# FORMULATION AND EVALUATION OF RUTIN TRIHYDRATE LOADED MICROSPONGES

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## ABSTRACT

The aim of the present study was to formulate rutin trihydrate loaded microsponges through quasi-emulsion solvent diffusion technique. Rutin trihydrate is a quercetin glycoside which possess effective antioxidant property with proved anti-aging effects but it is BCS class II drug. Ethyl cellulose served as the release-retarding polymer, while polyvinyl alcohol (PVA) functioned as the emulsifying agent in microsponges preparation. Formulations were prepared in varying ratios of drug: ethyl cellulose and stirring speed to assess the impact of composition on micro sponge properties. The optimized F9 formulation of microsponges prepared with drug: polymer ratio of 1:3 and stirring speed of 2000 rpm has shown sustained drug release of 99.40% up to 8 hrs. DSC & FTIR study confirmed good compatibility between drug and excipients. These results indicate that Rutin trihydrate loaded microsponges, formulated with ethyl cellulose and PVA, are a promising system for sustained topical anti-aging drug delivery system.

**Key Words:** Rutin Trihydrate, Microsponges, Quasi-Emulsion Solvent Diffusion Technique, ethyl cellulose, Anti-Aging.

## INTRODUCTION:

Microsponges, a novel drug delivery system, have emerged as a promising solution to address the challenges associated with poorly soluble drugs. This microsponge technology was developed by Won in 1987. The size of the microsponges generally ranges from 5 to 300 µm. These are microscopic, spherical, porous structures composed of polymeric materials offer a unique platform for enhancing the therapeutic efficacy of various medications, particularly those classified as BCS Class II under the Biopharmaceutics Classification System [1].

Microsponges are highly efficient drug delivery systems that prolong drug action for up to 12 hours while maintaining controlled release. Their large surface area enhances trapping capacity, and they are non-toxic, hypoallergenic, and stable against physical, chemical, and thermal factors. By increasing the solubility and bioavailability of drugs and decreasing toxicity, they improve therapeutic outcomes and prevent substance accumulation on the skin. They can easily entrap immiscible products and absorb oily skin secretions which actually enhances skin shine leading to greater consumer acceptability through improved tolerance and decreased irritability [2].

Rutin trihydrate is a naturally occurring flavonoid glycoside widely distributed in many plants such as Fagopyrum-esculentum (Buckwheat), Citrus species, & Sophora japonica. Chemically, it is known as quercetin-3-0-rutinoside, Rutoside, Vitamin P, and it consisting of the flavanol aglycone quercetin bound to the disaccharide rutinose. Rutin trihydrate exhibits multiple biological activities, including antioxidant, anti-inflammatory, Antimicrobial, Antifungal, Anti-cancer, hepatoprotective, & cardioprotective, Neuroprotective effects. Rutin trihydrate has Anti-inflammatory, Antibacterial and Anti-oxidant property, therapeutically useful in conditions such as Anti-Aging [3,4].

Rutin trihydrate belongs to BCS class II with poor water solubility and poor bioavailability [5]. The present study was designed to develop Rutin trihydrate microsponges with higher drug entrapment efficiency and lower particle size, to enhance the penetration deeper into the skin layers. The effects of variables including the drug: polymer ratio and stirring speed were examined.

**MATERIALS AND METHODS:**

Rutin trihydrate was purchased from Yarrow chem. Ltd., Mumbai, Poly vinyl alcohol from Yarrow chem. Ltd., Mumbai, Ethyl cellulose from Yarrow chem. Ltd., Mumbai, Dichloro methane from S.d.fine chem. Ltd., Mumbai.

1. **Preparation of Rutin trihydrate microsponges:**

Nine batches of microsponges F1-F9, were formulated using varying ratios of drug: polymer and stirring speed, as detailed in table 1. The quasi-emulsions solvent diffusion method was employed for the preparation Rutin trihydrate of microsponges. Rutin trihydrate and ethyl cellulose (EC) were dissolved in dichloromethane and ethanol to form the organic phase. Separately, polyvinyl alcohol was dissolved in distilled water to prepare the aqueous phase. The organic phase was added dropwise into the aqueous phase under magnetic stirring. Stirring was maintained for 3 hrs at room temperature to facilitate solvent evaporation

and microsponge formation. The dispersion was filtered using 0.45 µm Whatman filter paper, washed with distilled water, and dried at room temperature for 24 hours. The microsponges were then stored in desiccator to preserve dryness and prevent moisture absorption [6,7].

**Table: 1- Formulation Table of Rutin Trihydrate Microsponges:**

| **Formulation Code** | **Ingredients** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Internal Phase** | | | | **External Phase** | | |
| | Rutin trihydrate | Ethyl cellulose | DCM | Ethanol | PVA | Distilled water | Speed |
| F-1 | 0.5 | 0.5 | 5 | 5 | 1 | 200 | 1000 |
| F-2 | 0.5 | 1 | 5 | 5 | 1 | 200 | 1000 |
| F-3 | 0.5 | 1.5 | 5 | 5 | 1 | 200 | 1000 |
| F-4 | 0.5 | 0.5 | 5 | 5 | 1 | 200 | 1500 |
| F-5 | 0.5 | 1 | 5 | 5 | 1 | 200 | 1500 |
| F-6 | 0.5 | 1.5 | 5 | 5 | 1 | 200 | 1500 |
| F-7 | 0.5 | 0.5 | 5 | 5 | 1 | 200 | 2000 |
| F-8 | 0.5 | 1 | 5 | 5 | 1 | 200 | 2000 |
| F-9 | 0.5 | 1.5 | 5 | 5 | 1 | 200 | 2000 |

**2. Evaluation of Rutin trihydrate microsponges [8-13]:**

**a) Production/Percentage yield:**

The production yield of the micro sponges can be obtained by calculating accurately the initial weight of the raw materials and the last weight of the micro sponge. The dried micro sponges of each batch are weight separately and percentage yield is calculated by using following equation.

$$\textbf{percentage yield} = \frac{\text{Practical mass of microsponges}}{\text{Theoritical mass (drug+polymer)}} \text{x}100$$

**b) Particle Size:** The particle size distribution is evaluated with the help of optical or electron microscope. The size of the particles affects the consistency of the formulation and its stability. Particles larger than 30µm can impart grittiness and hence particles of sizes between 10 and 25µm are preferred in topical preparations. Particle size was determined using optical

microscopy at 10x and 40x. The micro sponges were placed on glass slide and observed under optical microscope. The size of 50-100 micro sponges was measured.

**c) Drug Excipient compatibility studies:**

**1) Fourier Transform Infrared Spectroscopic Analysis (FTIR) Studies:**

FTIR spectroscopy was done to identify the functional groups present and interaction between drug and excipients. FTIR spectra were developed for pure drug and formulation by potassium bromide, the disk was prepared by compression of 10 tons pressure for mins. Finally, disk was placed in a holder of FTIR machine and a spectrum was recorded from 4000cm $^{-1}$ to 5000cm$^{-1}$ band width.

**2) Differential scanning calorimetry (DSC) studies:**

DSC is a thermos analytical technique gives an insight into the melting behaviour of substance. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The pure drug and formulations were subjected to DSC studies using Perkin Elmer Pyre 1 series DSC equipment (Massachusetts USA) samples were sealed in 40 μL alumina pans an identical empty pan was used as a reference; all samples were scanned at 5°C/min with a 20 ml/min nitrogen purge from 20-320°C.

**d) Entrapment efficiency:**

Entrapment efficiency is the content of core material effectively entrapped in a formulation. It can be measured by an indirect method in which micro sponge suspension can be centrifuged at 2000 rpm for 10 min. The supernatant obtained can be suitably diluted with suitable solvent and the amount of free drug present in supernatant can be quantified using UV– Visible spectroscopy. The drug entrapment efficiency can be calculated using the following formula.

$$\textbf{Entrapment Efficiency} = \frac{\text{Actual drug content in microsponges}}{\text{Theoritical drug content}} \text{X}100$$

**e) Drug Content:**

50 mg of drug-loaded micro sponges are dissolved in 50 ml of pH 6.8 phosphate buffer. The solution is shaken thoroughly and filtered. The absorbance of the resulting solution is then measured using a UV–Visible spectrophotometer at 264 nm wavelength to calculate the drug content.

$$\textbf{Drug Content} = \frac{\text{Practical drug content}}{\text{Theoritical drug content}} X100$$

**f) *In-vitro* Drug Release studies:**

*In-vitro* release studies have been carried out using dissolution apparatus USP Type-I equipped with a modified basket consisted of 5µm stainless steel mesh. 900ml of phosphate buffer pH 6.8 was used as the dissolution medium, temperature was maintained at 37 ± 0.5°C and the rotation speed was set at 75 rpm. Sample aliquots were withdrawn from the dissolution medium and analysed by suitable analytical method (UV-spectrophotometer) at regular intervals of time.

**RESULTS AND DISCUSSION:**

Rutin trihydrate of microsponges were successfully prepared by quasi-emulsions solvent diffusion method. The prepared micro sponges were evaluated for the parameters like production yield, particle size, Entrapment Efficiency and drug content. The results of evaluations are shown in table no.2.

**Table no.2. Evaluation Results of Rutin trihydrate micro sponges**

| Formulation code | Production yield (%)* | Particle size (µm) | %EE* | % Drug Content* |
|---|---|---|---|---|
| F1 | 75.80 ± 0.027 | 10.62 | 80.2 ± 0.074 | 62.82 ± 0.049 |
| F2 | 88.34 ± 0.038 | 16.38 | 90.12 ± 0.068 | 69.50 ± 0.058 |
| F3 | 92.57 ± 0.025 | 19.95 | 93.60 ± 0.080 | 72.3 ± 0.060 |
| F4 | 65.50 ± 0.058 | 8.76 | 77.55 ± 0.068 | 60.59 ± 0.052 |
| F5 | 83.76 ± 0.026 | 14.5 | 89.50 ± 0.047 | 67.23 ± 0.054 |
| F6 | 94.6 ± 0.062 | 21.6 | 98.7 ± 0.083 | 75.20 ± 0.063 |
| F7 | 73.2 ± 0.034 | 9.82 | 79.40 ± 0.065 | 61.46 ± 0.056 |
| F8 | 82.76 ± 0.078 | 12.41 | 81.30 ± 0.077 | 63.98 ± 0.057 |
| F9 | 91.20 ± 0.086 | 16.7 | 91.20 ± 0.087 | 72.21 ± 0.068 |

*n=3, All the values are calculated as mean ± SD

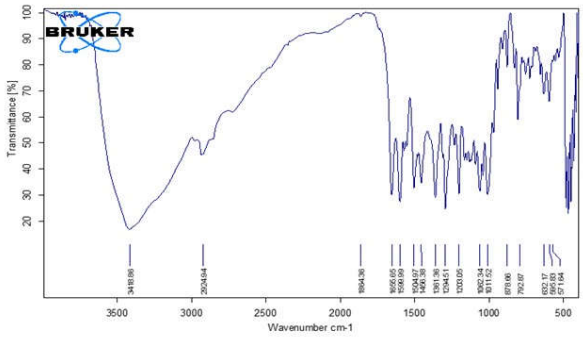
The production yield and Entrapment Efficiency results were found to be in the range of 65.5% to 94.6% and 77.55% to 98.7% respectively. The significantly higher values can be attributed to the low solubility of Rutin trihydrate in the external aqueous phase during the microsponge preparation. Adding more EC during the preparation of microsponges dramatically enhanced the production yield and Entrapment Efficiency of the microsponges because higher at level of EC, a larger amount of this polymer surrounded the drug units, resulting in encapsulating a larger amount of the drug. The drug content in microsponges ranged between 60.59% to 75.20%. Higher stirring speed decreased production yield because the heightened turbulence causes the polymer to adhere to the vessel walls, rather than forming microsponges.

The particle size of the prepared micro sponges was determined by optical microscopy. The microsponges were observed to be spherical and discrete under the microscope sponges. The

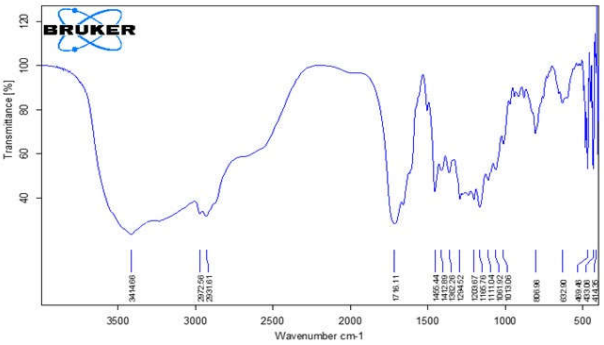
average particle size of the microsponges was found to be in the range of 8.76 to 21.6 µm. Increasing the concentration of EC produces microsponges with a larger size may be due to augmentation in the viscosity of the internal organic phase, which could in turn restrict the division of the globules into smaller particles. Higher agitation speeds created higher shear forces, resulting in smaller, finer microsponges.

### 7.1.3. DRUG EXCIPIENT COMPATABILITY STUDIES

#### a) FTIR STUDIES:




**FTIR Spectrum of Rutin trihydrate**




**FTIR Spectrum of Formulation**

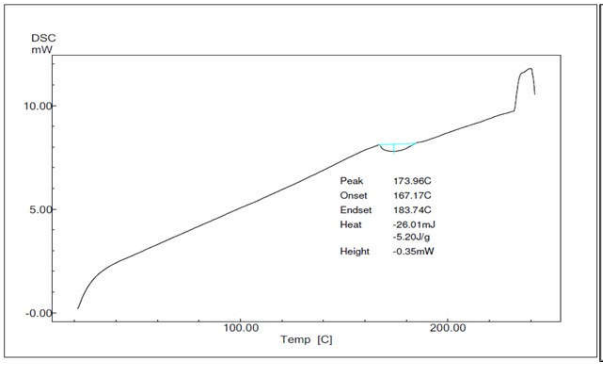
**Table no.7.2 FTIR Spectrum of Rutin trihydrate**

| Type of bond | Actual frequency range ($cm^{-1}$) | Observed frequency in pure drug spectra ($cm^{-1}$) | Observed frequency in Formulation spectra ($cm^{-1}$) | Functional group Conformation |
|---|---|---|---|---|
| O - H Streaching | 3200 – 3600 | 3418.86 | 3414.66 | Phenol |
| C - H Streaching | 2900 – 3100 | 2924.94 | 2931.61 | Alkane |
| C = O Streaching | 1650 -1665 | 1655.65 | 1655.44 | Ketone |
| C = C Streaching | 1500 – 1600 | 1599.99 | 1599.99 | Carbonyl |
| C - O – C Streaching | 1000 – 1300 | 1294.51 | 1294.52 | Ether |
| O - H Bending | 1300 – 1500 | 1361.36 | 1362.26 | Phenol |

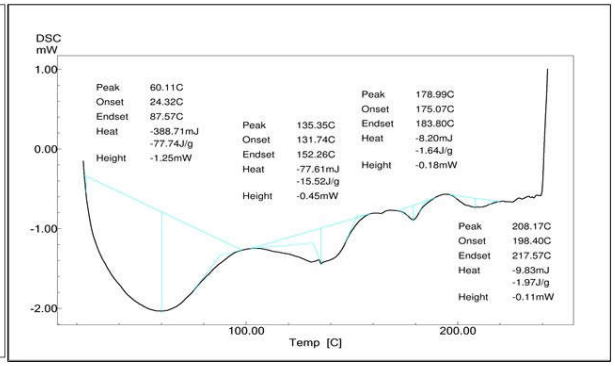
The characteristic peacks obtaind from FTIR spectrum of pure drug and formulation are depicted in figure no 1. The pure drug was analysed using FTIR, the peaks were observed at 3418.86, 2924.94, 1655.65, 1599.99, 1361.36, 1294.51 $cm^{-1}$ frequencies which were indicating that presence of O - H str, C - H str, C = O str, C = C, O - H ben, C - O - C confirming the drug

is pure rutin trihydrate. FTIR studies shows that drug and polymer were compatible with each other and there was no interaction found between them.

**b) DSC Studies:**




**DSC thermogram of Rutin trihydrate**




**DSC thermogram of Formulation**

DSC thermogram of pure drug Rutin trihydrate and formulation are shown in the figure no.2. An endothermic peak at 183.74 ºC was seen in the thermogram of pure drug, indicating the drug's melting temperature and reflecting its purity. Similar peak was observed at 198.40 ºC in thermogram of formulation, along with two other peaks at 135.35 ºC and 178.99 ºC related to the melting points of Ethyl cellulose and PVA respectively. This indicates absences of drug-excipient interaction.

***In-vitro* Drug Release studies:**

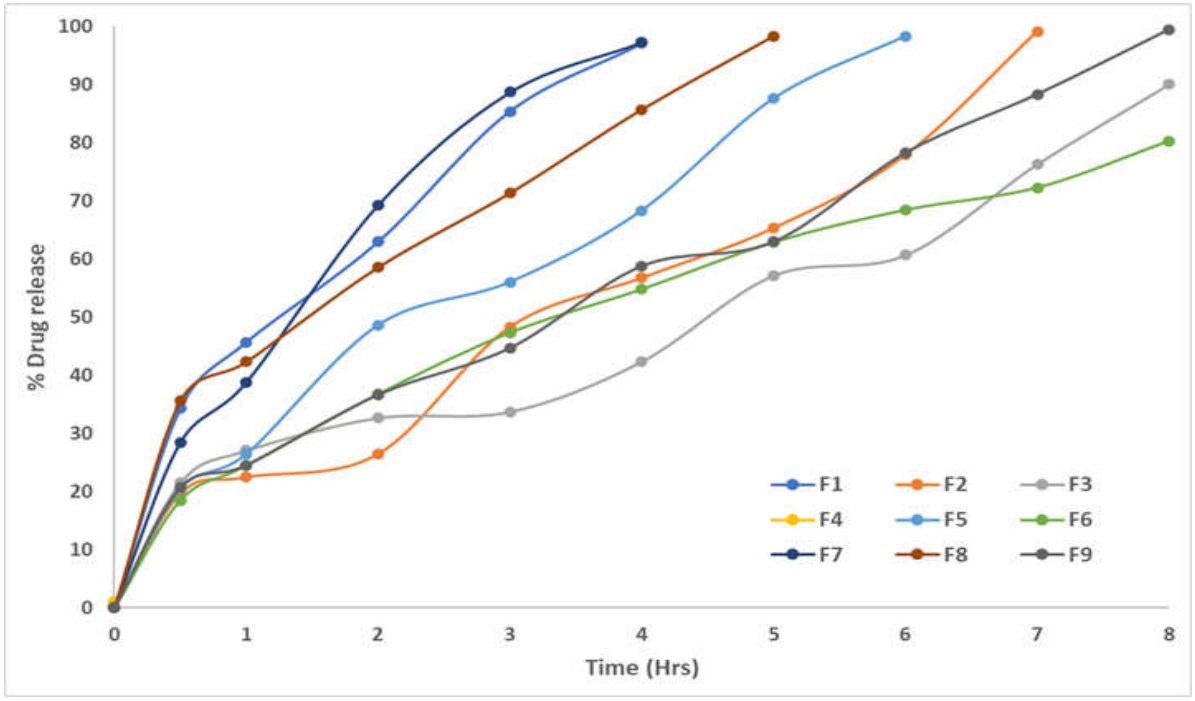



**Fig no.3: *In-vitro* Drug Release Plots of Rutin trihydrate micro sponges**

The *in-vitro* drug release profile of few rutin trihydrate micro sponges showed a sustained release of the drug for 8 hrs as illustrated in fig no. 3. The formulation F-9 prepared with drug: polymer ratio of 1:3 and stirring speed of 2000 rpm has shown sustained drug release of 99.40% up to 8 hrs. The formulation F3 and F6 sustained the drug release up to 8 hrs but with lesser % drug release.

The release from micro sponges was found to be fast over the initial time period, followed by prolonged drug release over a period of 8 hrs. The initial release of the drug may be due to the release of rutin trihydrate microsponges surface, whereas at the later stage, rutin trihydrate may be constantly released from the core of microsponges, which is responsible for the prolonged release. Increasing the amount of polymer causes a significant decrease in the drug release percentage. This is due to the fact that increasing the drug: polymer ratio increased the size of microparticle there by decreasing the effective surface area available to interact with the releasing medium and decreasing drug release. Faster stirring speed produced smaller particles, which enhances the surface area and resulting in a faster, more controlled drug release profile.

**CONCLUSION:**

Rutin trihydrate microsponges were successfully prepared using the quasi-emulsion solvent diffusion method with different ratios of drug: polymer (ethyl cellulose) and stirring speeds. The average particle size of Rutin trihydrate formulations were within the range of microsponges. With the increase in the concentration of polymer, the drug was surrounded by the thick polymer matrix retarding the diffusion of drug. Among all the microsponges, F-9 formulation prepared with drug: polymer ratio of 1:3 and stirring speed of 2000 rpm F9 showed the best performance, demonstrating good production yield, particle size, high entrapment efficiency, drug content and exhibited sustained drug release of 99.40% up to 8 hrs. FTIR and DSC studies showed good compatibility between the drug and excipients. Therefore, the developed rutin trihydrate-loaded microsponge can be further formulated as topical formulations like gels, creams, lotions and ointments for effective treatment of Anti-aging.

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