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An Innovative Formulation of Paracetamol Syrup by Oligomerization in the Presence of Citric Acid

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Abstract: An attempt was made to prepare Paracetamol syrup from the API powder of Paracetamol. Like other Paracetamol liquids which are bi-layer in nature (suspension form) the developed product is different. It is a single-layer liquid dosage form containing Paracetamol and other required excipients. During the evaluation of this developed product, it was found that it cannot only function as a conventional Paracetamol suspension but also can show better efficacy compared to other existing Paracetamol suspensions. The area of interest was entirely concerned with the smooth administration of the liquid through the oral route of administration. In contrast, after the formulation it was found that it can be administered through an IV channel. A lot of development has been done in terms of its texture and taste and finally, a positive result was obtained. This study also relates to conventional syrup and the improvisation of Paracetamol syrup in both oral and parenteral routes of administration. On the other hand, the field of the work was to make it more palatable and accessible to pediatric and geriatric patients compared to the conventional method. The evaluation research also includes that it can be useful for the veterinary sector. An interesting fact was that dry heating of the Paracetamol API produced oligomerization resulting rapid solubility in polar solvents in the presence of citric acid.

Keywords: Paracetamol API, Syrup, Citric acid, Oligomerization, Noyes Whitney Equation

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Introduction

Paracetamol and acetaminophen are two names of the same compound known as N-acetyl-para-aminophenol. In the 80s of the 19th century the drug was discovered by two young doctors at the University of Strasburg. They noticed that the drug had a small impact on intestinal parasites,

whereas, it can significantly decrease high temperature. Young doctors named Arnold Chan and Paul Heppa did the publication of their discovery and acetanilide was introduced into medical practice in 1886 under the name of antifebrin (Chan *et al.*, 1948). As soon as the drug came into production line it becomes very cheap. Later on Phenacetin and N-acetyl-p-aminophenol appeared to be the most satisfying compounds, which had been earlier synthesized by Morse *et al.* (1878). A German pharmacologist named Joseph von Mering performed the first clinical trials of these two acetanilide derivatives. On the basis of the obtained results he concluded that paracetamol was characterized by high toxicity similar to acetanilide. Therefore, phenacetin was the first derivative introduced into the medical practice in the year 1887. After that Phenacetin was widely used in other analgesic mixtures until the time when it got associated with the development of analgesic nephropathy after a long-term usage (Von Mering, 1893). Interstingly in the year 1948 an exceptional discovery was done by Bernard Brodie and Julius Axelrod. They concluded that paracetamol was the main active metabolite of acetanilide and phenacetin which is responsible for the analgesic and antipyretic action and that methemoglobinemia was induced by another metabolite named phenyl hydroxyl amine (Brodie *et al.*, 1948). Paracetamol (acetaminophen) is also known as non-steroidal anti-inflammatory drug which is commonly used to treat pain and fever and is typically used for mild to moderate pain relief. Paracetamol may be responsible for toxic overdosage particularly in neuropsychiatric patients. Paracetamol is both a prescription (prescribed by many physicians in different specialties) and an over-the-counter drug (Meremikwu and Oyo-Ita, 2002). On the other hand, Paracetamol is also used for treating severe pain e.g. cancer pain and post-operative pain in combination with opioid analgesics and is given orally, rectally and intravenously (McNicol *et al.*, 2005). Now days, paracetamol is on the World Health Organization's list of essential medicines, which considered as the most effective and safe medications needed in human health system (Walsh *et al.*, 2022). Importantly in pediatric cardiology, paracetamol is used to treat patient with ductus arteriosus (Sallmon *et al.*, 2016). Study found that Paracetamol does not inhibit cyclooxygenase enzyme outside the central nervous system, so that paracetamol is not effective as a general anti-inflammatory agent. However, inside the CNS, paracetamol partially inhibits cyclooxygenase enzyme. This also explains the effectiveness of paracetamol in treating fever and pain. Basically the analgesic action of paracetamol has been recognized due to its inhibition of the cyclooxygenase (COX) pathway in the central nervous system (CNS), falling the manufacture of pain-mediating prostaglandins, whereas it can also increase endocannabinoid transmission and amend by diminishing serotonergic inhibitory pathways (Sharma and Mehta, 2014). An interesting study found that paracetamol is lethal to the snakes, and has been suggested as a chemical control program for the invasive brown tree snakes where doses of 80 mg inserted into dead mice perhaps scattered by helicopter aero planes to kill snakes (Johnston *et al.*, 2002). A recent study found that Paracetamol derivatives with their N-substituted Acyclic Analogues and then substituted with a pro-drug can enhance its activity by forming cocrystal of Antibacterial and Antifungal and then can increase the analgesic activity of Paracetamol by attaching it to Dendrimers which can fasten the activities against *E. coli* and *Staphylococcus auerus* and they exhibit moderate to high antimicrobial activity (Kotagi *et al.*, 2024). Combination of Paracetamol and Magnesium Sulphate can be used in pain management during oral and maxillofacial surgery especially orthodontics (Khalili *et al.*, 2022). An exceptionally interesting separate line of research provides evidence on potentiation of the descending inhibitory serotonergic pathway to mediate the analgesic action of paracetamol, but with no evidence of binding to serotonergic molecules. Importantly,

AM404 as a metabolite for paracetamol has been proposed to activate the endocannabinoid and the transient receptor potential vanilloid-1 (TRPV1) systems. AM404 which is a novel metabolite for paracetamol was shown to activate the endocannabinoid system and can also activate the transient receptor potential vanilloid-1 (TRPV-1) channel, both of which are involved in the modulation of pain signaling and proposed to mediate the analgesic action of paracetamol (Högestätt *et al.*, 2005).

Materials and Methods

Collection of samples:

Paracetamol API/ $CH_3CONHC_6H_4OH$ (Active Pharmaceutical Ingredient) was collected from SRS Traders, Telengana, India (CAS No: 103-90-2), Citric acid/$C_6H_8O_7$ from Jay Kay Dye Chem Private Limited, Telengana, India (CAS No: 5949-29-1) and Sucralose/$C_{12}H_{19}Cl_3O_8$ from Sinochem Supply, Chain (CAS No: 56038-13-2) from Kolkata, India. Preservatives such as Sodium Methylparaben /$Na[CH_3(C_6H_4COO)O]$ and Sodium Propylparaben $C_{10}H_{11}NaO_3$ were collected from Alta Laboratories Ltd., Kolkata, India.

Preparation of sample/formulation:

As it is known that the Paracetamol API is partially soluble in water therefore 50 L of DM (Demineralized) water was taken. The Paracetamol API was heated at 60° to 70° C. Then after addition of DM water into the Paracetamol API it was stirred continuously for 30 min. Then after the checking of the pH of the solution, by adding Citric acid the pH was adjusted up to 5.4 and stabilized. After that by adding more DM water the volume was made up to 100 L. Then the coloring agent was added in sufficient quantity and Sucralose of 10 g added into 100 L of water. 100 g of Sodium Methylparaben and 20 g of Sodium Propylparaben was added finally to make the whole syrup. Significantly the drug presence was found 250 mg of Paracetamol per 10 ml of syrup.

Identification method of test sample:

The identification of the prepared Paracetamol syrup undergone some specific quality control tests e.g. viscosity, light transmittance test, visual inspection, pH measurement, and accelerated stability followed by physical stability study.

Test and evaluation of the prepared product:

In Ostwald Viscometer the obtained result was 20 centipoises in both cases (Paracetamol syrup treated with sweetening agent and Paracetamol syrup treated without sweetening agent). The viscosity was calculated by using the formula:

$$\eta l = (tl \times dl) / (tw \times dw)\ \eta w \qquad (1)$$

Where, Average time of flow of the liquid (tl) in seconds, Average time of flow of the water (tw) in seconds, Laboratory temperature in °C, Density of water at the laboratory temperature (dw) in g cm^{-3}, Density of liquid at the laboratory temperature (dl) in g cm^{-3}, Viscosity of water (ηw) in centipoises/s.

A digital pH meter (Globe Scientific Instruments Digital pH Meter 0-14 pH, GSI-011) was used, and the pH of the Paracetamol syrup was found 5.4. The functionality was based on Henderson–Hasselbalch equation which is:

$$pH = pK_a + \log_{10}(Base[A^-]/Acid\ [HA]) \qquad (2)$$

Where, pH = Acidity of a buffer solution, pK_a= Negative logarithm of K_a, A^-= Concentration of the conjugate base, HA = Concentration of an Acid

In case of the visual inspection, it was observed that no precipitation was found, no turbidity was found and no other impurity was found in the end product.

Results and Discussion

An explanatory observation could be drawn from the UV-Vis Spectrographs (Figs. 1, 2, 3) and IR Spectrographs (Figs. 4, 5, 6, 7, 8, 9, 10). From UV Vis spectra, The absorbance of paracetamol was ideally placed at 250 nm with addition of sucralose changing to 243 nm. The FTIR in different permutation of citric acid and sucralose along with paracetamol syrup, indicate no

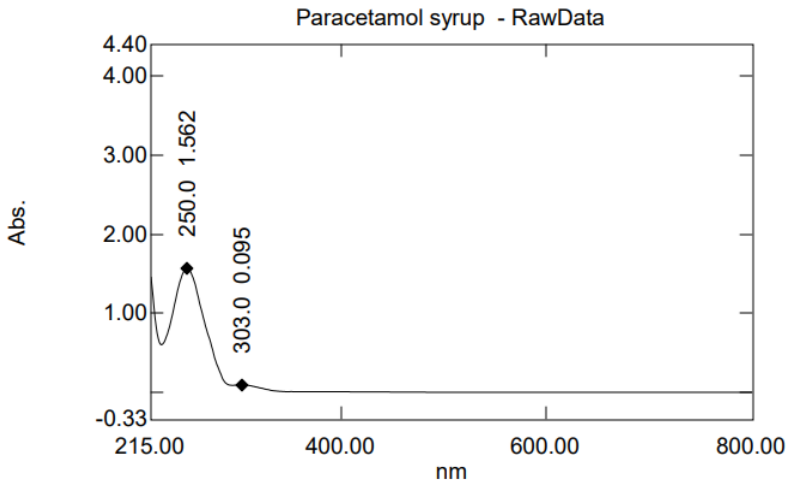

Fig. 1: At 250 nm the Paracetamol API is showing the absorbance without any dilution.

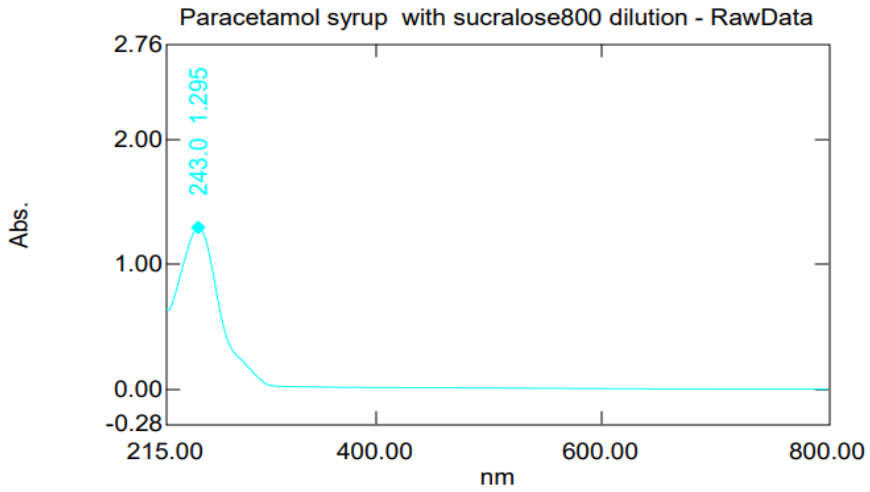

Fig. 2: At 243 nm the Paracetamol with Sucralose showing the absorbance after the dilution of 800.

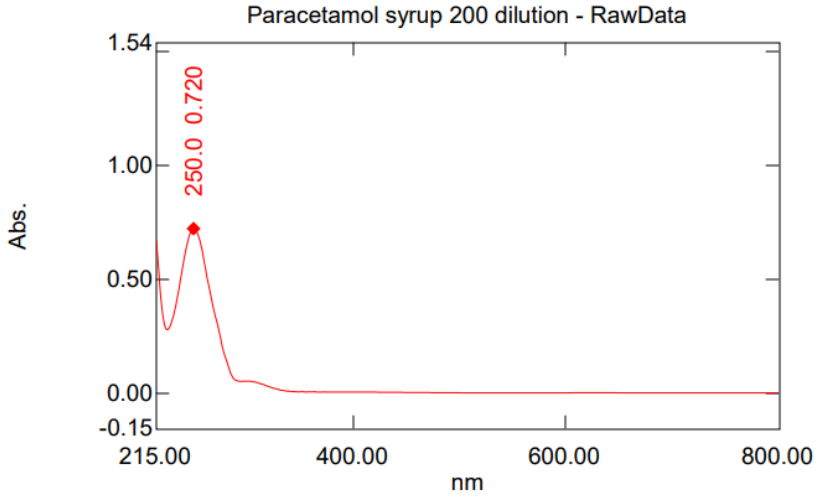

Fig. 3: At 250 nm the Paracetamol without Sucralose is showing the absorbance after an optimum dilution of 200.

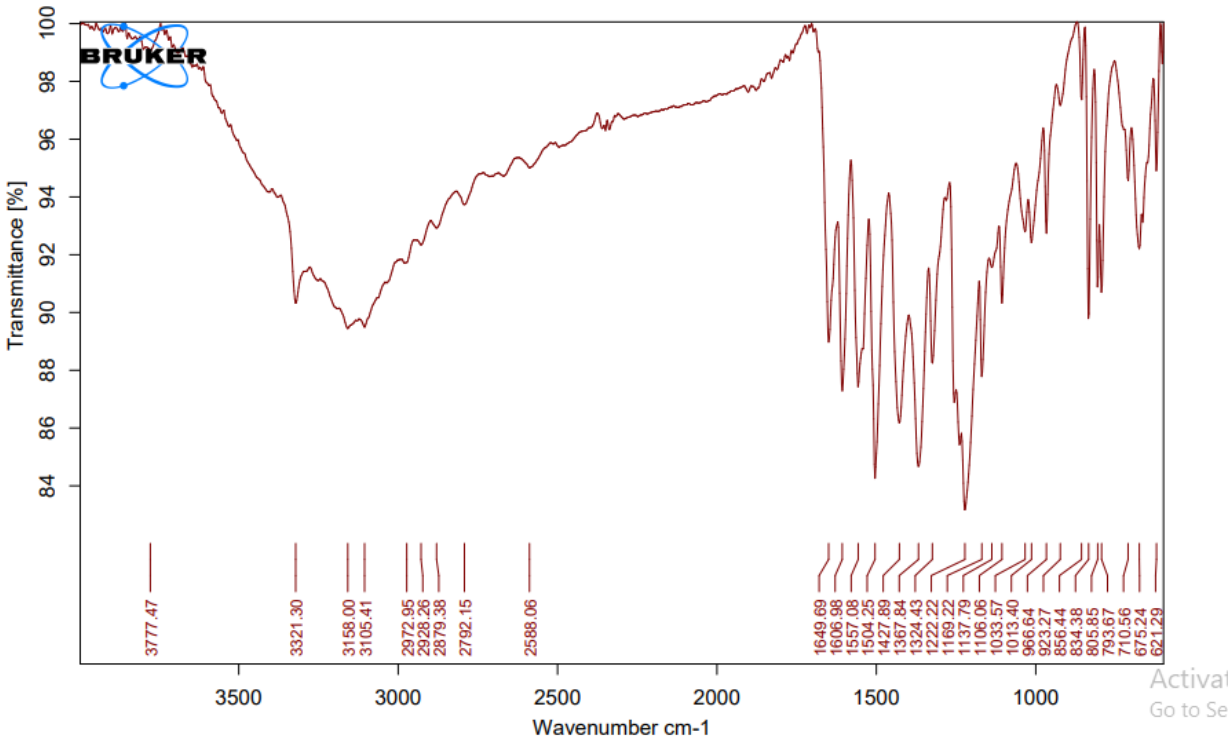

Fig. 4: The FTIR Spectrogram of Paracetamol syrup with Sucralose.

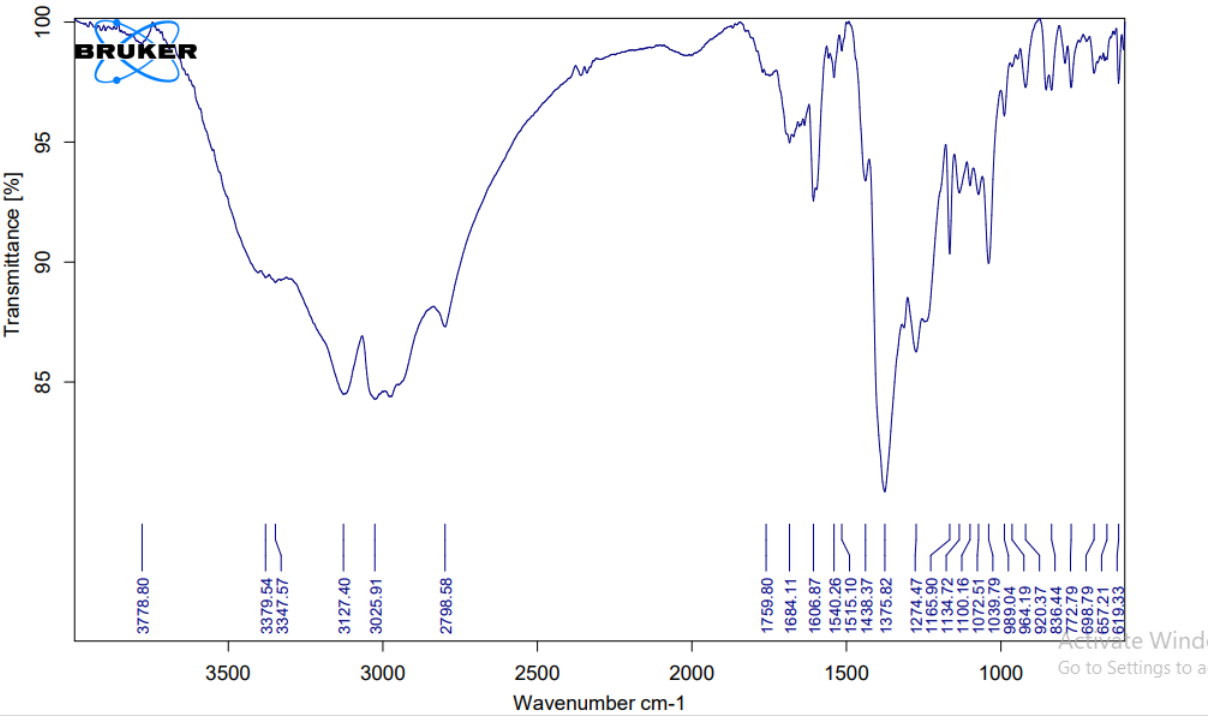

Fig. 5: The FTIR Spectrogram of Paracetamol Syrup without Sucralose.

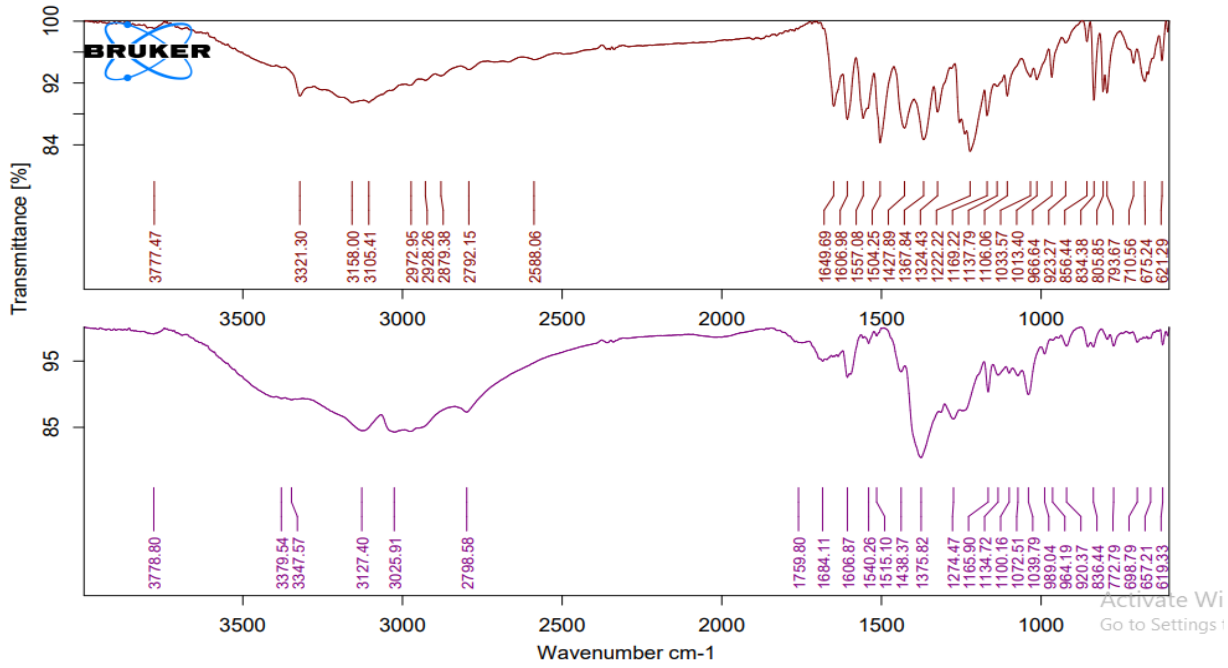

Fig. 6: A comparative study of the FTIR spectrogram of Paracetamol syrup with Sucralose and Parqacetamol syrup without Sucralose, respectively.

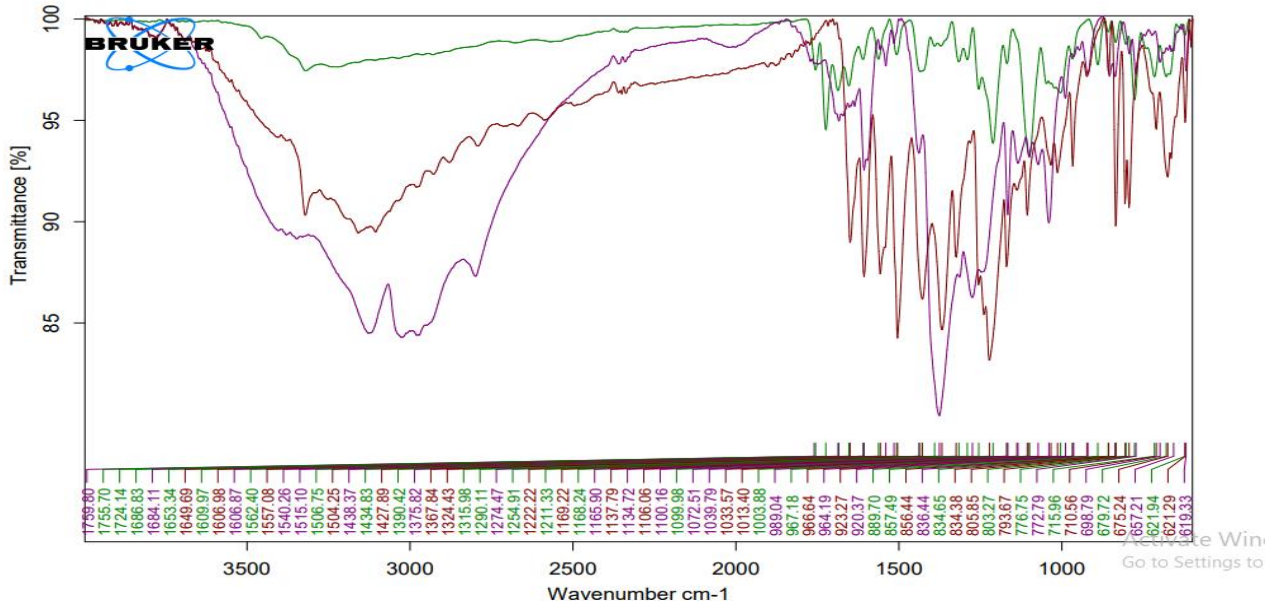

Fig. 7: A comparative study of the FTIR spectrogram of Paracetamol syrup with Sucralose and Citric Acid which is also the Physical Mixture (Green Line), Paracetamol syrup with Sucralose (Brown Line), and Paracetamol syrup without Sucralose.

significant chemical change with major peaks aligning to functional groups remaining intact.

As the Paracetamol API were triturated further in spite of being in a powder form therefore, the effective surface area becomes greater. The less amount of particle size can give more effective surface area by which the tablet can release its active constituents rapidly. It is highly recommended to keep the particle size lesser as far as possible. During the research work initially Sieve 85 was used where the particle size was 0.177 mm approximately. Then Sieve 120 was used where the particle size was 0.125 mm approximately which was responsible for more

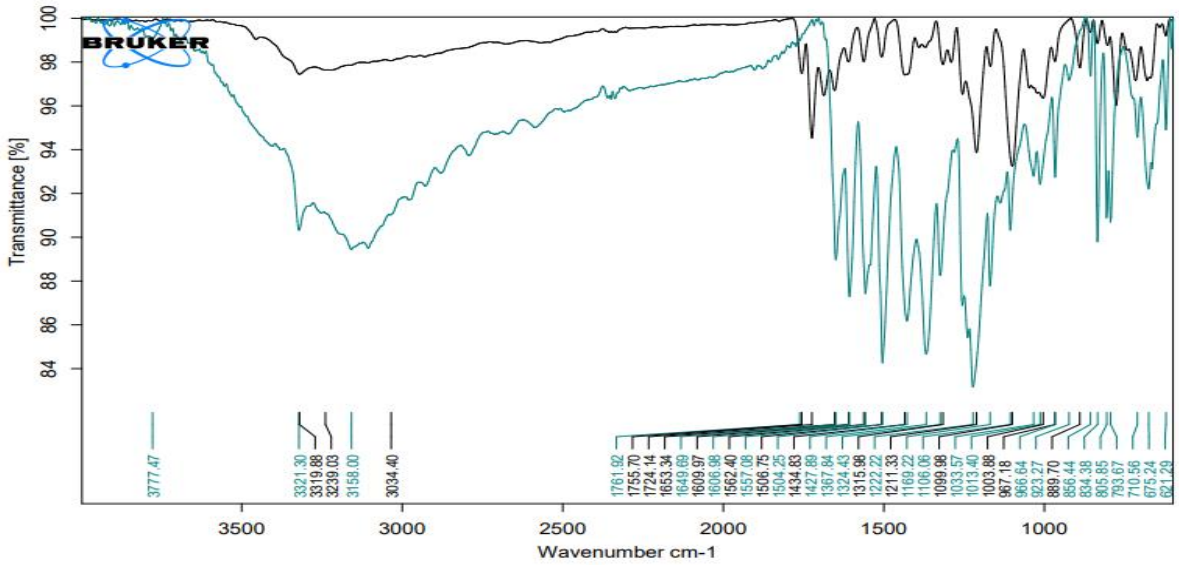

Fig. 8: A comparative accelerated stability study of the FTIR spectrogram of Paracetamol syrup with Sucralose and Citric Acid which is also the physical mixture (Black Line) and Paracetamol syrup with Sucralose.

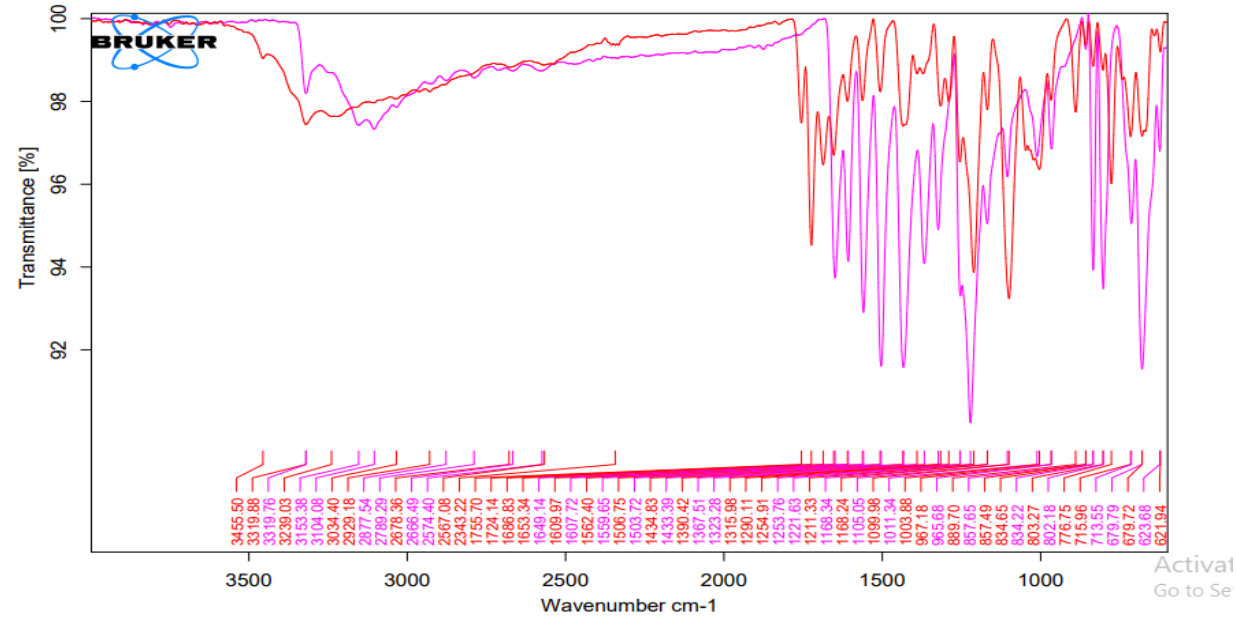

Fig. 9: A comparative accelerated stability study of the FTIR spectrogram of Paracetamol syrup with Sucralose and Citric Acid which is also the physical mixture (Red Line) and Paracetamol syrup without Sucralose.

effective surface area. It is recommended to use Sieve 170 or more in order to gain better outcome i.e. less than 0.100 mm of particle size to get highly effective result (Noyes and Whitney Equation).

The rate of change in concentration of dissolved material with time is directly proportional to the concentration difference between two sides of diffusion layer.

That is, $dc/dt = k (C_s-C_b)$ (3)

Where, dc/dt = Dissolution rate of Paracetamol, k = Rate constant, C_s= Concentration of the Paracetamol in the liquid, C_b = Bulk of the powder.

Modified Noyes and Whitney Equation could

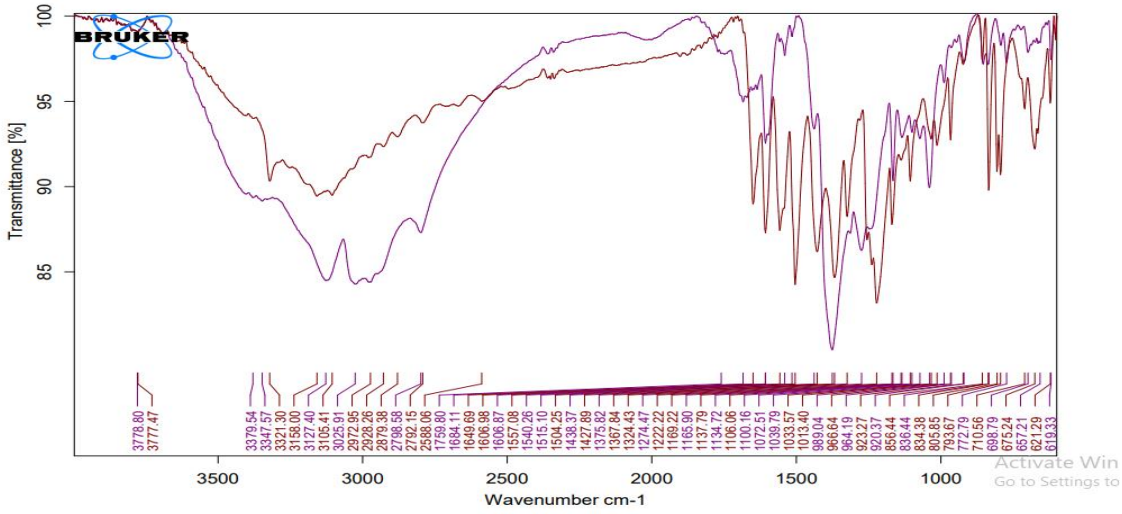

Fig. 10: A comparative accelerated stability study of the FTIR spectrogram of Paracetamol syrup with Sucralose (Brown Line) and Paracetamol syrup without Sucralose.

also be considered where Burner incorporated the surface area.

That is, $dc/dt = kA (C_s-C_b)$ (4)

Where, dc/dt = Dissolution rate of Paracetamol, k = Rate Constant, A = Surface area of dissolving powder C_s= Concentration of Paracetamol in liquid, C_b = Bulk of the powder and; Fick's law of diffusion has been incorporated later on where Diffusion coefficient, Thickness of stagnant diffusion layer, and Volume diffusion layer were considered.

That is, $dc/dt = DAk_{w/o} (C_s-C_b) / Vh$ (5)

Where, dc/dt = Dissolution rate of Paracetamol, $k_{w/o}$ = Water/Oil partition coefficient of Paracetamol (Applicable when the medium is milk) i. e for the babies [Not recommended while consuming milk/ breastfeed], A = Surface area of dissolving powder, D = Diffusion coefficient, C_s= Concentration of Paracetamol in dissolving liquid, C_b = Bulk of the powder, V = Volume of dissolution medium/Volume diffusion layer, h = Thickness of stagnant diffusion layer.

The obtained results clearly indicated a faster and relatively higher release of active ingredients (Acetaminophen) for the developed tea tablet formulation in respect to marketed Paracetamol suspensions. The data also indicates that the fineness of powder can produce a higher amount of active ingredient release which can also reduce the total amount of Paracetamol API powder used in conventional formulation.

It can be predicted that while preparing the formulation of Paracetamol syrup it can produce monomers to macromolecular complexes through a certain degree of polymerization while heating at the temperature of 70°C resulting the slow binding with the COX 1 and /or COX 2 inhibitor/s. On the other hand, the result also showed that the stability is higher in case of the physical mixture as compared to the rests. As both COX 1 and COX 2 have the affinity to bind with NSAIDs (Non-Steroidal Anti-Inflammatory Drug) it can slowly bind with COX active site by preventing the AA (Arachidonic Acid) reaches to the catalytic pocket and inhibits the Prostaglandin biosynthesis, after the consumption or administration.

According to BP (British Pharmacopoeia) the drug content in the prepared formulation was found 250 mg per 10 ml or 125 mg per 5 ml. Here in that case the formulation without Sucralose is recommended. However, significant drug content was found in both Paracetamol syrup formulations with or without Sucralose (99.96%

approximately). On the other hand, it was also found that there is no microbial contamination or any other impurities found in the batch sample of year 2022 and 2023 respectively. Therefore, the shelf life of this formulation is optimum (After the accelerated stability study). It is easily water soluble or can be administered orally if required.

Conclusion

Thus, the evaluation tests proposed the pioneering in the research of the formulation of Paracetamol syrup. An interesting fact has been identified that the Paracetamol/Acetaminophen syrup while combined with Sucralose and Citric acid can release the drug slowly resulting the sustained release and can show better efficacy compared to the existing formulations. On the contrary, the commercially available Paracetamol/Acetaminophen formulations are biphasic liquid dosage form whereas; the formulated syrup is single phase liquid dosage form. Hence, further research and other improvisation are going on to formulate the parenteral by enhancing its efficacy in terms of its tonicity adjustment and pH optimization. Therefore, in near future the same formulation can be used in parenteral way and can be able to play a crucial role in veterinary sector too.

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Conflict of Interest

Authors do not have any conflict of interest regarding this research work.

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