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Original Article

Preparation and Evaluation of Glimepiride Floating Microsphere for Effective Management of Diabetic Mellitus

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ABSTRACT
Floating gastroretentive drug delivery system is the choice for delivery of the drugs with shorter half-life and drug mainly absorbed from the stomach or duodenum. The floating microspheres of the antidiabetic drug glimepiride were developed to address the lower half issues with the drug. The development of formulation four formulations done using a different concentration of ethyl cellulose and HPMC-k15m. Formulation F2 selected as optimized formulation on the basis of drug entrapment, percent yield, and *in-vitro* buoyancy test. The value of drug entrapment and percent yield were found to be 76.90% and 78.69% respectively. The prepared formulations were found stable during stability testing at ambient conditions.
Keywords: Glimepiride, floating microspheres, ethyl cellulose, HPMC, drug entrapment, antidiabetic

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INTRODUCTION

The design of oral control drug delivery systems should be primarily aimed to achieve more predictable and increased bioavailability. Now a day's most of the pharmaceutical scientist is involved in developing the ideal novel drug delivery system. This ideal system should have the advantage of a single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site **(Wen *et al.*, 2015)**. Scientists have succeeded to develop a system and it encourages the scientists to develop control release systems. Control release implies the predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimisation of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose **(Adepu *et al.*, 2021)**. However, this approach is be filled with several physiological difficulties such as the inability to restrain and locate the controlled drug delivery system within the desired region of the GIT due to variable gastric emptying and motility. Furthermore, the relatively brief GET in humans which normally average 2-3 hrs 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 **(Hua, 2020).**

Kumar and Shrivastava (2021) have formulated and characterised the floating microsphere of verapamil hydrochloride by using a modified Quasi-emulsion diffusion technique using polymers like ethyl cellulose, eudragit L 100, polyethylene oxide and HPMC. **Rajpali and Gupta (2020)** have formulated Nizatidine loaded floating microspheres by the solvent diffusion evaporation method using polymers hydroxypropyl methylcellulose (HPMC) and

microcrystalline cellulose (MCC) to prolong the gastric retention time of the drug for the therapeutic management of gastric disorders like ulcers. Furthermore, **Bharadwaj *et al.*, (2014)** have developed floating microsphere of the 5-fluorouracil were using modified solvent evaporation technique to prolong gastric residence time, to target stomach cancer, and to increase drug bioavailability.

Glimepiride (GLP) is second generation new sulfonyl urea oral antidiabetic. GLP is poorly soluble in acidic environment. When it is given orally in healthy people, it absorbs rapidly and completely. However, its absorption is erratic in diabetic patients due to impaired gastric motility or gastric emptying **(Sola *et al.*, 2015)**. This erratic absorption of glimepiride becomes clinically significant, since the efficacy of short acting sulfonylurea is dependent upon the absorption rate of the drug. GLP has a half-life of (5-7 hrs) and it reaches a peak plasma concentration after 2-3 hrs. It is mainly absorbing from the upper GI tract, which makes GLP as a suitable candidate for gastro retentive dosage form in order to prolong the GRT **(Basit *et al.*, 2012)**. Hence, to overcome the above-mentioned drawbacks the present study aims to increase the therapeutic efficacy, reduces the frequency of administration, improves the bioavailability and patient compliance by developing Glimepiride as floating Drug Delivery System (FDDS) for controlled release and increased gastric retention time.

Materials and Methodology

Chemicals

Glimepiride (GLP) obtained as gift sample from Lupin Ltd. Mumbai, India. However, ethyl cellulose and HPMC-K15 is obtained from Wockhardt Ltd. HPMC, Acetone, were purchased from CDH India. All other chemicals and reagents were used of analytical grade.

Preformulation study

The obtained drug was evaluated for the organoleptic characteristics, solubility, melting point and partition coefficient.

Infrared spectroscopy

The FTIR studies were performed for the identification and compatibility testing with excipients. The drug sample was scanned on IR spectrophotometer between 400-4000 cm-1 using KBr disc. The obtained IR spectrum was interpretated with the structure of GLP.

Differential scanning calorimetry (DSC)

DSC curves were obtained in a Perkin-Elmer (Pyris 1 DSC) cell using aluminium crucibles with about 2 mg of samples, under a dynamic N2 atmosphere (flow rate: 50 mL/min) and at a heating rate of 10°C/min in the temperature range 25 - 400°C.

Preparation of Floating Microsphere of Glimepiride

All the ingredients along drug and with additional ethanol are dissolved, using a syringe, solution was sequentially dropped into appropriate quantity into light liquid paraffin. Light liquid paraffin was stirred with a mechanical stirrer at 1000 rpm at 50°C temperature for 45 min. The floating microspheres were gradually hardened and the hardened microspheres were collected by filtration. They were washed several

times with petroleum ether and dried in vacuum oven at ambient temperature for 24 hr. The yield calculated by dividing the weight of the collected microspheres by the total weight of the non-volatile components uses for preparing the microspheres

Table 1: Formulations of the Floating Microspheres Prepared

Sr. No	Formulation Code	Drug (mg)	Ethyl cellulose (mg)	HPMC-K15 (mg)
1.	F_1	1	1	0.5
2.	F_2	1	0.5	1
3.	F_3	1	1	1
4.	F_4	1	0.5	0.5

In-vitro release studies

The drug release rate from GLP floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly. A weighed amount of floating microspheres equivalent to 2 mg drug were dispersed in 900 ml of 0.1 N HCI (pH 1.2) maintained at 37±0.5°C and stirred at 50 rpm. One ml sample was withdrawn at

predetermined intervals and filtered and equal volume of fresh dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples analysed spectrophotometrically at 225 nm to determine the concentration of drug present in the dissolution medium.

Measurement of mean particle size

The mean size of the microspheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyser (Horiba Instruments) at a scattering angle of 90°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement.

Percentage yield

The prepared microspheres with a size range of 589-783µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} \times 100$$

Drug Entrapment

The various formulations of the floating microspheres were subjected to drug content. 100 mg of floating microspheres from all batches were accurately weighed and crushed. The powdered of microspheres were dissolved with 10 ml ethanol in a 100 ml volumetric flask and make up the volume with 0.1 N HCl. This resulting solution is then filtered through whatmann filter paper No. 40 **(Mahale *et al.* 2019)**. After filtration, from this solution, 10 ml was taken out and diluted up to 100 ml with 0.1 N HCl. The percentage drug entrapment was calculated as follows.

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

***In-vitro* % Buoyancy test for microspheres**

The floating properties of the microspheres were evaluated, using an *in-vitro* % Buoyancy test for microspheres. The in vitro buoyancy was determined, as per the method described by **Pingale et al., (2021)** in a 250 mL beaker containing 0.1N HCl, pH 1.2, maintained at 37 ± 0.5°C in a water bath. The hollow microspheres were separated by mechanical agitation. Their physical state was observed for 24 h.

Characterization of Floating Microspheres by Scanning Electron Microscopy (SEM)

From the formulated batches of Floating microspheres, formulations (F2) which showed an appropriate balance between the percentage release were examined for surface morphology and shape using scanning electron microscope Jeol Japan 6000. The sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 10 KV during scanning. Microphotographs were taken at different magnification and higher magnification (200X) was used for surface morphology.

Drug Release kinetics

In order to elucidate mode and mechanism of drug release, the *In-vitro* data was transformed and interpreted at graphical interface constructed using various kinetic models. The zero-order release Eq. (1).

$$Qt = Qo + Kot \quad (1)$$

Where Qt is the amount of drug released in time t, Qo is the initial amount of the drug in the solution and Ko is the zero-order release constant

The first order Eq. (2) describes the release from the system where release is concentration dependent.

$$\log Qt = \log Qo + K1\ t /2.303 \quad (2)$$

Where Qt is the amount of drug released in time t, Q is the initial amount of drug in the solution and K1 is the first order release constant. Higuchi described the release of drug from the insoluble matrix as a square root of time as given in Eq. (3)

$$Qt = KH \sqrt{t} \quad (3)$$

Where Qt is the amount of drug released in time t, KH is Higuchi's dissolution constant.

Stability studies for optimized formulation

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of

environmental factors such as temperature, humidity and light and to establish a retest period for the drug substance or a shelf life for drug product and recommended storage conditions. In general, a drug substance should be evaluated under storage condition (with appropriate tolerances) that test its thermal stability and if applicable, its sensitivity to moisture. Three types of storage conditions are used i.e. Long term, Accelerated and where appropriate, Intermediate.

Table 2: General guideline for stability study

Study	Storage conditions	Minimum time period covered by data at submission
Long term	25±2°C/60±5% RH or 30±2°C/65±5% RH	12 months
Intermediate	30±2°C/65±5% RH	6 months
Accelerated	40±2°C/75±5% RH	6 months

Table 3: Sampling Intervals

Storage conditions	Sampling intervals
Real time storage 30°C/75% RH	0 and 6 months
Accelerated 40°C/75% RH	0 and 6 months

Accelerated Testing, are the studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies.

RESULTS AND DISCUSSION

In preformulation studies was found that GLP slightly soluble in basic pH and poorly soluble in water, 0.1 N HCL, acetate buffere pH 4.5. The partition behaviour of drug was examined in *n*-octanol: water, *n*-octanol: PBS (6.8) system. Partition co-effient in *n*-octanol: buffer (pH 6.8) was 2.79 while in *n*-octanol: water it was 3.09.

The GLP was identified by FTIR studies showing major peaks relevant to reference sprectra. GLP presented characteristic peak at 3369 cm^{-1} due to NH streching, 2930 cm^{-1} due to CH streching and 1707 cm^{-1} can be assigned to C=O streching, 1358 cm^{-1} can be assigned to C-O streching. When the data obtained from FTIR spectra is compared with the spectra with drug and excipient we found that there are similar peaks for functional groups in GLP, this shows that the GLP is compatible with the excipients.

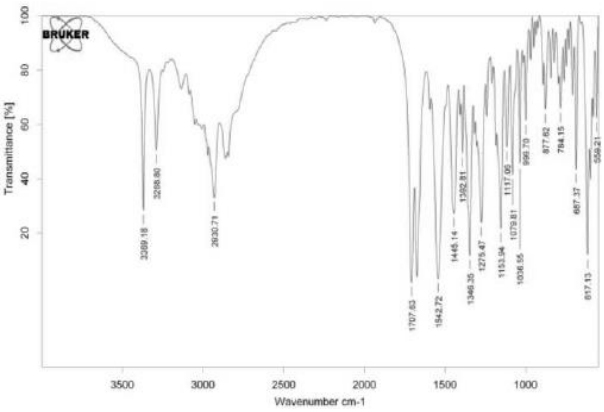

Fig 1. IR Spectra of GLP

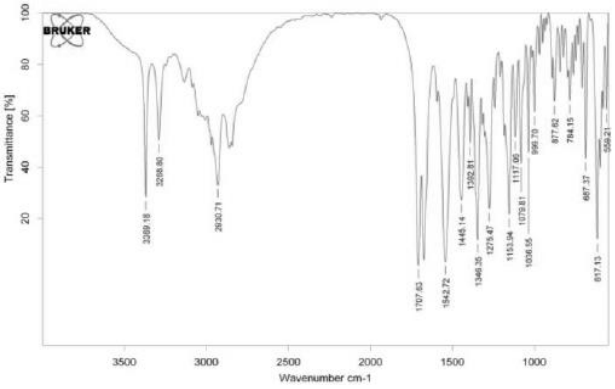

Fig 2. IR Spectra of Drug + Excipient

It was found that the drug sample shows a characteristic peak on 213.85^{0}C under DSC studies which shows that the sample contains GLP and GLP with excipients shows the melting at 215.21^{0}C. It shows that the GLP is compatible with excipients under study (Hekmatara et al. 2006).

The results of drug Entrapment and percent yield for different Formulation is given in table 4. The drug release kinetics study of batch F2 of Glimepiride floating microspheres follows the zero order drug release as regression coefficient was 0.9913.

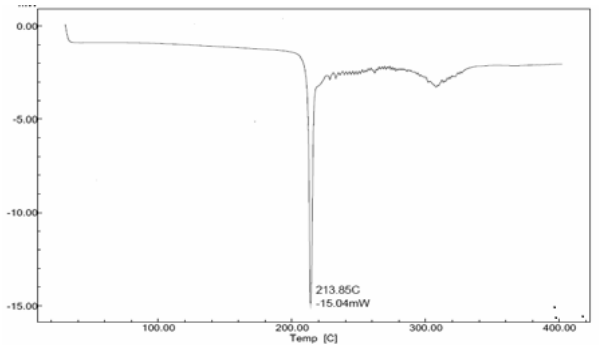

Fig 3. DSC Spectra of GLP

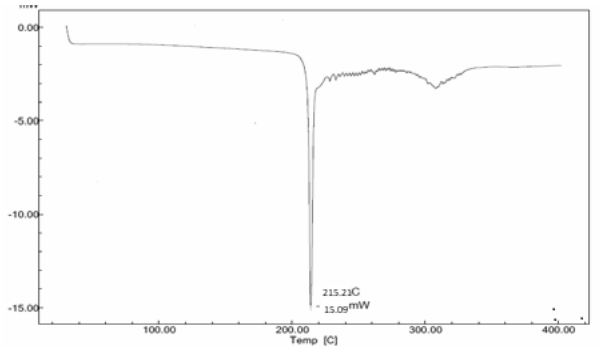

Fig 4. DSC Spectra of Physical mixture

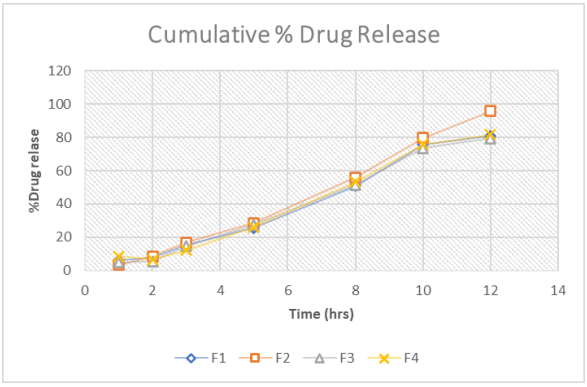

Fig. 5. Cumulative percent drug release

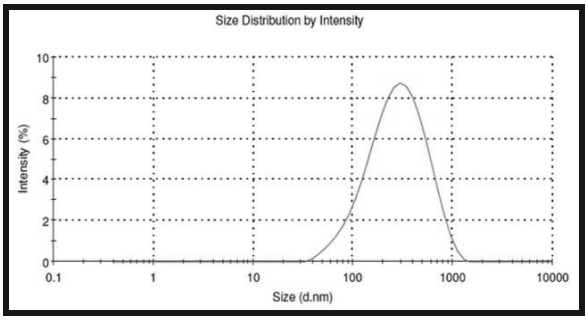

Fig 6: Particle size analysis

Table 4. Drug Entrapment for Different Formulation

Formulation	Drug entrapment (% w/w)	Percent Yield (%)
F_1	56.59	73.83
F_2	76.90	78.69
F_3	65.83	74.56
F_4	70.63	71.85

The time required for the microspheres to rise to the surface and float was determined as floating lag time (1 min 38 sec) and total duration of time (more than 12 hrs) by which dosage form remain buoyant is called total floating time and about 68.43% of microspheres remain buoyant for 12 hrs.

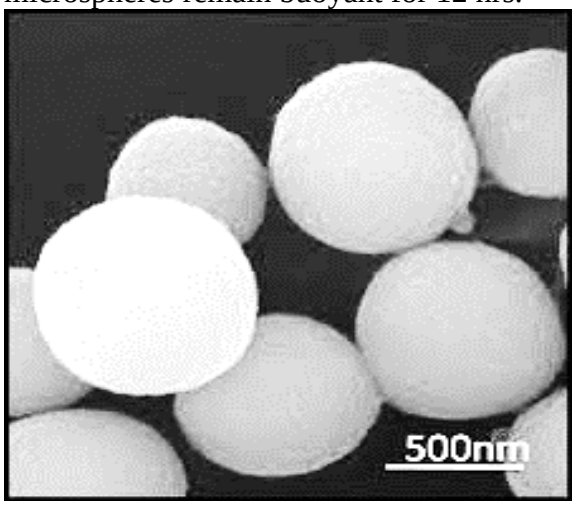

Fig 7: Scanning Electronic Microscopy Image of Optimised Formulation F-2

The results of particle size of the prepared F2 batch was microspheres was found to be 684±97.06nm. The R^2 value for F2 batch was determined using Korsmeyer-peppas model was 0.8572, for Higuchi model was 0.9493, for first order was 0.8335 and for Hixon Crowell cube root model was 0.9221. The drug release kinetics study of batch F2 of Glimepiride floating microspheres follows the zero order drug release as regression

coefficient was 0.9913.

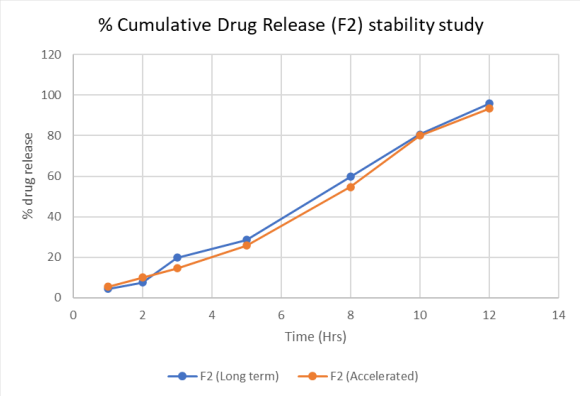

Fig. 8 Percent Cumulative Drug Release (F2) stability study

The optimised formulation F2 was taken and accelerated stability study was performed by taking a suitable quantity of microspheres. The microspheres were placed in an air-tight glass container at 40±2°C/75±5% RH. At suitable sampling interval, the samples were withdrawn and evaluated. It was found have suitable stability profile in terms of the cumulative drug release.

CONCLUSION

Present investigation an attempt has been made to increase the therapeutic efficacy, reduces the frequency of administration improves the bioavailability and patient compliance by developing the GLP floating microsphere system for controlled release and increased gastric retention time. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment.

From experimental results, it was conclusively demonstrated that GLP floating microspheres with ethyl cellulose and HPMC K15m polymers can be successfully formulated by an emulsification-solvent evaporation method. Formulations employing individual polymers as well as their combinations showed optimum results of which formulation containing ethyl cellulose and HPMC-k15m in ratio of (0.5:1) in the evaluated parameters.

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