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## Original Article

# A study on the effects of different surfactants on morphology and drug release of Repaglinide Microspheres

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### ABSTRACT:

**Objectives:** To rationalize the use of surfactants by preparing Repaglinide Microspheres using two types of Surfactants, Tween 80 and Span 80 and study their effects on different characteristics of the microspheres. **Methods:** The microspheres were produced by emulsion solvent evaporation method, using the Eudragit RS100, Ethylcellulose, Tween 80 and Span80. **Results and discussion:** The microspheres were free flowing in nature. The surfactant concentration was found to be greatly affected the microspheres size distribution and dissolution. Scanning Electron Microscopy was done to study the surface morphology of the microspheres. Results have indicated that the incorporation of hydrophilic surfactant (Tween 80) gave larger microspheres, where as incorporation of the hydrophobic surfactant (Span 80) gave smaller microspheres and hydrophilic surfactant containing microspheres had higher drug release rate compared to hydrophobic surfactant containing microspheres. **Conclusion:** Microspheres containing repaglinide was prepared successfully by using an emulsion solvent evaporation technique.

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## INTRODUCTION

Microspheres play a very important role as particulate drug delivery system because of their small size and other efficient properties. Microspheres are characteristically free flowing solid powders, which consist of proteins or synthetic polymers, which are biodegradable in nature. The solvent- evaporation method of microencapsulation involves the use of emulsification of a solution containing polymer and drug with an additional medium in which the drug and polymer cannot dissolve. Surface active agents play a significant role in microsphere formulation by emulsification. They have the properties of adsorbing to the interface and stabilizing the emulsion droplets by preventing their aggregation [1]. In microencapsulation by solvent evaporation method, surfactants play an important part in the final characteristics of the microcapsules.

Tween 80 (polysorbate 80) and Span 80 (sorbitanmonooleate) are two of the most commonly surfactants used interchangeably by different authors [2]. Release of active ingredients from conventional topical formulations over an extended period is quite difficult. These vehicles require high concentrations of active agents for effective therapy because of their low efficiency of delivery system, resulting into irritation and allergic reactions in significant users [3]. The sustained release of drug is still one of the main objectives of drug delivery systems, which are designed to achieve a prolonged therapeutic effect by continuously releasing the drug over a prolonged period after administration of a single dose.

Diabetes mellitus (DM) is a set of related diseases in which the body cannot regulate the amount of sugar (specifically, glucose) in blood. Diabetes is a condition characterized by the body's inability to regulate glucose (sugar) level in blood.

Repaglinide, an antidiabetic drug, induces rapid onset short lasting insulin release. It is administered before each meal to control postprandial hyperglycaemia: as dose may be omitted if a meal is missed.

Thus, the aim of the present study was, to prepare repaglinide microspheres by the encapsulation of drug particles in Eudragit RS100 and ethyl cellulose to investigate the effect of surfactants on morphology and the drug release from the microspheres.

## MATERIALS AND METHODS

Repaglinide was obtained as a gift sample. Eudragit RS 100 from Evonik Industries AG and Ethyl Cellulose from S.D. Fine chemicals Mumbai. All other chemicals and solvents used were of analytical grade.

### Preparation of Microspheres

Repaglinide microspheres were prepared by emulsion solvent evaporation technique. (Atrey & Laldusanga) Different amounts of Eudragit RS-100, Ethyl cellulose and their combinations were dissolved in 8.5 ml acetone separately by using magnetic stirrer (Remi equipment Mumbai, India). The core material, Repaglinide was added to the polymer solution and mixed for 15 min. Then the polymer drug dispersion was poured into 50 ml of liquid paraffin (light) containing varying concentrations of dispersing agents. The whole system was then stirred for about 4 hours at 900 RPM. After stirring process is over the liquid paraffin (light) was decanted off and the microspheres formed were collected and washed 4-5 times with 50 ml portions of n-hexane to completely remove the remaining oil and dried at 50°C in vacuum drier for 6 hours and collected for further studies [2, 4].

### Infrared Spectroscopy

IR spectra of Repaglinide (pure drug, polymer and surfactants) were recorded using Perkin Elmer Spectrum between the ranges of 500 to 4000  $\text{cm}^{-1}$ . The resultant spectra were then compared with standard reference (IP 1996) and observe for any type of deviation from the standard.

### Particle size analysis

The particle size of the microspheres was determined by using an optical microscope (Magnus MLX-DX, Olympus). The microspheres were examined by optical microscope and size of the microspheres was measured by using a pre-calibrated ocular micrometer and stage micrometer. About 200-300 particles of each formulation were observed and counted.

### Scanning Electron Microscopy (SEM)

A scanning electron microscopy (JSM-6500, Germany) was used to characterize the surface topography, texture and to examine the morphology of the microspheres after gold coating. A small amount of microspheres was spread on glass stub. Afterwards, the stub containing the sample was placed in the scanning electron microscope chamber. The scanning electron photomicrograph was taken at the acceleration voltage of 10 KV, chamber pressure of 0.6 mm Hg, original magnification 500 [4].

### Drug entrapment efficiency

50 mg of dried microspheres were weighted accurately and drug was extracted from microspheres by digesting for 24 hours in 10 ml of 6.8 pH phosphate buffer solution. During this period, the suspension was agitated. After 24 hrs the suspension was centrifuged at 2000 rpm for about 3 minutes. The supernatant obtained was assayed spectrophotometrically for drug contents. The drug entrapment efficiency (DEE) was determined as:

$$\text{DEE} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

### Bulk Density and Flow Property:

Accurate weight (W) of microspheres was transferred into a 100-ml graduated cylinder to obtain the apparent volume (V).

The bulk density was calculated in gram per ml by the following formula:

$$\text{Bulk Density} = \frac{W}{V}$$

The flow property of microspheres was evaluated using Carr's Index. The results were averaged from three determinations.

$$\text{Carr's Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

### In-vitro drug release:

The *in vitro* dissolution studies were carried out in 900 ml of 0.1N HCl, at  $37 \pm 0.5^\circ\text{C}$  and 50 rpm by using USP type II dissolution test under sink conditions. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 24 hrs, and the sample were replaced with fresh dissolution medium to maintain the sink condition. The samples were filtered through a membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 242 nm using a model 1700 Shimadzu, double-beam spectrophotometer (Shimadzu, Japan). Cumulative percentage drug release was calculated using an equation obtained from a standard curve and same studies were performed in 6.8 pH phosphate buffer solutions [6].

### Stability studies

Selected formulation of microspheres stored in amber colored glass bottle at  $25 \pm 1^\circ\text{C}$  and  $40 \pm 1^\circ\text{C}$  and  $50 \pm 1^\circ\text{C}$  for a period of 40 days and observed for any change in percentage residual drug content at the time interval of 10 days for 40 days. Results show in Fig. 13 to 14.

## RESULTS AND DISCUSSION

An attempt has been to modify the repaglinide release from the microspheres, the formulations were prepared in which the increasing amount of polymer (Eudragit RS 100 & Ethyl cellulose) were added to the fixed amount of repaglinide with different amount of surfactants as variables. Optimization and proper control of these variables were essential for the formation of discrete and spherical microspheres.

### Drug-Excipients compatibility studies

For the successful preparation of dosage form is the compatibility between the polymer and the drug. The FTIR analysis for drug alone and in combination with polymer and surfactants were carried out. In the absence of any interaction, the IR spectrum of mixtures shows peak patterns corresponding to those of the individual components. In the events that interaction occurs, this was indicated in the IR spectrum of a mixture by the appearance of one or more new peaks or the disappearance of one or more peaks corresponding to those of the components. The principal IR peaks of pure repaglinide, Eudragit RS 100, Ethyl cellulose, Tween 80 and Span 80 are shown in figures 1 to 6 respectively. There were no considerable changes in the IR peaks of mixture of drug and polymer when compared to pure repaglinide. These observations indicated the absence of interaction between repaglinide with polymer and surfactants [1].

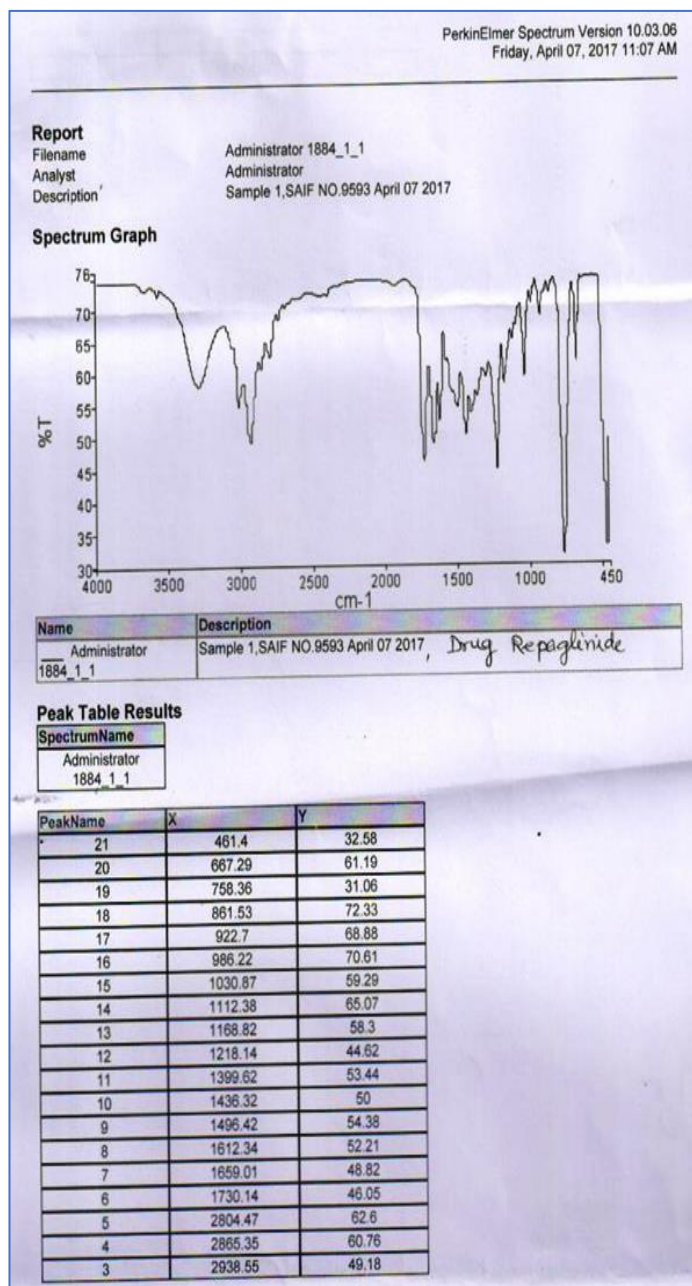


Fig. 1: FTIR Study of Repaglinide

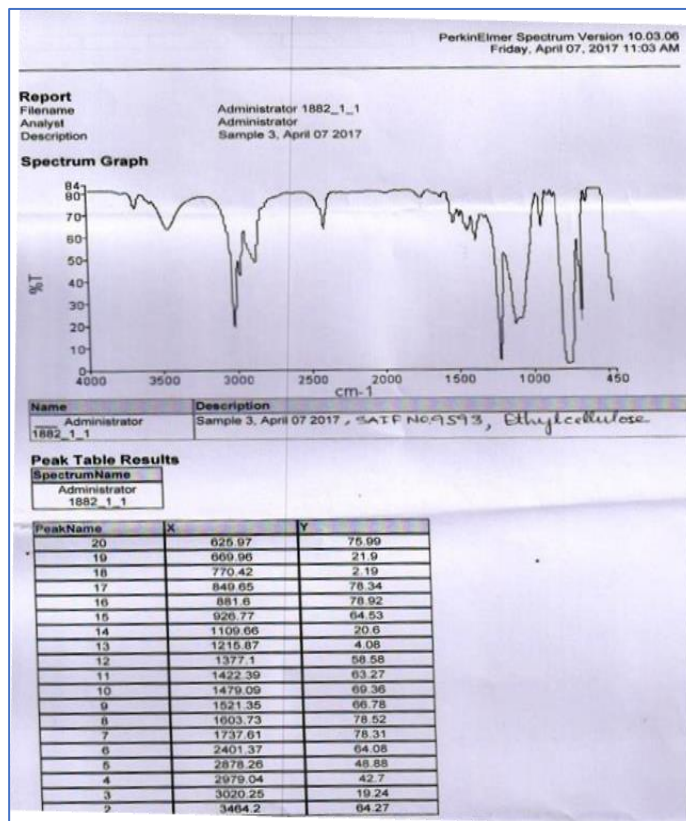


Fig. 2: FTIR Spectrum of Ethyl cellulose

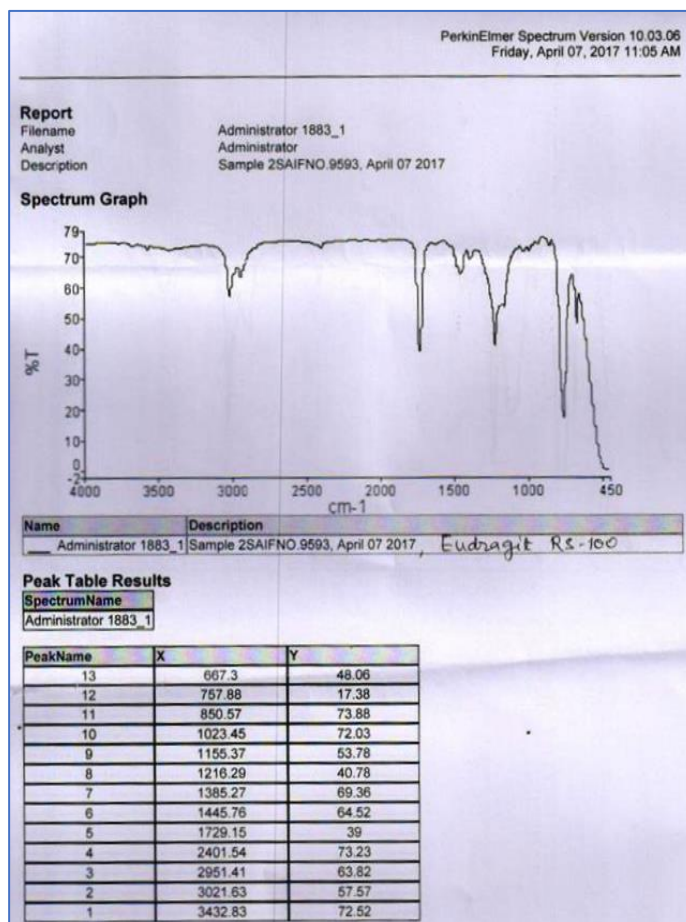


Fig. 3: FTIR Spectrum Eudragit RS-100

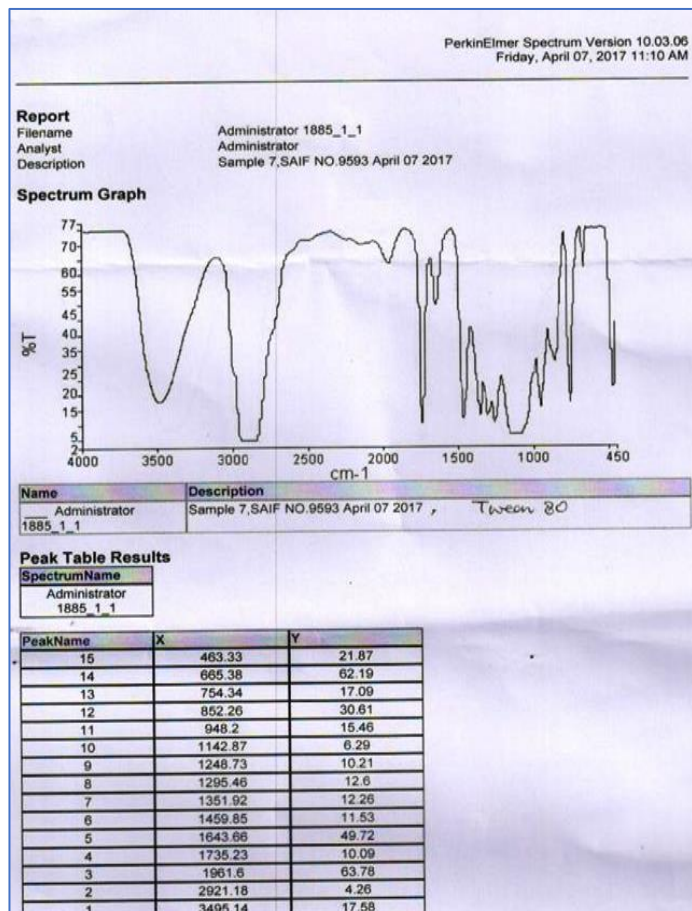


Fig. 4: FTIR Study of Tween 80

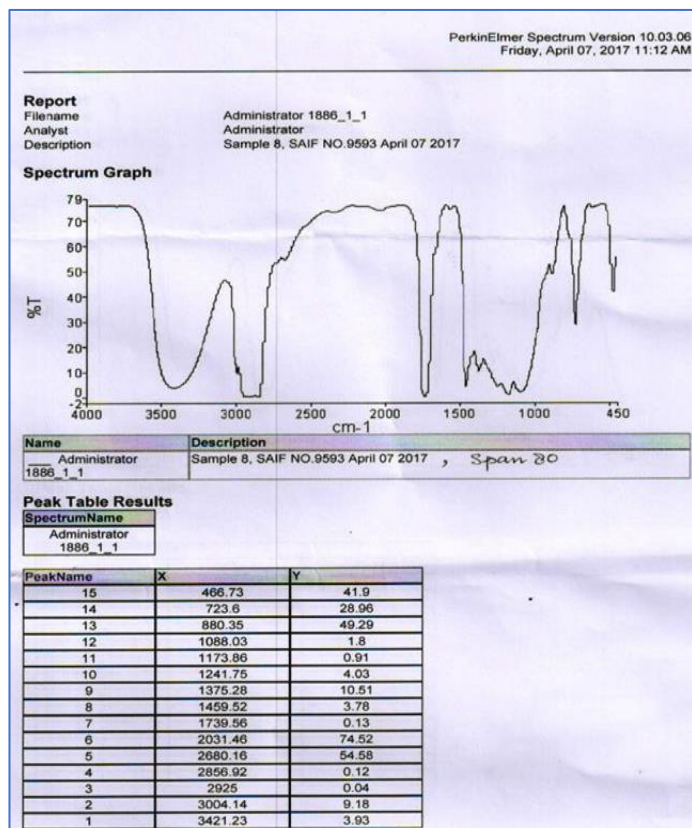


Fig. 5: FTIR Study of Span 80

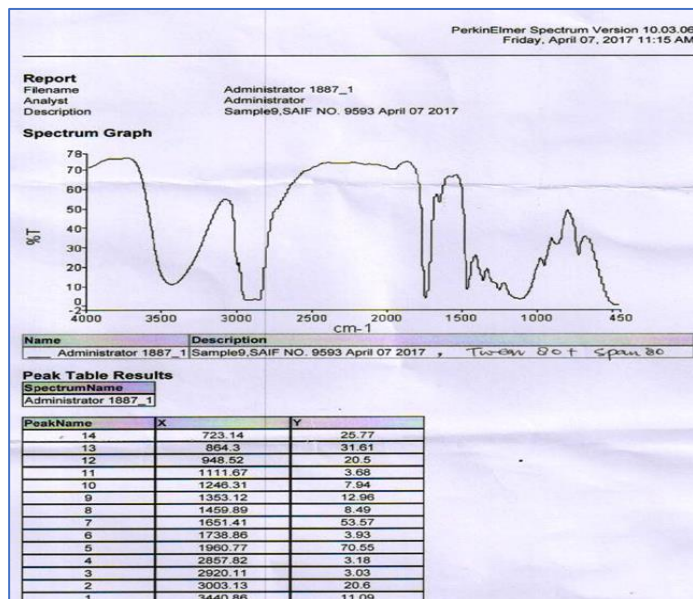


Fig. 6: FTIR Study of Tween 80 + Span 80

**Average particle size**

The prepared microsphere by solvent evaporation method was found to be spherical and free flowing in nature. The average particle size of the formulations was found to be in between. Two types of surfactants used have an influence on the particle size distribution of the microspheres (figure 7). The hydrophobic surfactant span 80 (sorbitan monooleate, HLB 4.3) is found to produce smaller particle size microspheres compared to hydrophilic surfactant Tween 80 (polyoxyethylene 20 sorbitan monooleate, HLB 14.9). Span 80 is oil soluble and produces a stable emulsion when the dispersion medium is oil. This may explain why smaller particle sizes are obtained with span 80. The concentration of surfactant/ dispersing agents also affects the particle size. For both types of surfactants used, the higher concentration of surfactant resulted in production of smaller particle size. This is due to better stabilization of internal droplets with increase of surfactant concentration preventing coalescence. Also, when more amount of surfactants are added, there is an accelerated dispersion of microcapsules in the micro-encapsulation system [14].

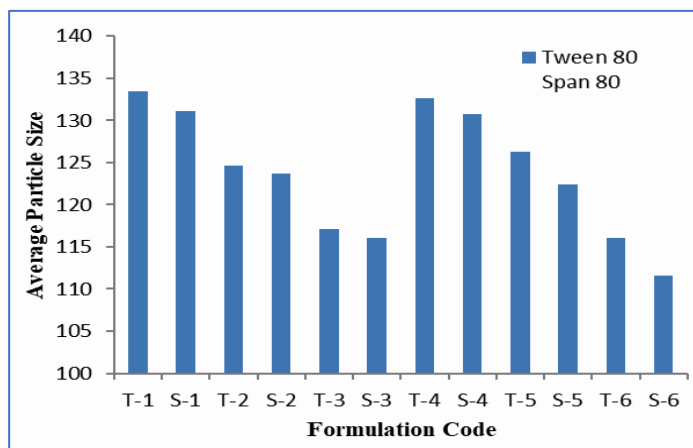
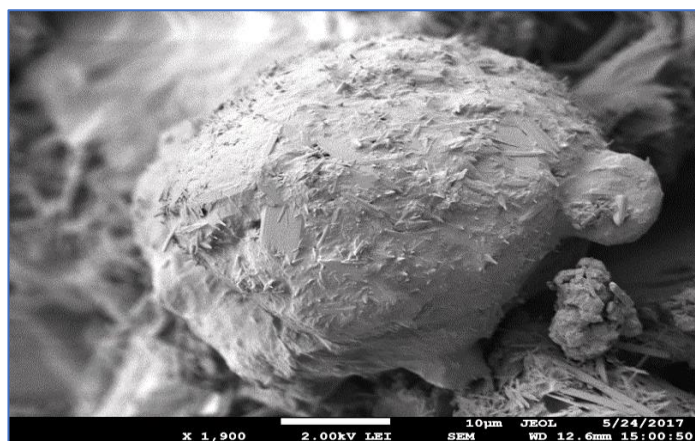


Fig. 7: Histogram showing average particle size of Repaglinide Microspheres

## SEM study

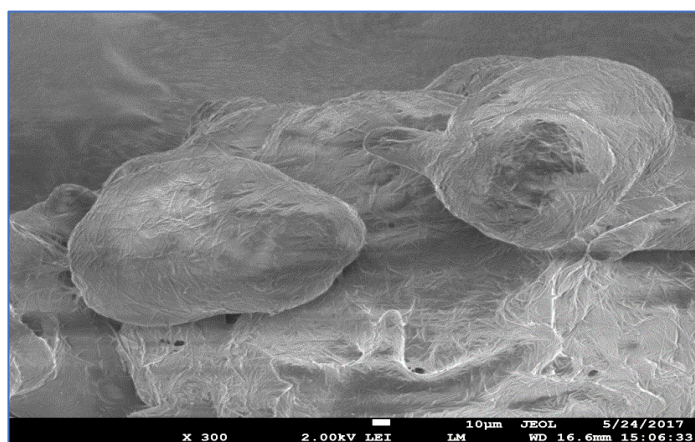
Results of SEM showed that microspheres were of spherical in shape with smooth surface. The porous nature and characteristics internal structure of the microspheres, a hollow cavity inside enclosed with the rigid shell constructed with drug and polymer was clearly evident as shown in figures 8 to 10.



**Fig. 8:** Scanning Electron Photomicrograph of RM 4 Microsphere



**Fig. 9:** Scanning Electron Photomicrograph of RM 6 Microsphere



**Fig. 10:** Scanning Electron Photomicrograph of RM 10 Microsphere

## Entrapment efficiency

The entrapment efficiency ranged from 41.18 to 64.22 (table 1). The entrapment efficiency was also found to be dependent on nature of polymer used in the formulation. The entrapment efficiency of the drug depended on the solubility of the drug in the solvent and continuous phase. The entrapment efficiency was determined at phosphate buffer of pH 6.8. Higher percentage entrapment was found when the percentage of surfactant was increased from 0.2% to 1%. This is true in both types of surfactants used but among all the formulations the optimum drug entrapment efficiency was found in tween 80 (1%). [9, 11].

**Table 1: Drug Entrapment efficiency & Average particle size**

Formulation Code	Drug Entrapment Efficiency	Average particle size (µm)
RM-1	44.10	133.50
RM-02	58.42	124.68
RM-03	64.22	117.10
RM-04	43.10	131.06
RM-05	57.32	123.70
RM-06	61.89	116.10
RM-07	42.10	132.68
RM-08	56.32	126.28
RM-09	63.42	116.10
RM-10	41.18	130.70
RM-11	55.53	122.40
RM-12	62.89	111.62

## *In-vitro* drug release study

Release of drug from the microspheres was evaluated. The reason for the slow dissolution rate of drug may also be attributed to low solubility of repaglinide in acidic pH. An *in-vitro* release study reveals that as the surfactant concentration was increased at constant polymer to drug ratio, the rate and amount of drug release was also increased. This may be due to the increase in wettability and better solvent penetration as the surfactant increased. This effect was observed in both types of surfactants taken. The type of surfactant taken also affects the *in vitro* release behavior of the microspheres (Figures 11-12).

Two types of surfactants Tween 80 and Span 80 were taken. *In vitro* release study in phosphate buffer pH 6.8 shows that the rate of drug release was faster in case of hydrophilic surfactant (Tween 80), this is due to the hydrophilic nature of surfactant, microspheres prepared using span 80 were expected to release the drug faster than microspheres prepared using Tween 80 due to their smaller particle size. But increased surface area available for drug release was not effective enough as compared to hydrophilic nature of the microspheres. But within the same type of surfactant, increase in surfactant concentration leads to reduced particle size, increase surface area and increased drug release.

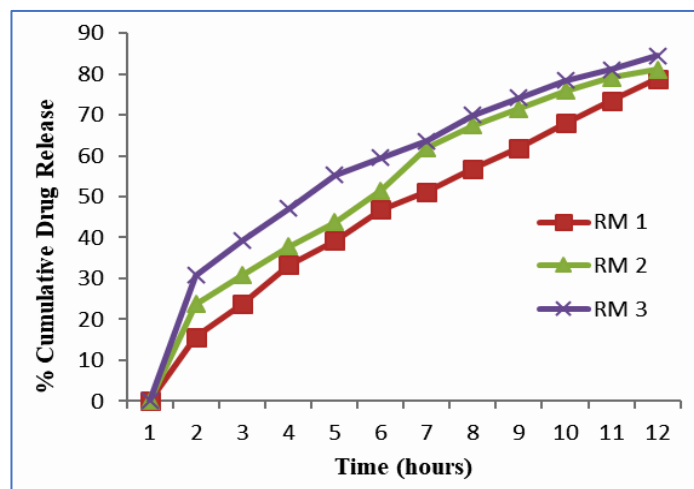


Fig. 11: Effect of Tween 80 concentration on drug released (D: P= 1:1)

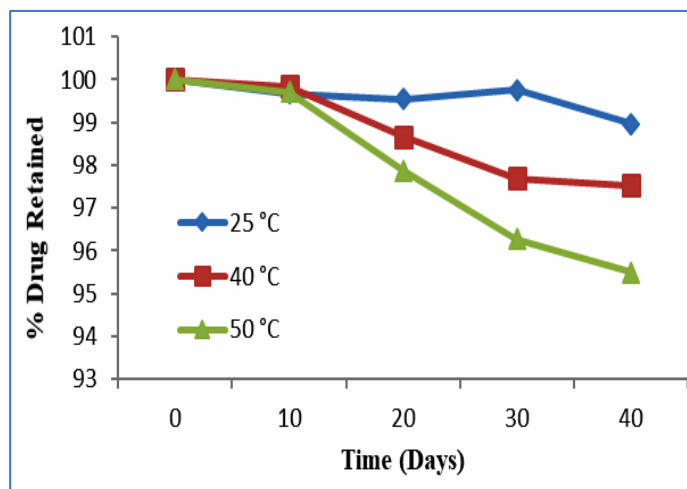


Fig. 14: Stability Study of formulations RM 4 (Containing Span 80) (at 25°C, 40°C & 50°C)

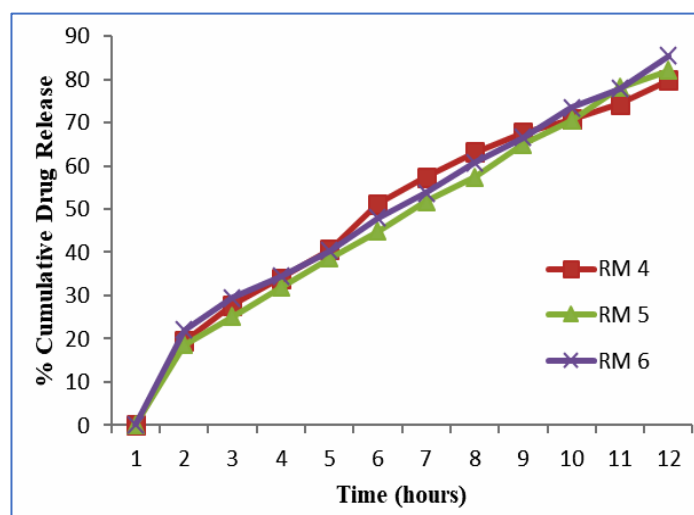


Fig. 12: Effect of Span 80 concentration on drug released (D: P= 1:1)

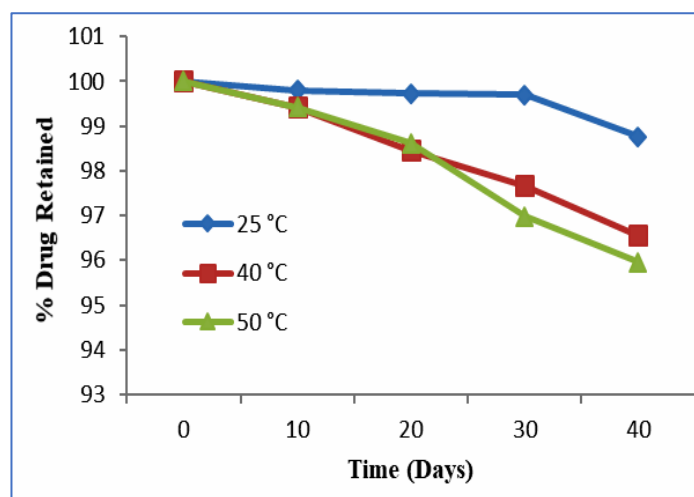


Fig. 13: Stability Study of formulation RM 1 (Containing Tween 80) (at 25°C, 40°C & 50°C)

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