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# FORMULATION AND EVALUATION OF SITAGLIPTIN MUCCOADHESIVE MICROSPHERES USING DIFFERENT POLYMERS BY HEAT STABILIZATION METHOD

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## ABSTRACT

In this present study was to formulate and evaluate sustained release microsphere gel loaded sitagliptin in order to maintain a sustained drug concentration in serum for longer period of time, which may result in enhanced absorption and thereby improved bioavailability. The results of compatibility studies by infrared spectroscopy and differential scanning calorimetry showed no interaction between the drug and polymers. The microgel of sustained release microspheres of sitagliptin phosphate were successfully prepared by non-aqueous solvent evaporation technique. All formulations F1 to F9 micropheres were evaluated for particle size analysis mean particle size range 30.32 to 42.75 µm. Mean particle size range of sitagliptin microspheres were in the range of suitable size range. The F8-EH shows the maximum drug content values of 97.92% Percentage Encapsulation efficiency of the F8 – 48.65 %. As the polymer concentration was increased the drug entrapment efficiency % was increased due to increase in the viscosity of the solution. The present investigation state that if the drugs are soluble in the solvent system, it results in high drug encapsulation efficiency than that of dispersed in the solvent system. The elimination of the drugs from the prepared microspheres highly dependent on the concentration of the polymer used, as the amount of the polymer increased the encapsulation efficiency of the microsphere increased because of the good matrix formation.

**Key Words:** microsphere gel, sitagliptin, encapsulation efficiency

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## INTRODUCTION

### *Introduction to Microsphere*

For many decades, medication of an acute disease or a chronic disease has been accomplished by injectables and suppositories as carriers. To achieve and then to maintain the concentration of drug administered within the therapeutically effective range needed for medication, it is often necessary to take this type of drug delivery systems several times in a day. This results in a fluctuated drug level and consequently undesirable toxicity and poor efficiency. This factor as well as other factors such as repetitive dosing and unpredictable absorption leads to the concept of controlled drug delivery systems (1-3). The word new or novel in the relation

to drug delivery system is a search for something out of necessity. An appropriately designed sustained or controlled release drug delivery system can be major advance toward solving the problem associated with the existing drug delivery system (4, 5).

The objective of controlled release drug delivery includes two important aspects namely spatial placement and temporal delivery of drug.

- Spatial placement relates to targeting a drug to a specific organ or tissue, while
- Temporal delivery refers to controlling the rate of drug delivery to the target tissue (6).

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is be dilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable motility and relatively brief gastric emptying time (GET) in humans which normally averages 2-3 hr through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. The objective in designing a controlled release system is to deliver the drug at a rate necessary to achieve and maintain a constant drug blood level. This rate should be similar to that achieved by continuous intravenous infusion where a drug is provided to the patient at a rate just equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time, i.e release from the dosage form should follow zero-order kinetics.

Hence aim of the study is to formulate Sitagliptin muccoadhesive microspheres using different polymers by heat stabilization method.

## MATERIALS AND METHODS

### *Compatibility Studies*

A proper design and formulation of a dosage form requires considerations of the physical, chemical and biological characteristics of both drug and excipients used in fabrication of the product. Compatibility must be established between the active ingre-dient and other excipients to produce a stable, efficacious, attractive and safe product. If the excipient(s) are new and if no previous literature regarding the use of that particular excipient with an active ingredient is available, then compatibility studies are of paramount importance. Hence, before producing the actual formulation, compa-tibility of sitagliptin with different polymers and other excipients was tested using the Fourier Transform Infrared Spectroscopy (FT-IR) technique.

### Formulation Studies

### *Heat stabilization technique*

Drug is dispersed in mixture of 5ml of 1%w/v albumin solution, 5ml of 2%w/v chitosan in 2% acetic acid and pour into 5ml of 15% w/v gelatin solution (water) containing 1.5% w/v $CaCO_3$ and syringe in to 25ml of liquid paraffin containing 0.5% w/v span 80 gently stirred for 10min at 60-70$^0$c and 1000rpm ( w/o emulsion is formed) then it is cooled at 50 $^0$c for 30min , washed with petroleum ether and dried at 45$^0$ c (Table-1).

***Table-1 Prepared formulation of Floating Beads***

| S.No. | FORMULATION CODE | DRUG:POLYMER RATIO | POLYMER RATIO (ALBUMIN: CHITOSAN) |
|---|---|---|---|
| 1 | **F1** | **1:1** | **1:1** |
| 2 | **F2** | **1:1.5** | **1:2** |
| 3 | **F3** | **1:2** | **1:3** |

| | | | |
|---|---|---|---|
| 4 | **F4** | **1:1.5** | **2:1** |
| 5 | **F5** | **1:2** | **1:1** |
| 6 | **F6** | **1:2.5** | **2:3** |
| 7 | **F7** | **1:2** | **3:1** |
| 8 | **F8** | **1:2.5** | **3:2** |
| 9 | **F9** | **1:3** | **1:1** |

***In vitro drug release study***

The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± $0.5^0$C, 100 rpm) using the USP type – I rotating basket method in 0.1N HCl (900ml). A quantity of accurately weighed microspheres equivalent to 100 mg sitagliptin each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 288nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed 0.1N HCl maintaining sink conditions throughout the experiment (7-9).

## RESULTS AND DISCUSSION

### Evaluation and characterisation of microspheres

### Percentage yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle andwastage of the drug- polymer solution, adhesion ofpolymer solution tothe magnetic bead andbeads lost during the washing process. The percentage yield was found to be in the range of80 to 88% for microspheres containing albumin and chitosan. The percentage yield of the prepared microspheresis recorded in Table-2.

### Drug Entrapment Efficiency

Percentage Drug entrapment efficiency of Sitagliptin ranged from 62.66 to 88.66% for microspheres containing albumin and chitosan. The drug entrapment efficiency of the prepared beads increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared beads is displayed in Table-2.

**Table-2 Percentage Yield and Percentage Drug Entrapment Efficiency Of The Prepared Microspheres**

| S.No. | Formulation code | % yield | Drug Content (mg) | %Drug entrapment efficiency |
|---|---|---|---|---|
| 1 | F1 | 80 | 79.40 | 62.66 |
| 2 | F2 | 83.33 | 78.66 | 64.4 |
| 3 | F3 | 85 | 78.70 | 66.66 |
| 4 | F4 | 86 | 79.5 | 70 |
| 5 | F5 | 82.22 | 71.07 | 73.2 |
| 6 | F6 | 80 | 72.25 | 75 |

| | | | | |
|---|---|---|---|---|
| **7** | F7 | 88 | 85.29 | 88.66 |
| 8 | F8 | 87 | 83.5 | 86.66 |
| 9 | F9 | 80 | 83.01 | 83.73 |

**Evaluation of pre-compression parameters of Sitagliptin Microspheres**

Sitagliptin Microspheres were prepared and observed for micro particle analysis (Table-3).

**Table-3 Data For Sitagliptin Microspheres For Micro Particle Analysis (F1-F9)**

| Formulation code | Bulk density (g/cc) | Tapped density (g/cc) | Carr's Index | Hausner Ratio | Angle of repose(θ) |
|---|---|---|---|---|---|
| **F1** | 0.45±0.045 | 0.52 ± 0.09 | 15.60±0.2 | 1.15±0.02 | 28.06 ±0.31 |
| **F2** | 0.45±0.045 | 0.50 ± 0.07 | 12.23±0.6 | 1.11±0.04 | 27.58± 0.15 |
| **F3** | 0.44±0.044 | 0.50 ± 0.09 | 12.58±0.8 | 1.13±0.08 | 28.44± 0.11 |
| **F4** | 0.45±0.045 | 0.52 ± 0.04 | 15.19±0.1 | 1.15±0.06 | 28.36± 0.13 |
| **F5** | 0.44±0.044 | 0.52± 0.01 | 15.48±0.6 | 1.18±0.08 | 28.52± 0.19 |
| **F6** | 0.45±0.045 | 0.51 ± 0.04 | 13.48±0.8 | 1.13±0.09 | 29.32± 0.19 |
| **F7** | 0.51±0.045 | 0.59 ± 0.04 | 14.48±0.8 | 1.15±0.09 | 29.69± 0.19 |
| **F8** | 0.45±0.045 | 0.52±0.04 | 15.19±0.1 | 1.15±0.05 | 27.36±0.23 |
| **F9** | 0.44±0.04 | 0.50±0.1 | 12.58±0.8 | 1.13±0.09 | 29.33±0.16 |

All the formulations were evaluated for bulk density, tapped density, % compressibility, hausner's ratio and angle of repose. The results of % compressibility, hausner's ratio and angle of repose were found to be <16, <1.25 and <30 respectively. These results show that the formulations have excellent flow properties.

***In Vitro* studies**

Among all the formulations F7 shows more sustainity after 9 hour where as all other shows optimum sustainity like F7 but F7 shows highest drug release at 12Hr where as remaining all other shows less percent of drug release so F7 was optimized as best formulation (Fig-1-3).

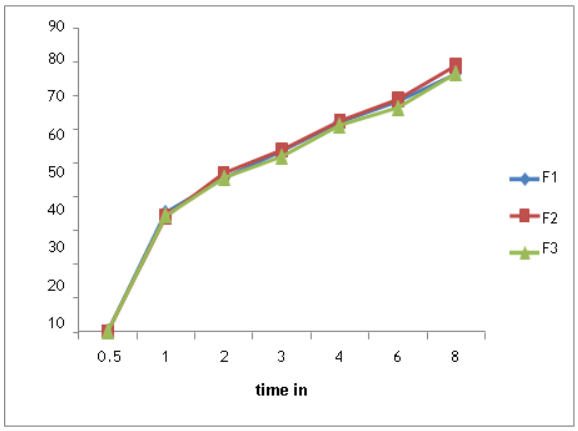


**Fig-1 Dissolution profile of Sitagliptin Microspheres (F1, F2, F3 ) formulations**

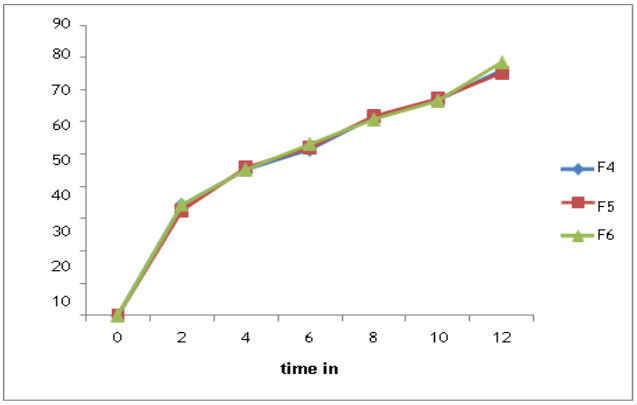


**Fig-2 Dissolution profile of Sitagliptin Microspheres (F4, F5, F6) formulations**

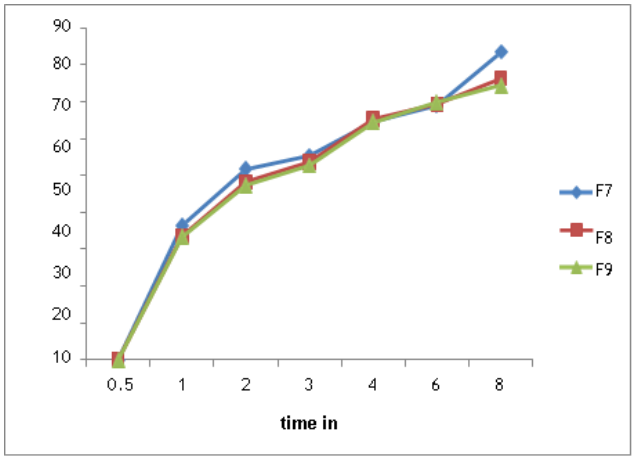


**Fig-3 Dissolution profile of Sitagliptin Microspheres (F7, F8, F9) formulations**

## CONCLUSION

The present study has been a satisfactory attempt to formulate a microspheres of Sitagliptin, a new anti diabetic drug giving a controlled release of the drug. From the experimental results it can be concluded that, FT-IR study shows no significant shifting of the peaks therefore it confirms the short term stability of the drug in the beads. Biocompatible polymers like can be chitosan and albumin used to formulate microspheres. Good percentage drug entrapment and practical yields were obtained with both the polymers. The flow properties of all formulations were within the acceptable range and therefore they could be easily filled into capsules. Cumulative percentage drug release significantly decreased with increase in polymer concentration. Thus, the formulated microspheres seem to be a potential candidate as an oral controlled drug delivery system in prolonging the drug release and increasing the bioavailability of drug.

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