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Evaluation of glipizide microspheres formulated by solvent evaporation method

[*1] Maya Sharma, [2] PK Choudhury, [3] Zainab Munawar Ali
[1, 2] Department of Pharmaceutical Sciences, Mohanlal Sukhadia University, Udaipur, Rajasthan, India
[3] Pacific College of Pharmaceutical Sciences, Pacific University, Airport Road, Udaipur, Rajasthan, India

Abstract
The aim of the study was to formulate and evaluate sustained release microspheres of water insoluble anti-diabetic drug Glipizide. Drugs that are easily absorbed from the gastrointestinal tract (GIT) with a short half life are eliminated quickly from the blood circulation. To encounter this, the oral sustained (SR) have been developed as these release the drug slowly in to the GIT and maintain a constant drug concentration in the serum for a longer duration of time. Glipizide is commercially available as tablet but causes gastric irritation. The study was undertaken to convert it into multiple unit dosage form which could release the drug uniformly throughout the stomach, suppressing the irritation. Various parameters affecting the behavior of floating multi-particulate in oral dosage form were studied.

Keywords: microspheres, sustained release, glipizide, floating microspheres

Introduction
Diabetes develops when the level of blood sugar increases due to insufficient or ineffective insulin secretion from the pancreas.Blood sugar is then released via urination, leading to "sugary urine", or diabetes.The disease gives rise to multiple complications, and in severe cases, coma, so patients are adviced to receive long-term treatment to maintain stability in blood sugar, levels thereby reducing the risk of complications.
Glipizide is an antidiabetic drug used to treat type 2 diabetes mellitus. It is available as single dosage formulation for conventional and sustained release tablet for oral use. An ideal dosage form is one, which attains the desired therapeutic concentration of drug in plasma and maintains it for entire duration of treatment [1].

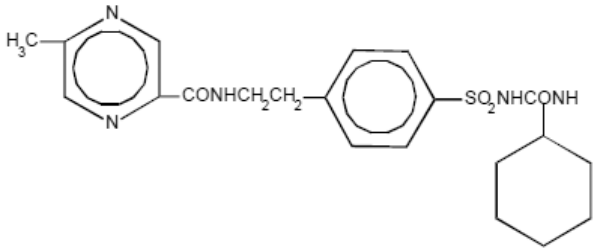

Fig 1: The Chemical Structure of Glipizide

It is extensively metabolized by the liver (90%) and only 10% is excreted unchanged by the kidney. It produces hypoglycemia due to its shorter half-life. Contraindications have been reported as hepatic dysfunction and renal insufficiency. It can be used in patients with moderate to severe renal impairment [2]. The 3 and 4-OH metabolites of glipizide have fragile hypoglycemic activity. The 3-OH of glyburide has virtually no action, while the 4-OH has some hypoglycemic activity. Less than 10% of the dose undergoes hydrolysis to inactive metabiolites [3, 4].
Eudragit RS 100 is an anionic copolymer of methacrylic acid and methyl methacrylate with free carboxyl groups in powder form. The ratio of the free carboxyl groups to the ester groups is approximately 1:2. The polymer (Eudragit RS-100) is soluble in water above pH 6.0. Due to its low content of free carboxyl groups, it dissolves less rapidly than Eudragit RL 12.5 and Eudragit L 100-55. It can also be used for a targeted delivery in the ileum or colon region. The site of drug release and its release-rate from the dosage form can be altered by combinations of different types of Eudragit RL. These polymers provide pH independent drug release that can be used for formulating the sustained release, ideal for oral dosage forms [5].

Experimental Procedure
Glipizide IP was provided by Kreative organics (p) Pvt Ltd Hyderabad while Eudragit RS100 was obtained from Otto chemi Pvt Ltd Germany. All other solvents and chemicals were of analytical grade.

Eudragit RS microspheres of glipizide
The required proportions of Eudragit RS and drug were dissolved in a mixture of ethanol and di-chloromethane (1:1). This solution was added to a 0.2% sodium lauryl sulfate (SLS) solution drop wise. It was stirred at 1000 rpm for about an hr until complete evaporation of the solvent. The product was air dried and stored in amber colored bottles and kept in desiccator until used.

Evaluation of microspheres
Percentage yield
The percentage yield of the microspheres was calculated for each batch by dividing the weight of microspheres by the total weight of drug and polymer (Table-1).

Percentage Yield= practical yield/theoretical yield x 100

Table 1: Percentage yield

S. No.	Sample no.	Drug: Polymer	Percentage yield
1.	GES1	1:0.5	84.5%
2.	GES2	1:1	85.7%
3.	GES3	1:1.2	73.2%
4.	GES4	1:1.4	72.0%
5.	GES5	1:1.6	71.0%
6.	GES6	1:1.8	69.6%
7.	GES7	1:2	75.5%

Size distribution and size analysis

The microspheres were separated into different size fractions by sieving for 10 mins using a mechanical shaker containing standard sieves as per Indian Pharmacopoeia specifications. The particle size distribution was determined and mean particle size of microspheres were calculated by the formula

$$\text{Mean particle size} = \sum \frac{(\text{Mean particle size of the fraction} \times \text{weight fraction})}{\Sigma\,(\text{Weight fraction})} \quad \text{Eqn.1}$$

Study of Floating behavior of microspheres

This study was undertaken to study the floating behavior of various polymer combinations in various formulations. For this, 50 mg of microspheres were placed in each of four 50 ml beaker containing 20 ml of 0.1N HCl and 0.02% Tween 80. The beaker was shaken in a shaker at 37 ºC ± 0.5 ºC at 40 rpm. Floating microspheres were collected at 4th, 8th and 12th hr of study and dried until constant weights were obtained [12]. The percentage of floating microspheres was calculated by the following equation:

$$\%\ \text{Floating microsphere (B \%)} = \frac{\text{Weight of floating microspheres after time t}}{\text{Initial weight of floating microspheres}} \times 100$$

Differential scanning calorimetry (DSC)

Thermograms of drug, polymers microspheres were obtained using DSC 822e (Mettler Toledo) Calorimeter. No interactions between the drug and polymer were seen. Both showed separate peaks in thermogram (Fig 2).

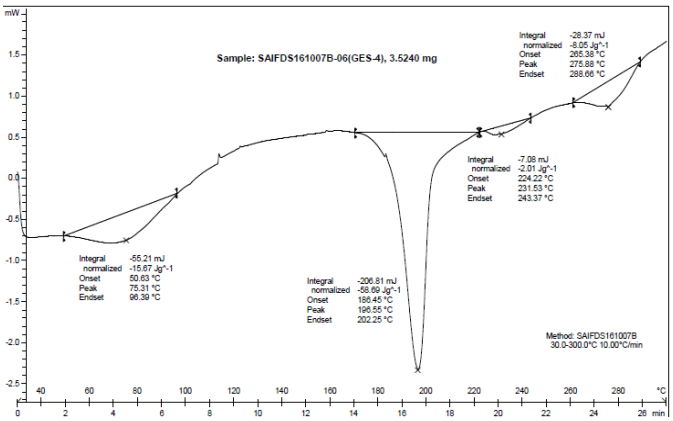

Fig 2: DSC thermograph of glipizide eudragit microspheres (sample GES-4)

Entrapment efficiency

The prepared microspheres were dissolved in suitable solvent and the drug was extracted by adding extracting solvent to this system [13].

Microspheres (20 mg) were added to 100 ml of phosphate buffer solution of pH 6.8, stirred for 24 hrs and then dissolved completely by thorough trituration for 2 hrs. A sample (1 ml) was withdrawn and analyzed spectrophotometrically at λ max 276 nm. The entrapment efficiency was calculated from the theoretical amount and the actual amount of the drug in dry microspheres (Table 2).

Drug entrapment efficiency (%) = Calculated drug content/theoretical drug content x 100

Table 2: Physicochemical properties of the Eudragit microspheres (D: P: 1:0.5 to 1:2)

Eudragit RS Microspheres of Glipizide							
Sample Code	**Entrapment (%)± S.D**	**Shape**	**Color**	**Swell. Index (%)**	**Angle of Repose (degree) ± S.D**	**Tapped Density**	**Floating (%) ± S.D**
GES1	79.7 ± 0.20	spherical	White	25.5	26º 56’	0.333	21.0 ± 0.2
GES2	89.4 ± 0.52	spherical	White	27.3	31º 32’	0.357	15.3 ± 1.0
GES3	89.9 ± 0.11	spherical	White	28.7	30º 41’	0.384	14.8 ± 1.3
GES4	91.0 ± 0.10	spherical	White	30.1	33º 69’	0.416	15.5 ± 1.1
GES5	79.2 ± 0.05	spherical	White	32.3	34º 43’	0.416	13.7 ± 1.8
GES6	64.8 ± 0.05	spherical	White	33.5	37º 40’	0.454	14.9 ± 1.5
GES7	75.6 ± 0.10	spherical	White	35.1	40º 60’	0.454	16.5 ± 2.1

(n = 3) for all results.

In-vitro drug release of microsphere

In-vitro release studies of the microspheres were carried out using 200 ml of dissolution medium contained in a glass diffusion cell agitated at 100 rpm and maintained at 37 ± 0.5 ºC by buffer change method. Accurately weighed samples of microspheres were put in the donor cell after suspending in 5 ml of the same buffer. At pre-set time intervals; 5 ml of aliquots were withdrawn and replaced by an equal volume of fresh pre-warmed dissolution medium [14-15]. The aliquots were analyzed spectrophotometrically at λ max 276 nm for drug content after filtration and dilution(s); where needed. All the readings were taken in triplicate and results were depicted as ± S.D.

Results and Discussion

The formulations had average particle size in the range of 101-400 µm, Carr’s index between 11-22%, Hausner ratio within 1.28 and angle of repose within the range of 26^0 to 40^0, which is within acceptable limit for microspheres. An increase in Drug: polymer proportion increased the average particle size of the microspheres.

The polymer concentration directly affected the

morphological and release characteristics of the formulations. Formulation with low polymer concentration like sample GES1, 2, 3 and 4 lead to uneven surface while high concentration of polymer (sample GES 5, 6 and 7) lead to smooth surfaces and even sized microspheres. The size proportionality increased with increase in polymer concentration. The release of drug from microspheres with low polymer concentration is fast reaching a maximum of 98% in 9-10 hrs (sample GES1) and slower to about 63-40% when polymer concentration is high during the same period (sample GES5, 6 and 7). The percentage yield 56-87% ranged from 71 to 86% (Table 1) and percentage entrapment 76% to 91% (Table 2). The swelling index increased while floating behavior decreased with increased polymer concentration (Table 2).

The formulations were white, spherical, discrete and smaller in size. No aggregations were observed when formulated at a stirring speed of 1000 rpm. The size of microspheres was in range of 101 to 400 µ (fig 3)

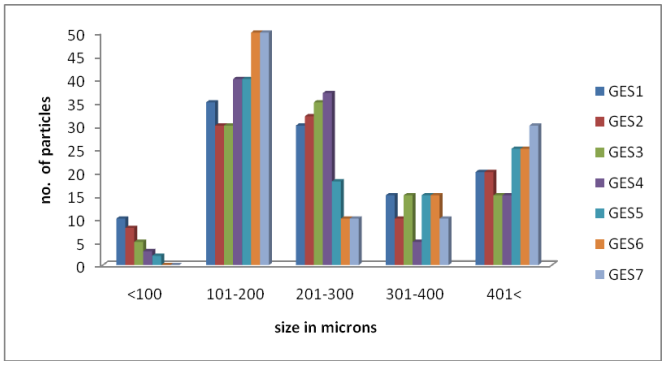

Fig 3: Size distribution of Eudragit microspheres

Release of the drug from floating microspheres was evaluated in dissolution media with varying pH as 1.2, 4.0, 6.0, 6.8, and 7.4 by buffer change method. pH 1.2 for 1 hr, pH 4.0 for 1 hr, pH 6.0 for 3 hrs, pH 6.8 for 3 hrs & pH 7.4 for 2 hrs. The release rate of Glipizide was almost linear with time for the first 10 hrs. Eudragit RS, ammonio methacrylate copolymers charged with ammonio functional groups, thus ionic drugs may interact with film in the presence of ionic drugs. Degree of swelling of membrane is affected by the drug, the pH well pH of solutions & effects of ionic strength. Membranes of ammonio copolymers or their pseudo latex solutions are insoluble in aqueous media; but, are swellable and permeable to drug.

Most of formulations i.e. GES1, 2, 3, 4 and 5 release about 68-51% of the drug within 7 hrs finally reaching a maximum of 98 to 63% respectively in 10 hrs dissolution run. Samples GES6 and GES7 with maximum polymer concentration released only about 48-55% of the drug in 10 hrs. An increased release was observed with all formulations which could be due to the dragging of drug to periphery of microspheres on reaching alkaline pH and sustaining the release. The polymer being swellable in all physiological pH and released the drug from the microspheres by diffusion kinetics (figure 4). The *in-vitro* kinetics regression values for Zero order and Higuchi equations were 0.985 and 0.984 respectively as compared to the First order, Korsmeyer peppas and Hixon crowel with values of 0.834, 0.797 and 0.914 respectively.

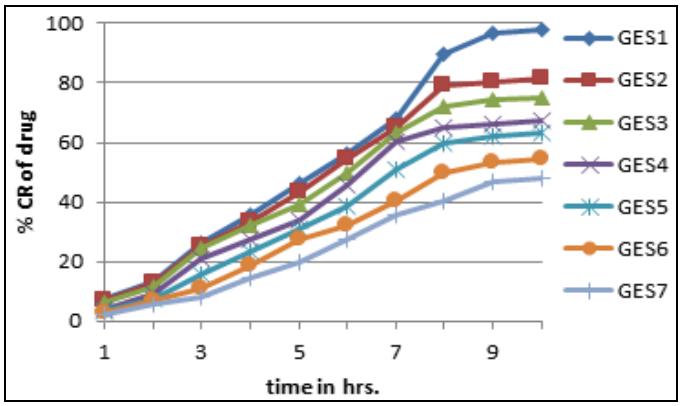

Fig 4: *In-vitro* release graph GES1-GES7

Table 3: *In-vitro* release kinetic equation data of eudragit microspheres (D: P- 1: 0.5 to 1:2)

Sample Code	Zero order	First order	Higuchi	Korsmeyer Peppas	Hixson Crowell
	R_0	R_1	R_H	R_K	R_{HC}
GES1	0.985	0.834	0.983	0.797	0.914
GES2	0.978	0.954	0.978	0.777	0.970
GES3	0.975	0.966	0.973	0.780	0.974
GES4	0.964	0.960	0.961	0.810	0.964
GES5	0.979	0.968	0.975	0.845	0.978
GES6	0.983	0.977	0.982	0.869	0.981
GES7	0.985	0.975	0.984	0.900	0.979

R= regression coefficient value
n=3

Conclusion

Eudragit microspheres of Glipizide were prepared using sodium lauryl sulphate (SLS) as the dispersing medium. Addition of SLS helps in decreasing the size of multi-particulate system. All microspheres were white, spherical, free flowing with size ranging from 101 to 400µ.

This method resulted in satisfactory yield, better entrapment of drug and swelling properties. The floating behavior was better in formulations with low polymer concentration. Sample GES1, 2 and 3 released above 73-90% of drug till the 8th hr while sample with higher polymer content (sample GES4, 5, 6 and 7) released a maximum of 48-67% but sustained the effect from 8th hr onwards.

In-vitro release profile showed greater drug release in formulations containing lesser proportion of polymer. Release of drug depended on the thickness of the polymer layer. SampleGES2 and GES3 showed a release of 75-81% in 10 hrs dissolution run. Sample GES7 showed an yield and entrapment of about 76%, but low floating behavior of about 17%.

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Conflicts of interest: There are no conflicts of interest.

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