

Review on: Preparation and Evaluation of Paracetamol *Emulsion* *dosage Form*

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ABSTRACT

The objective of this review article is to summarize literature data pertinent to potential excipient effects on intestinal drug permeability and transit. Despite the use of excipients in drug products for decades, considerable research efforts have been directed towards evaluating their potential effects on drug bioavailability. Potential excipient concerns stem from drug formulation changes (e.g., scale-up and post-approval changes, development of a new generic product). Regulatory agencies have established *in vivo* bioequivalence standards and, as a result, may waive the *in vivo* requirement, known as a biowaiver, for some oral products. Biowaiver acceptance criteria are based on the *in vitro* characterization of the drug substance and drug product using the Biopharmaceutics Classification System (BCS). Various regulatory guidance documents have been issued regarding BCS-based biowaivers, such that the current FDA guidance is more restrictive than prior guidance, specifically about excipient risk. In particular, sugar alcohols have been identified as potential absorption-modifying excipients. These biowaivers and excipient risks are discussed here.

Keywords- Paracetamol, Emulsion, Water and oil.

I. INTRODUCTION

A biphasic system with two immiscible liquids, of which one (the dispersed phase) is finely and evenly scattered as globules throughout the second phase, is known as an emulsion (the continuous phase). Emulsions are a thermodynamically unstable type of mixture.[1-2]

To stabilise the system, a third agent—the emulsifier—is introduced. By creating a thin film around the globules of the dispersed phase, the emulsifier stabilises the system. The dispersed phase, also known as the continuous phase, can range in consistency from a semisolid to a mobile liquid. Consequently, the medicinal emulsions range from creams to lotions (low viscosity) (high viscosity). The dispersed phase typically comprises particles that are between 0.1 and 100 m in size.[3]

Advantage of Emulsion of Dosage Form:

- Increase the palatability of oils and oil-soluble drugs.
- The aqueous phase is easily flavoured.
- The rate of absorption is increased.
- It is possible to include two incompatible ingredients, one in each phase of the emulsion

Disadvantage Of Emulsion of Dosage Form:

- Before usage, the preparation must be thoroughly shaken.
- Measuring a dose requires a certain level of technical accuracy.
- Stability may be affected by storage conditions.
- Heavy, challenging to move, and prone to container breaking.

Types of Emulsion:[4]

- Water in oil emulsion (W/O)
- Oil in Water emulsion (O/W)

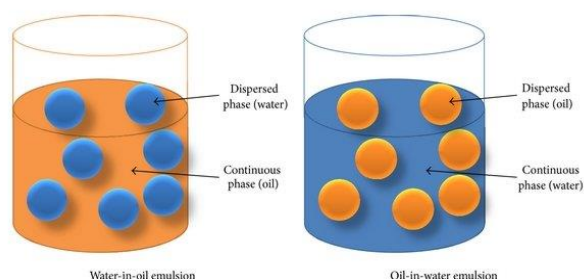


Fig: 1 Phase of Emulsion

Water in Oil Emulsion (W/O): Water-in-oil (W/O) emulsions are made up of an aqueous phase that is dispersed into a continuous oil phase in the form of tiny droplets. The cosmetic, pharmaceutical, agricultural, and food industries all have a lot of promise for W/O emulsions.

For instance, this kind of emulsion can be used to load protein pharmaceuticals, immobilise enzymes, and encapsulate medications. Because of its structure, hydrophilic chemicals can be delivered to the emulsified system and perform a variety of functions, including antioxidant and antibacterial ones.[3,4]

Although the kinetic transition to the water/oil split phases can be so gradual, the emulsion may be regarded as metastable. Due to the high mobility of water droplets, which results in sedimentation, flocculation, or coalescence, W/O emulsions often exhibit less stability than their oil-in-water (O/W) counterparts. Additionally, because the oil continuous phase has a low electrical conductivity, only steric forces are anticipated to sustain this form of emulsion.

An oil-in-water emulsion is an emulsion in which water serves as the dispersion medium or continuous phase and oil acts as the dispersed phase. If handled improperly, the W/O or O/W emulsion in the petroleum business can potentially result in significant financial losses. O/W emulsions are frequently referred to as reverse emulsions since W/O emulsions are more prevalent than O/W emulsions. [4,5]

- **Oil in Water Emulsion (O/W):** A water-in-oil emulsion is a form of emulsion in which the continuous phase often consists of hydrophobic substances like oil and the dispersed phase typically consists of water. The W/O type makes up more than 95% of the crude oil emulsion that forms in the oil field. Three elements are present in the W/O emulsions: water, a surfactant, and a solvent.

Oil is the dispersed phase that is spread into the continuous phase, water, when an emulsion is "oil-in-water." A water-in-oil emulsion reverses the roles. Butter is a water-in-oil emulsion, whereas milk is an illustration of an oil-in-water emulsion.

- **Multiple emulsions:** It is possible to come across different emulsions, such as water-in-oil-in-water (W/O/W) and oil-in-water-in-oil (O/W/O). The majority of the time, a combination of hydrophilic and

hydrophobic surfactants is used to stabilise multiple emulsions. Very small droplets suspended in larger droplets that are likewise spread in a continuous phase make up the more sophisticated Multiple emulsions.

II. DIFFERENCE BETWEEN WATER IN OIL (W/O) VS OIL IN WATER (O/W)

Customers occasionally inquire as to what separates an oil-in-water emulsion from a water-in-oil emulsion. The usage of emulsifying agents differs significantly since some are more compatible with one phase than the other. An oil-in-water emulsion is likely to be easier to create with an emulgent that is easily soluble in water than one that is not. The type of liquid suspended within the other is the main distinction between an oil-in-water and a water-in-oil emulsion, aside from anything else.

Emulsification process: [6-10]

- **General Method:**

Typically, an O/W emulsion is made by completely separating the oily phase into tiny globules, encasing each globule in an emulsifying agent envelope, and thus globules are suspended in the aqueous phase. In contrast, the W/O emulsion is created by entirely splitting the aqueous phase into tiny globules, encasing each globule in an emulsifying agent envelope, and then suspending the globules in the oily phase.

- **Phase Inversion Method:**

This approach creates a W/O emulsion by first adding the aqueous phase to the oil phase. When extra water is added at the inversion point, the emulsion inverts it results in an O/W emulsion.

- **Dry Gum Method:**

Emulsions created in the moment are often manufactured using the continental or dry gum approach. This process involves combining the emulsifying agent (often acacia) with the oil, which is then combined with the aqueous phase to create the emulsion. The differences between Continental and Dry Gum Methods percentage of components.

- **Wet Gum Method:**

The proportion of the elements is the same in this approach as it is in the dry gum method; the preparation method is different. Here, the emulsifying agent's mucilage, often acacia, is generated. The oil is then gradually infused into the mucilage using perpetual trituration.

Stability of Emulsion:[11]

The stability of emulsion products is a crucial factor, yet evaluating emulsion stability is challenging. The absence of dispersion phase coalescence, absence of creaming, and pharmaceutical emulsion stability is all preserving its outward attributes, such as grace, aroma, colour, and look. Flocculation, creaming, coalescence, and breaking are the four events that can cause an emulsion to become unstable.

Temperature can alter the physical properties of oil/water interfacial films, and the solubility of surfactants in oily and aqueous phases can have an impact on emulsion stability. Additionally, the viscosity of the emulsion, particularly in its oily phase, can be reduced by raising the temperature. Emulsions are thermodynamically unstable, and after a certain amount of time, their characteristics can alter. Therefore, it is crucial to discuss the emulsions' thermodynamic and kinetic stability in order to have a better understanding of the mechanism underlying emulsion stability.

Mechanisms of emulsion stabilization:[12]

Emulsions are used in many industries, including those that produce and refine petroleum as well as those that deal with food and medicine. In general, the interface film and surfactant adsorption mechanism have an impact on the emulsion stability. Emulsions are stabilised using four different methods. The following four phenomena are electrostatic repulsion, steric repulsion, the Marangoni-Gibbs effect, and thin film stabilisation. These four mechanisms are discussed in the ensuing subsections.

• **Electrostatic repulsion:[12]**

The interaction of the electrical double layers around the charged droplets produces electrostatic force, which tends to avoid droplet contact. An ionic surfactant is adsorbed to cause this process. Due to the low dielectric constant of the continuous phase, electrostatic repulsion does not significantly contribute to the stabilisation of water-in-oil emulsions. The strength of the interfacial film surrounding the dispersed droplet, not electrostatic forces, is what makes the emulsion stable.

• **Steric repulsion:[13]**

Steric stabilisation is typically observed in systems that have non-ionic surfactants and polymers as stabilisers. The surfactant molecules in this method will cover the scattered water droplets, and the surfactant tail deposited on the surface of the particles inhibits close contact between droplets. Since these kinds of stabilisers contain a polar component with a strong affinity to the aqueous phase or water and a polar part with a strong affinity to oil, they are primarily responsible for stabilising W/O emulsions.

• **Marangoni – Gibbs effect:[12]**

Emulsions can be stabilised via the Marangoni-Gibbs effect, which works by preventing the continuous phase from draining out from between two opposed droplets. As the droplets come closer to one another, their surface area deforms, resulting in this appearance. The film layer tries to drain as the droplets form a parallel surface as they move toward one another. Additionally, the durability of the emulsion in this phenomenon is due to the interfacial film and surfactant adsorption mechanisms. Emulsion stability is determined by the Marangoni-Gibbs effect. Thin film stabilization. A stiff and viscoelastic layer surrounds the water droplets in this stage, preventing the droplets from coalescing.

• **Thin film stabilization:**

A stiff and viscoelastic layer surrounds the water droplets in this stage, preventing the droplets from coalescing. This process, which is dependent on the chemistry, solubility, and diffusion and adsorption kinetics of asphaltene, can be fairly complicated.

Paracetamol:[15-20]

One of the most often prescribed drugs in the world, paracetamol (also known as acetaminophen) is an antipyretic, non-opioid analgesic, and non-steroidal anti-inflammatory medicine (NSAID). After being used in medicine for the first time in 1893, paracetamol was prohibited for more than 60 years because of worries that it might cause methemoglobinemia. After three different research teams refuted the toxicity theory, paracetamol was introduced as an oral formulation in the United States in 1950. With over 200 million prescriptions written each year in the USA and over 25 billion non-prescription doses sold, it is now widely used in both prescription and over-the-counter versions, making it the most frequently prescribed drug in the country.

The precise mode of action of paracetamol is still up for debate despite its widespread use. There are several ideas, but the one that holds up the best is that it works similarly to NSAIDs by inhibiting the cyclooxygenase pathways. The peripheral anti-inflammatory and anti-platelet response found with NSAIDs is absent with paracetamol, though. The cannabinoid, nitric oxide synthase, and serotonergic pathways have all been connected to paracetamol in more recent research, both directly and indirectly. The general belief is that paracetamol works primarily at its core site of action and has minimal, if any, side effects.

In hospitals, intravenous (IV) paracetamol was first used in 1985 and is recommended when enteral administration is impractical. Therefore, critically ill and surgical patients make up the majority of those getting IV paracetamol. There aren't many prospective controlled trials proving IV paracetamol's effectiveness and safety in surgical and critically ill patients, despite recent research suggesting an increase in its use. This demonstrates a dependence on the drug's current safety profile, which is based mostly on its oral preparations. Therefore, it is crucial to spot any variations in formulations as well as any undiscovered side effects that are specific to IV paracetamol.

• **Organoleptic Properties:[18,19,20]**

White crystalline powder or odourless, colourless crystals with a little unpleasant taste.

• **Solubility:**

14000 mg/L in water (at 25 °C). Slightly soluble in hot water, soluble in cold water. Soluble in methanol, ethanol, dimethylformamide, and ethylene; freely soluble in alcohol. Almost insoluble in petroleum ether, pentane, and benzene; somewhat soluble in ether; and soluble in dichloride, acetone, and ethyl acetate.

• **Melting point:**

M.P= 169-170.5 °C.

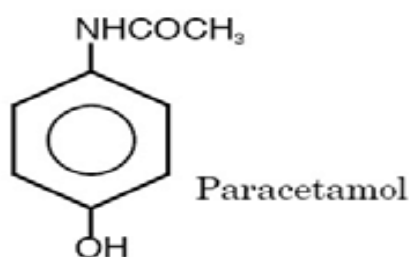
Boiling point is above 500°C.

• **Biopharmaceutical classification:**

Paracetamol was first categorised as a BCS class III compound (very soluble and poorly permeable), but after the WHO expert committee on requirements for pharmaceutical preparations produced a technical report, it was changed to a BCS class I compound (very soluble and permeable). An API is deemed to be "very permeable" when it is absorbed to a level of 85% or higher.

• **General information:**

• **2D structure:**



Molecular Formula: C₈H₉NO₂

Molecular Weight: 151.165 g/mol

Density: 1.293 g/cu cm at 21°C.

Partition coefficient (Log P): 0.5

pH: Saturated aqueous solution (5.5-6.5).

pKa: 9.5 (25 C °)

III. MATERIALS AND METHODS:

[21][22][23]

We received paracetamol as a free sample from Apex Laboratories in Chennai. S.D. Fine provided the PEG 4000, PEG 6000, urea, sodium hydroxide (NaOH), and potassium dihydrogen phosphate. Mumbai-based chemicals limited. The carriers that were utilised were all of an analytical calibre.

Preparation of solid dispersion:

The medication was dissolved in the molten solution after the carriers (PEG 4000, PEG 6000, and urea) were precisely weighed and melted to create solid dispersions. Fusion technique a method that was utilised to create solid dispersions. In a china dish, the right amount of paracetamol was added, along with the necessary amounts of carriers (PEG 4000, PEG 6000, and urea), to create the formulations' requisite drug to carrier ratios, as given in Table 1. The mixture was then heated to a predetermined temperature while being constantly stirred to melt the medication and carrier. The melted substance was poured onto porcelain tile to set before cooling in an ice bath. The prepared solid dispersions were 80# filtered, ground, and stored in a desiccator.

Preparation of physical mixture and drug content uniformity:

The desired drug/carrier's ratio (as specified) was achieved by softly grinding the medicine

paracetamol and carriers (PEG 4000, PEG 6000, and urea) in a mortar for 2 minutes. The powder was then run through sieve no. 80. The finished product was kept in a desiccator for subsequent examination. Using a solid dispersion of 100 mg equivalent of paracetamol in a pH 5.8 phosphate buffer as the solvent, the homogeneity of the drug content was assessed. The estimation was carried out at 243nm in a UV/Visible spectrophotometer.

Physical characterization and saturation solubility study: [24][25]

In conical flasks containing 10 ml of distilled water, the surplus formulations (PMs and SDs) were added. The conical flasks were then shaken on a rotary shaker for 48 hours at 37°C. Afterward, the flasks were filtered and eliminated. Following the proper dilution with distilled water and comparison with the solubility of pure drugs, suitable aliquots were taken out of the filtered solution and examined for the drug content.

FTIR study of pure drug and all preparations:

To prepare the pellets for FT-IR analysis, potassium bromide (KBr) was used for all formulations including paracetamol. The pellets were tested using an FT-IR instrument. FTIR Perkin ElmerGermany's Spectrum 1000 spectrometer for collecting infrared spectra

Drug content analysis:

Accurately weighed preparations equivalent to 20 mg were transferred to a 100 ml volumetric flask and dissolved in phosphate buffer pH 5.8. Phosphate buffer pH was used to fill the capacity 5.8 is satisfactory. The absorbance of the aforementioned solution was measured at 243 nm using the appropriate blank solution following the proper dilution. Using a calibration curve, the paracetamol drug content was determined.

In vitro release studies:

For dissolution investigations, a sample that was precisely weighed was taken. At predefined intervals, sample aliquots were taken out and used to measure the absorbance at 243 nm with phosphate buffer pH 5.8 as the dissolving media to check for drug release. Every time a volume was withdrawn, the same volume of fresh medium was substituted.

Drug content analysis:

There is a drug content that ranges from 95.72% to 107.63%. All of the PMs and SDs had substantial drug concentration and had small standard deviations of the outcomes. There is evidence that the medication is uniformly disseminated throughout the powder mixture. As a result, it appears that the procedure utilised in this work to create SDs can be repeated.

In vitro dissolution study:[26]

For the purpose of choosing the most appropriate carriers, the formulation of a solid paracetamol dispersion with several carriers, such as PEG 4000, PEG 6000, and urea, was examined. These carriers were discovered to hopeful since they underwent no chemical change while the solid dispersion was being

prepared. The solubility rate of paracetamol in pH 5.8 phosphate buffer increased noticeably when it was solidly dispersed with carriers PEG 4000, PEG 6000, and urea.

The amount of paracetamol that was dissolved increased with the ratio of carriers, and the T50% and T80% values were lowest with the SDs of urea (i.e., 1:1:1:5). The ratio of paracetamol: PEG 6000 (SD6) exhibited (1:5) maximum above other formulations, demonstrating that a higher concentration of matrix created with PEG 6000 in the ratio 1:5 improved the dissolution Rate.

Characterization of Paracetamol raw powder:[27]

• Melting point:

The capillary tube method, which satisfies the standards of the BP and USP, was used to determine the melting point of paracetamol. A capillary glass tube with one side sealed was filled with enough paracetamol powder to create a compact column of (4-6) in height (mm). The melting point, which is the temperature at which the final solid drug particle in the tube transitioned into liquid phase, was measured after the tube was placed within an electrical melting point equipment and the temperature was steadily raised.

• Determination of Paracetamol λ_{max} :

Because they are typically aromatic or have double bonds in their structures, the majority of medications absorb UV light in the range (200 - 400 nm).

The stock solution of paracetamol in ethanol (0.1 mg/ml) was made and appropriately diluted then scanned using a UV-visible spectrophotometer to determine the drug's maximum concentration

• Calibration curves of Paracetamol:

The calibration curve for paracetamol in ethanol was created by creating serial dilutions from the stock solution at various concentrations (1, 2, 3, 10, 20, 30, 40, and 50 g/ml). At the expected max, the prepared samples underwent spectrophotometric analysis. Each sample's measured absorbance was plotted against concentration. Additionally, the calibration curves for paracetamol in 0.1N HCl were created by making serial dilutions from the stock solution (0.01 mg/ml) at the same max at various concentrations (1, 2, 3, 5, 6, 7, 8, and 10 g/ml).

• Preparation of Paracetamol emulsion formulas:

Formulae of paracetamol O/W emulsion with the codes (B1-B7) were created using various types and ratios of oils, constant drug concentration (250mg/5ml), and surfactant.

The overall preparation process can be summed up as follows:

1. In the mortar, dissolve 1 g of paracetamol in the amount of oil indicated (with trituration).
2. Include 0.2 mL of tween 20. (emulsifier).
3. Gradually introduce water (as portions).
4. Pour the mixture into a graduated cylinder (with a stopper), shake it, and then pour 20 mL of D.W. into the container.

To achieve the ideal ratio, the surfactant proportions (0.25–10%) were also change.

➤ Characterization of Paracetamol emulsion formulas:

• Visual inspection:

The following criteria may be used for visual assessment of emulsions: not obvious, no oil separation, no phase separation, practically free of visible particles, no turbidity or precipitation, and colour change of no more than one degree.

• Assay of drug loading:

A suitable organic solvent, such as ethanol, is added to the specified volume (5ml) of the chosen paracetamol emulsion, followed by sonication. The filtered sample is then measured spectrophotometrically at the predetermined maximum.

• Dissolution test:

Using type II USP apparatus (Paddle method) at temperature (37 °C) and stirring, accurately measured volumes of paracetamol emulsion and commercially available paracetamol suspension (250mg/5ml) were carefully introduced into the dissolution media (500ml of 0.1N HCl). Speed (25 rpm) (25 rpm). Five millilitres of samples were routinely removed from a fixed location in the vessel and replaced with an equivalent amount of fresh 0.1N HCl solution every so often (not for more than 30 minutes). The withdrawn samples were filtered, appropriately diluted, and spectrophotometrically examined at a maximum wavelength of 243 nm.

IV. RESULT AND DISCUSSION

1. Characterization of Paracetamol raw material:

4.1.1 Melting point determination:

Pure Paracetamol powder's observed melting point ranged from (169–171 °C). The stated sample result was within the reference limit (10), proving the paracetamol powder's purity.

4.1.2 Determination of Paracetamol λ_{max} :

The spectrums displayed in figure were obtained by scanning the stock solution of paracetamol in ethanol in the UV region between 200 and 400 nm (6).

When paracetamol was dissolved in ethanol, its maximum UV wave length was 243 nm, which is about the reference point.

Prospects for the Dosage Form of Paracetamol Emulsion:[28][29][30]

It is commonly known that paracetamol (acetaminophen) is a top non-prescription antipyretic analgesic medicine. New formulations to accomplish rapid absorption for a quick onset of action and delayed absorption to lengthen the duration of action for regular long-term dosing are likely to be among the developments of the future. Rectal administration also needs better dose formulations. The use of paracetamol as an adjuvant to postoperative analgesic and for fever

control in the intensive care setting has been significantly expanded because to the availability of intravenous paracetamol. Only a few nations currently offer intravenous paracetamol, but it appears certain that it will eventually be offered much more broadly. In the small percentage of overdose patients who appear too late for successful N-acetylcysteine antidotal treatment, liver failure may still result from the overuse of paracetamol as a popular self-injury agent. The research of the molecular mechanisms underlying paracetamol hepatotoxicity is receiving a lot of attention, and it is believed that future developments may allow for the prevention of liver failure in all patients, regardless of presentation delays. The processes underlying paracetamol's therapeutic effects and its impact on the various isoforms of cyclo-oxygenase are also of great interest.

V. CONCLUSION

The fundamentals of emulsions are unquestionably successful, and their fundamental understanding of physicochemical qualities and stability is what allows them to develop and produce superior pharmaceutical emulsions with skill and efficiency. Based on the findings of our investigation, we determined that the same concentration and quantity of the active ingredient in paracetamol in the emulsion dosage form as in the suspension dosage form, as well as a higher rate of dissolution than in the suspension, make the emulsion dosage form a successful concept for production. It may, however, have more stability issues and a shorter shelf life than suspension, which could be prevented by including the right excipients in the recipe.

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