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Preparation And Evaluation Of Eudragit Loaded Curcumin Microspheres

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Abstract

Curcumin a natural compound which ishighly potent, nontoxic, bioactive agent found in turmeric and has been known for centuries as a household remedy to many ailments. Among the potent anticancer agents, curcumin has been found to be very efficacious against different types of cancer cells. The main disadvantage that it has low aqueous solubility and poor bioavailability. Hence, the curcumin loaded microspheres were prepared by solvent evaporation method using Eudragit S 100. Microspheres of different ratios were prepared and evaluated forloading efficiency, process yield, particle size, zeta potential, in vitro drug release, and stability studies. The polymer-based microspheres have a particle diameter ranging approximately 28μm and a zeta potential 0.2 mV. There was a steady increase in the entrapment efficiency on increasing the polymer concentration in the formulations. No appreciable difference was observed in the drug content and in vitro release of product during 6 months in which microspheres were stored at 5°C and at room temperature. According to the data obtained, thispolymer-based delivery system opens new and interesting perspectives as drug carriers.

Keywords*: Microspheres, Eudragit S 100, Curcumin,Solvent evaporation technique.*

1. INTRODUCTION

Natural compounds obtained from plants have a capability of getting attention from the scientific community, because of their ability to check and prevent the onset and progress of cancer and also possess the several medical applications. Among them, curcumin is a natural polyphenol compound found in the rhizome of Curcuma longa L (CUR)(Zingiberaceae). The plant native is from India and South-East Asia. Turmeric is a perennial herb, up to 1.0 m in height.India is the largest producer of turmeric. It has a wide range of pharmacological activities including antioxidant, antitumor, anti-inflammatory and antiamyloid, anti-cancer, anti-diabetic properties. However, the clinical deployment of this promising molecule has been limited by its poor water solubility i.e., less than 1 μg/ml, low oral bioavailability and rapid metabolism. Several formulation strategies have been developed for the improved outcome of CUR. To enhance the potency of CUR a number of alternative DDS have been investigated, which includes liposomes, polymer-based micro/nanoparticles and polymeric micelles. Among this the polymer-based microspheres have the potency to sustain the release of hydrophobic CUR. This colloidal drug delivery systems have been examined for their use in tumour therapy.

The poor solubility of CUR inwater is the only factor that limits the use of free curcumin for cancer therapy, which in turn limits its systemic bioavailability.[1] Polymer-based microsphere drug delivery is investigated as this delivery route is known to overcome many factors associated with the delivery of free drugs. Eudragit possesses some ideal properties of a polymeric carrier for microspheres such as biocompatibility, biodegradability, non-toxicity, and low cost. The Eudragit polymers due to their unique properties, have made significant contributions to many types of formulations. Hence, the main aim of the work is to formulate eudragit microspheres containing Curcumin by solvent evaporation method, and to evaluate its physicochemical characteristics such as shape, particle size, zeta potential, drug loading capacity and in vitro release characteristics.[2]

2.MATERIALS AND METHODS

2.1.Materials

Curcumin was provided as gift sample from Natural remedies, Bangalore.

2.2.Preparation of microspheres

Microspheres were prepared by solvent evaporation technique using the quantity of drug and other excipients as given in the Table 1. The polymer (0.1-0.5gm) and the drug (0.1gm) were co-dissolved in a water immiscible organic solvent (10 mL) was poured into 100 mL of water containing PVA (0.25%). Kept under mechanical stirring with a three-blade propeller (REMI- RQ 122). Then, stirring was maintained for 2 hrat 1200 rpm, leading to a total evaporation of the solvent (chloroform). The microspheres were then recovered by filtration, washed with deionized water and dried in a desiccator for the next 48 hrs.[3]

2.3.Characterization of prepared microspheres

2.3.1.Particle size studies

By using an optical microscopy method, the particle size of microspheres was determined. Approximately, 100 microspheres were counted using a calibrated microscope.[4]

2.3.2.Drug polymer interaction (FTIR) study

FTIR spectroscopy was performed on Shimadzu IR spectrophotometer, model 840, Japan, to check drug polymer interaction and stability of drug. FT-IR study was carried on pure curcumin, eudragit and physical mixture of curcumin.[5]

2.3.3.Drug entrapment efficiency

Microspheres equivalent to 5 mg curcumin were crushed using a glass mortar and pestle. Then, they were suspended in 25 ml of phosphate buffer pH 7.4. After 24 hrs, the solution was filtered and 1 ml of the filtrate was diluted 10 times and analysed for the drug content by UV-visible spectrophotometer at 426 nm. The drug entrapment efficiency was calculated using the following formula:[6]

Entrapment efficiency = (actual drug content/theoretical drug content) ×100.

2.3.4.Surface morphology study(SEM)

The SEM analysis was carried out using a scanning electron microscope. Prior to examination, samples were mounted on an aluminum stub using a double-sided adhesive tape and making it electrically conductive by

coating with a thin layer of gold (approximately 20 nm) in vacuum. The scanning electron microscope was operated at an acceleration voltage of 5 kV and resolution of 3400.[7,8]

2.3.5.DSC study

The excipients were mixed individually with the pure drug in a ratio of 1:1, and the DSC study was performed. DSC of the bulk drug curcumin was performed using DSC instrument (Perkin Almer, U.S.A.) for measurement of the heat loss or gain resulting from the physical or chemical changes within a sample as a function of temperature. About 6-7 mg of the individual component or drug excipient combinations were weighted in aluminium DSC pans, and hermetically sealed capsules were prepared with aluminium lids. An initial ramp was used to jump the temperature to 40°C and then a constant heating rate of 10°C/minutes was used up to 300°C under nitrogen atmosphere.[9]

2.3.6.*In vitro* drug release study

The *in vitro* release of curcumin microspheres was done in phosphate buffer pH 7.4 for 12 hrs in USP-I Basket-type dissolution apparatus at a temperature of 37°0±0.5°C. The volume of the dissolution medium was 900 ml and agitated at 100 rpm throughout the study. Microspheres equivalent to 100 mg of drug were taken and they were transferred to the basket. The sample was taken in every 1 hour for 12 hrs. To maintain the sink condition, the samples withdrawn were replaced with an equal volume of dissolution medium. After suitable dilution, samples were analysed by UV-visible spectrophotometer at 426 nm.[10,11]

2.3.7.Accelerated stability studies of microspheres

Stability studies were performed according to ICH guidelines. The stability study was carried out using the batch F2. Formulation F2 was divided into 3 sets of samples and stored at 5□± 3□C in refrigerator and stored in hot air oven at room temperature for (37 ± 2°C, 65% ± 5% RH) and their % drug content and *in vitro* releases were determined for every 1 month. Similarly, an accelerated stability study was carried out by storing the selected formulation at (45 ± 2°C,75% ± 5% RH) for a period of 3 months. Drug content of all samples were determined by the method as in drug content at 0 month, 3months and 6 months. *In vitro* release study of formulation F2 was also carried at 0 month, 3months and 6 months of storage.[12]

3. RESULTS AND DISCUSSION

3.1.Drug excipient compatibility study using FT-IR

FT-IR spectrum of drug, polymer and drug-polymer mixture is shown in Figs. 1, 2 and 3 respectively. From the FT-IR spectra of drug and drug polymer mixture, it was found that drug and polymer are compatible with each other.

3.2.Drug excipient compatibility study using DSC

When comes to preparation of a drug formulation, it becomes necessary to evaluate the interactions between the drug and the polymer. The DSC thermogram of pure curcumin shows a sharp endothermic peak at 182°C which corresponds to its melting point. The thermogram of curcumin with Eudragit S 100 shows sharp endothermic peak at 184.63°C. Thus, the thermal data shown in the Figs. 4 and 5 thus,does not show any interaction between the drug and polymer.

3.3.Physico-chemical characteristics

The average entrapment efficiency (%) of curcumin microsphere formulations is shown in Table 2 and was found to be 58.75%, 84.23%, 70.86%, 64.29% and 78.15% in the formulations F1, F2, F3, F4 and F5. The average entrapment efficiency of the formulations increased with increasing polymer concentration. The maximum entrapment efficiency (84.23%) was observed in formulation F2 which is shown in Fig. 6. The change in drug entrapment may be due to poor aqueous solubility and high binding capacity of drug on polymer surface.

3.4.Surface morphology study (SEM)

The microspheres prepared by solvent evaporation method have good spherical shape with smooth surface in its morphology, and the particles were distributed uniformly without forming any clump and it is shown in the Fig. 7. Particle sizes observed in SEM photomicrographs are in the same line as determined by optical microscopic method.

3.5.*In vitro* release of microspheres

Cumulative percentage drug released for F-1, F-2, F-3, F-4 and F-5 after 12 h were found to be 69.70%, 81.58%, 73.39%, 63.14%, 72.23% respectively. F2 formulation which showed maximum drug release. Hence F2 formulation was considered as an ideal formulation. Fig. 8

3.6.Stability studies

The results of drug content of ideal formulation F2 after 6months of stability testing at different storage conditions were shown in Fig. 9. *In vitro* release profiles for the same formulation stored at different storage conditions were also showed in Fig. 10. On comparing this data with the previous data of F2, it was observed that there was a slight decrease in drug content when the formulation was stored at 5□± 3□C, Room temperature and at 45□ ± 2˚C/75% RH.

4. CONCLUSION

In conclusion, F2 formulation containing drug: polymer ratio 1:2 was found to be the best microsphere formulation based on drug content, drug entrapment efficiency, particle size morphology, zeta potential and *in vitro* release. The stability studies were carried out for the selected formulation F2. The stability studies showed that maximum drug content and closest *in vitro* release to previous data was found for F2 stored at 5□± 3□C, Room temperature and at 45□ ± 2˚C/75% RH. Thus,microspheres of curcumin (F2) with ratio 1:2 was found to be spherical, discrete and free flowing and able to control the drug release effectively.

5.Acknowledgements

Authors are thankful to natural remedies for providing the drug as a gift sample for this work.

FIGURES AND TABLES

Table: 1 Formulation details of Eudragit S 100 microspheres of Curcumin

Formulation code	Drug-polymer ratio	PVA (%)	Time (hr)	RPM
F1	1:1	0.25	2	1200
F2	1:2	0.25	2	1200
F3	1:3	0.25	2	1200
F4	1:4	0.25	2	1200
F5	1:5	0.25	2	1200

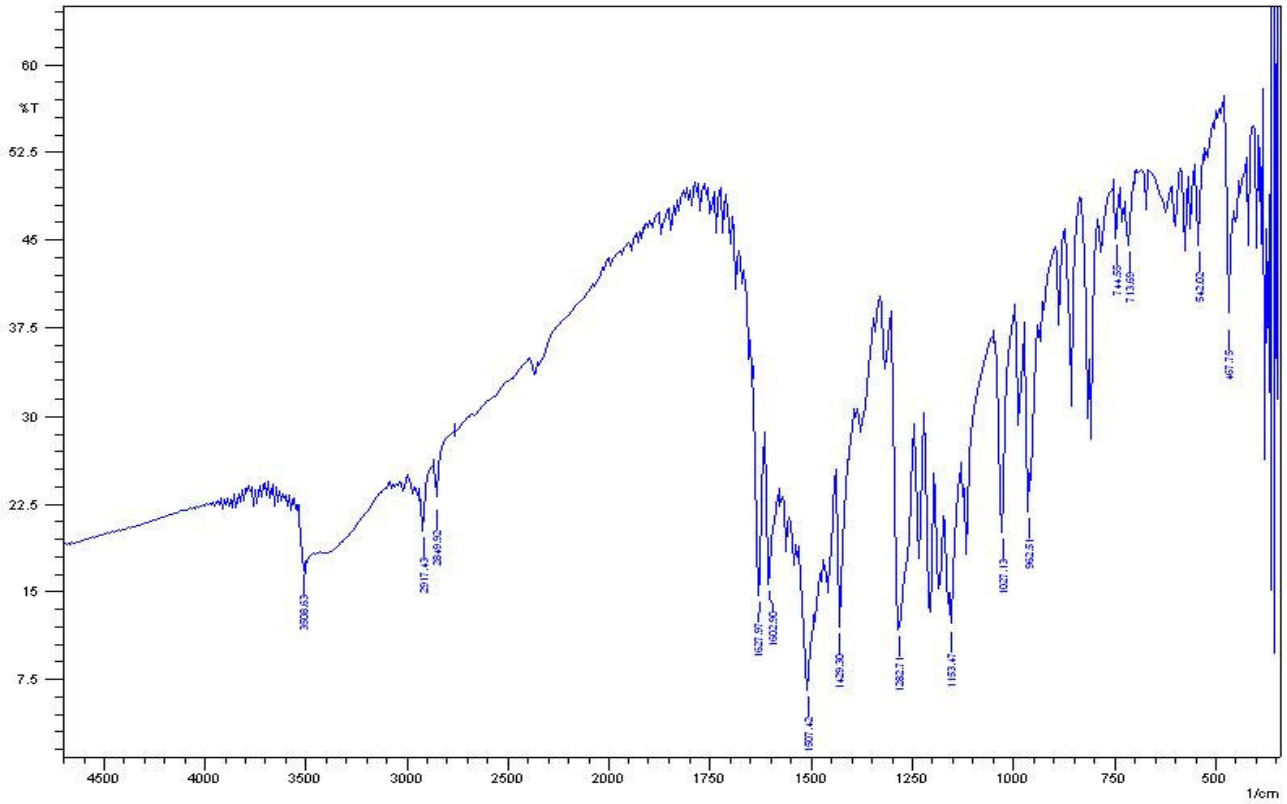

Figure 1: Fourier transform infrared spectra of curcumin

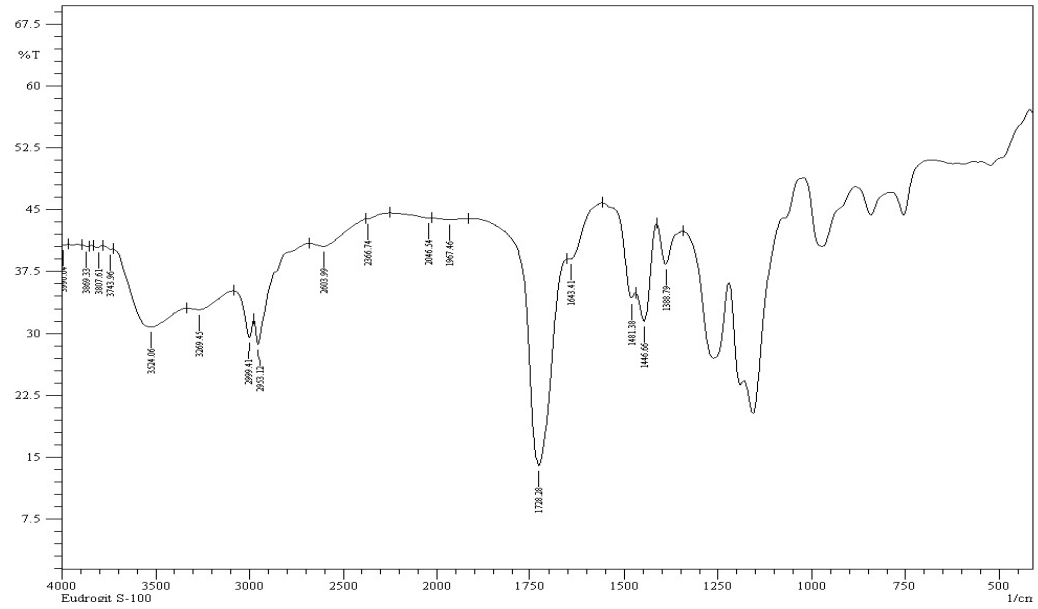

Figure 2: Fourier transform infrared spectra of polymer (Eudragit S 100)

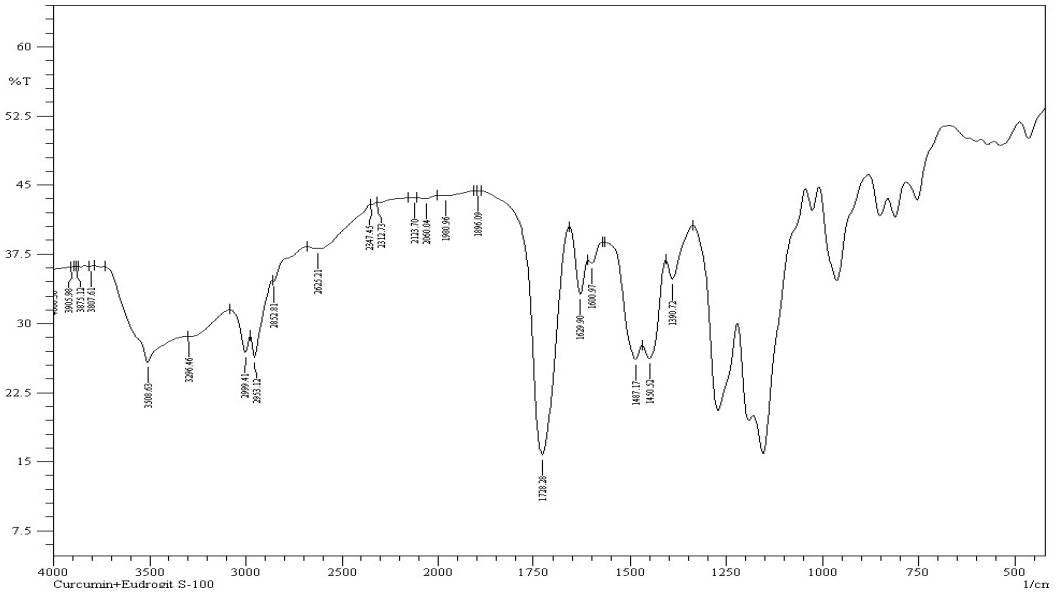

Figure 3: Fourier transform infrared spectra of physical mixture of drug and polymer (Eudragit S 100)

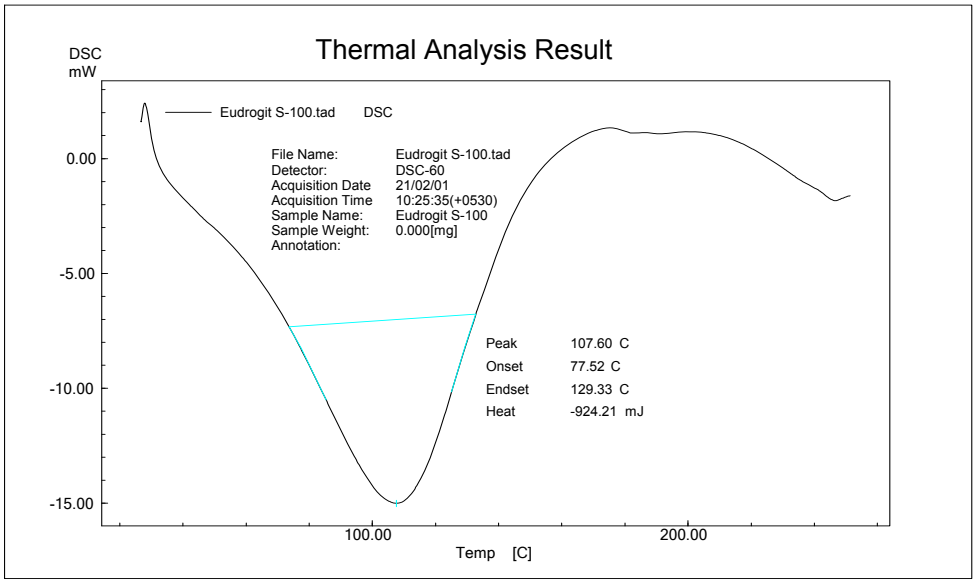

Figure4: Differential scanning calorimetry study of polymer (Eudragit S 100)

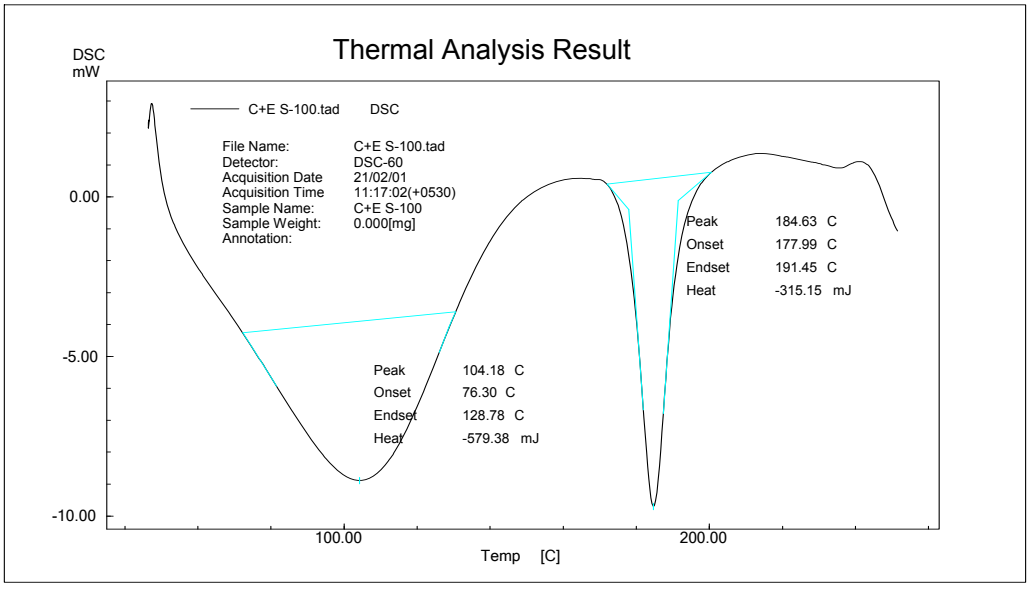

Figure 5: Differential scanning calorimetry study of physical mixture of drug and polymer.

Table 2: Percentage yield, drug content and entrapment efficiency of Formulations F1-F5

Formulation code	%yield	%Drug content	%Entrapment efficiency
F1	56.23	43.65	58.75
F2	83.05	74.16	84.23
F3	71.47	65.22	70.86
F4	62.19	53.54	64.29
F5	72.86	68.92	78.15

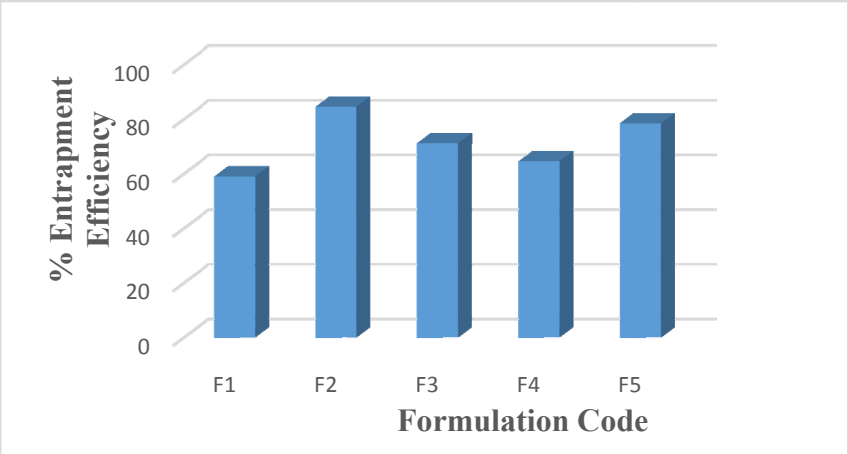

Figure 6: Percentage Entrapment Efficiency of Formulations F1-F5

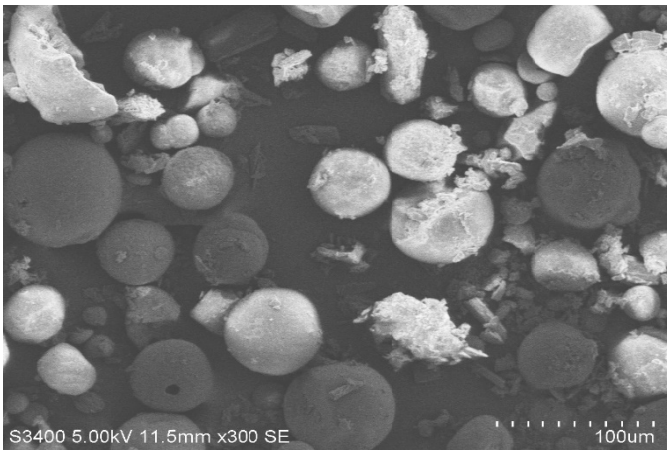

Figure 7: Scanning electron microscopy of curcumin microsphere

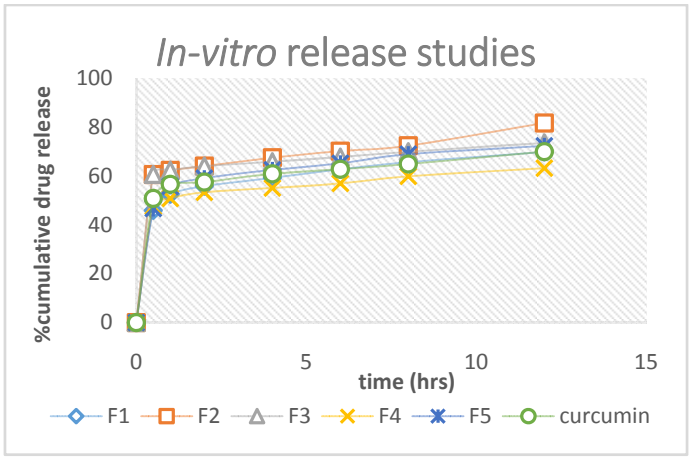

Figure 8: Comparative *in vitro* release profiles of Curcumin microspheres

Table 3: Stability study - % Drug Content of Formulation F2 after three months of storage at 5º± 3ºC, room temperature 37º± 2ºC/65%RH and 45º± 2ºC/75% RH.

Temperature in ºC	% Drug content
5º ± 3º C	87.45
37º ± 2º C/65%RH	86.32
45º ± 2º C/75%RH	79.02

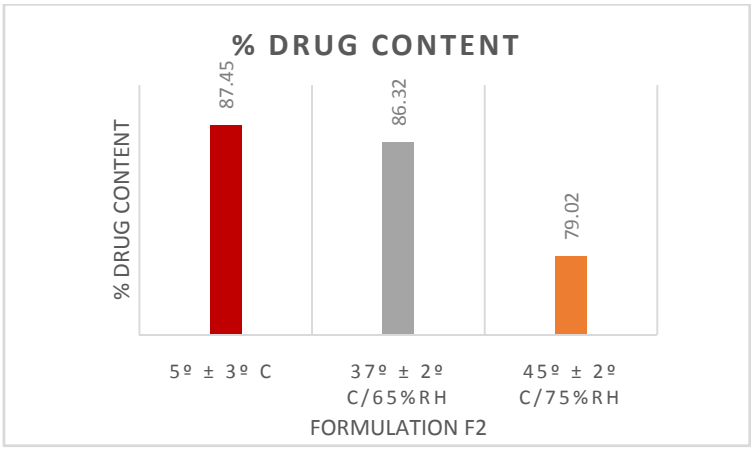

Figure 9: Stability study - % Drug Content of Formulation F2 after three months of storage at 5º± 3ºC, room temperature 37º± 2ºC/65%RH and 45º± 2ºC/75% RH.

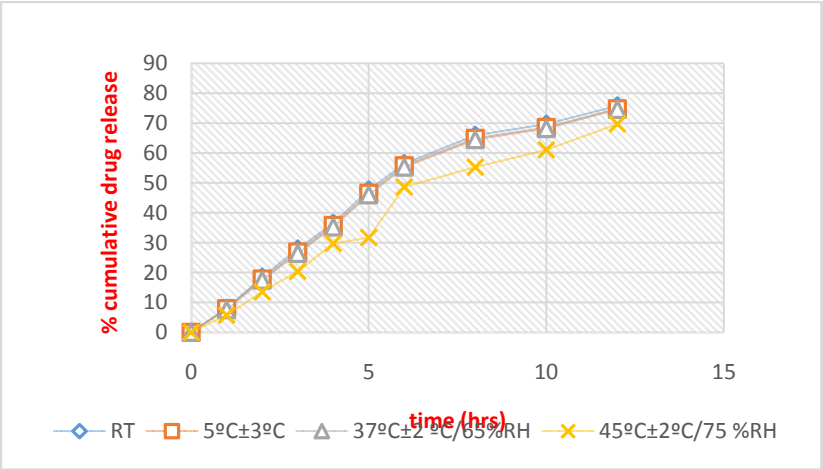

Fig. 10: Stability study - in vitro Drug Release of Formulation F2 after three months of storage at 5º± 3ºC, room temperature 37º ± 2ºC/65% ± 5% RH and 45 ± 2ºC/75% ± 5% RH.

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