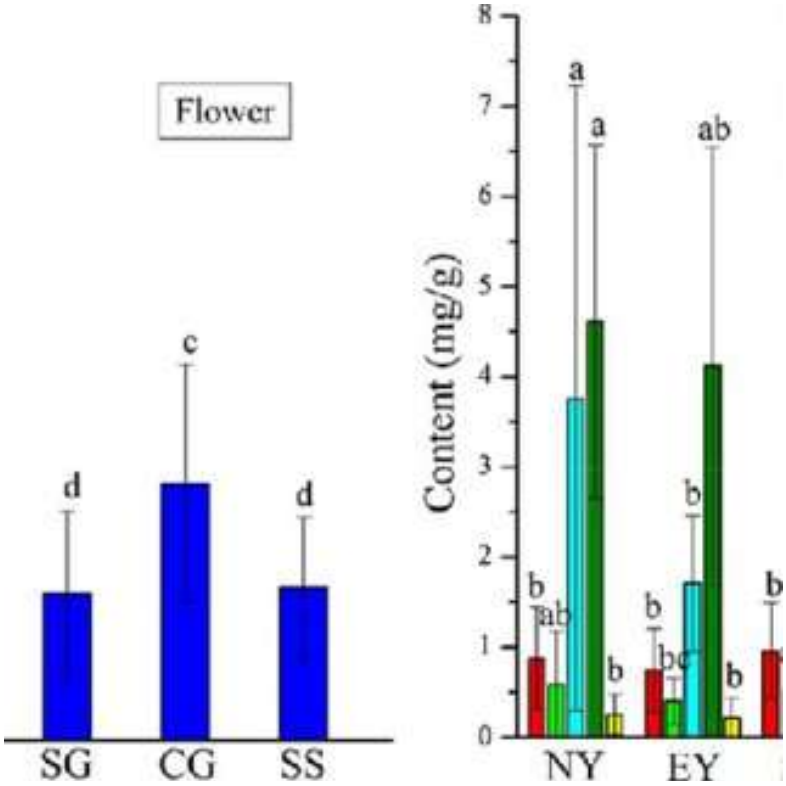

Graph of sugar

OVERDOSE

Liver damage is possible in adults and adolescents (≥ 12 years) who have taken 7.5 g or more paracetamol. Excessive amounts of a toxic metabolite (usually sufficiently detoxified by glutathione when normal doses of acetaminophen are ingested) are thought to irreversibly bind to liver tissue. Ingestion of 5g or more paracetamol can lead to liver damage if the patient has risk factors (see below).[30]

Risk factors

Liver damage is possible in adults and adolescents (≥12 years of age) who have taken 7.5g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) become irreversibly bound to liver tissue. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).[26-32]

Risk factors

If the patient

a) Is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

b) Regularly consumes ethanol in excess of recommended amounts

c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia. [44-46]

If the patient is

a) on prolonged treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampin, St. John's wort or other drugs that induce liver enzymes.O
b) Regularly consumes more than recommended amounts of ethanol
c) Glutathione is likely to be depleted, e.g. Eating disorders, cystic fibrosis, HIV infection, starvation, cachexia. [38]

Symptoms

Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, hyperhidrosis, malaise, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. This can include hepatomegaly, liver tenderness, jaundice, acute liver failure and liver necrosis.[39]

Abnormalities in glucose metabolism and

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metabolic acidosis may occur. They can increase blood bilirubin, liver enzymes, INR, prothrombin time, blood phosphate, and blood lactate.In severe poisoning, liver failure can lead to encephalopathy, bleeding, hypoglycemia, cerebral edema and death. Acute renal failure with acute tubular necrosis, strongly indicated by flank pain, hematuria, and proteinuria, can develop without severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Haemolyticanemia (in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency): Haemolysis has been reported with the use of paracetamol overdose in patients with G6PD deficiency.[50]

Management

Prompt treatment is essential when treating a paracetamol overdose.Despite the absence of significant early symptoms, patients should be urgently hospitalized for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of the overdose or the risk of organ damage. Treatment should be in accordance with established treatment guidelines, see the BNF overdose section.[30-34] Activated charcoal treatment should be considered if the overdose was taken within 1 hour. The plasma concentration of paracetamol should be measured 4 hours or later after dosing (earlier concentrations are unreliable).Treatment with N-acetylcysteine can be used up to 24 hours after taking paracetamol, but the maximum protective effect is achieved up to 8 hours after ingestion. The effectiveness of the antidote decreases dramatically after this time. If necessary, patient should receive[35-40]

N-acetylcysteine intravenously according to the established dosing regimen. If vomiting is not a problem, oral methionine may be a suitable alternative for remote, out-of-hospital areas. Management of patients with severe hepatic impairment beyond 24 hours post-dose should be discussed with the NPIS or a liver department.[40-45]

6. Pharmaceutical particulars

6.1 Incompatibilities

None stated

6.2 Shelf life

24 months

6.3 Special precautions for storage

Store below 25°C. Protect from light. Store in the original package.

6.4 Nature and contents of container

Bottles:	Amber (Type III) glass bottle
Closure:	HDPE, child resistant, tamper
Pack sizes:	evident, EPE wadded closure
Dosing	100ml and 500ml
device:	2.5/5ml double ended polypropylene spoon.

6.5 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.[45-55]

II. CONCLUSION

Due to the pharmacology of acetaminophen, it is important to choose an appropriate dose to achievemaximum and minimize side effects. In children, paracetamol 15 mg/kg is the appropriate dose to treat fever. In the treatment of pain in children, the minimum dose of paracetamol to be used is 15 mg/kg. According to WHO guidelines, paracetamol is the only available option for pain management in children under 3 months; in this case, the dose of 10 mg/kg every 4-6 h should be recommended [18]. For effective pain control, acetaminophen should be given in timed doses rather than as needed. Theright dose of acetaminophen provides effective treatment for pain and fever equivalent to treatment with NSAIDs, making it an effective and safer treatment option in this setting.

Only paracetamol and ibuprofen seem to be recommended for fever reduction in children [15]. It is not recommended to use them in combination or alternately with paracetamol and ibuprofen. Furthermore, while ibuprofen is not approved for use in children under the age of three months and is contraindicated in patients with chickenpox and those with dehydration and pneumonia, acetaminophen can be used from birth and in patients with dehydration [13,14]. Paracetamol appears to be the drug of choice for analgesia in children with mild to moderate pain, with an optimal dose of 15 mg/kg every 4–6 h (maximum 4 times daily) [83].Notably, paracetamol is also the drug of choice for the treatment of mild to moderate neonatal pain [83]. Finally, to avoid toxicity, only standard doses should be used, with doses calculated by weight and age; Attention should also be paid to clinical factors or concomitant medications that may increase the risk of toxicity.

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