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Research Article

Development of Sustained Release Multiple Unit Pellets of Glipizide using Pectin, Microcrystalline Cellulose and Eudragit L-100

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ABSTRACT

The aim of the present investigation was to develop sustained release Glipizide matrix pellets for Type II diabetis mellitus. The Glipizide matrix pellets were prepared by extrusion-spheronization method using different hydrophilic polymers such as pectin, microcrystalline cellulose (MCC) and Eudragit L-100 in various proportions to retard and prolong the release of Glipizide. The prepared matrix pellets were characterized through Infrared Spectroscopy (FTIR), Differential Scanning Colorimetry (DSC), circularity, roundness, pellips, percent drug content, percent production yield, and *in vitro* drug release. The *in vitro* dissolution studies showed that GSR 6 formulation had released (90.07 ±0.67) the drug in a controlled profile for 12 h which containing pectin (30%), MCC PH-101 (35%), Eudragit L-100 (26%) and Polyvinylpyrrolidone (PVP) K-30 (5%) w/w. The DSC and FTIR studies revealed that there was no interaction between drug and excipients. Stability studies were carried out for optimized formulation GSR 6 according to ICH guidelines. Stability studies (40±2^{0}C/75±5% RH) for a period of 3 months indicated that Glipizide was stable in matrix pellets. In comparison, drug dissolution profile with marketed Glipizide (Glytop 10®) SR Tablet (98.23±0.88 % release), formulation GSR 6 drug release was found to be lesser up to 12 h. In conclusion, different hydrophilic polymers (Pectin, Microcrystalline Cellulose, Eudragit L-100 and Polyvinylpyrrolidone K-30) at optimum ratios in matrix pellets had a promising potential for sustained release.

INTRODUCTION

The considerable growth and development in sustained drug delivery system can be attributed to several advantages that these products offer improved patient compliance, better therapeutic efficiency, potential for cost saving and patentability and opportunity for extending product life-cycle which can be achieved by better control of plasma drug levels and less frequent dosing . The most convenient way to achieve sustained release of active agent involves physical blending of drug with polymer matrix, followed by direct compression, compression molding, injection molding, extrusion or solvent casting which results either in monolithic device or in swellable hydrogel matrix [1-2]. When taken as an aggregate, directly compressed hydrophilic matrices are the demand of today's fast going era with both a scientific and economic appeal.

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Since the cost of synthesizing a new polymeric substance and testing for its safety is enormous [3].

Site-specific, targeted sustained drug delivery using novel formulation design approach would help to improve the systemic absorption and minimize dosing frequency. The basic rationale for sustained and controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and pharmacological parameter inherent in the second route of administration [4-5].

Pellets are a dominating player in the world of multiparticulate oral drug delivery and their use is on rise these days. Pellets are of great interest to the pharmaceutical industry for a variety of reasons. When pellets containing the active ingredient are administered *in vivo* in the form of suspensions, capsules, or disintegrating tablets,

they offer significant therapeutic advantages over single unit dosage forms. Because pellets having small size (<2 mm) and hence disperse freely in the gastrointestinal tract, they invariably maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering drug bioavailability. When formulated as modified release dosage forms, pellets are less susceptible to dose dumping than the reservoir type, single-unit formulations. Controlled release pellets are manufactured either to deliver the bioactive agent at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time. While these results have been traditionally achieved through the application of a functional coating material, at times the core pellets themselves have been modified to provide the desired effect [6-9].

Extrusion-spheronization was reported to be an effective technique for the preparation of CR multiparticulate formulations of bioactive agents. When pellets dried, they were having an extremely low friability and were ideally suited for film coating [10]. The interest in pellets as a dosage form (filled into hard capsules) has increased continuously, because their multiparticulate nature offers important pharmacological and technological advantages over conventional single-unit solid dosage forms [11]. To produce pellets by wet extrusion-spheronization the formulation must contain a pelletization aid and meet specific rheological requirements for the process [12]. Among the various types of multiple-unit dosage forms, pellets have attracted more attention due to their unique clinical and technical advantages. Extrusion-spheronization is one of the most popular methods of producing spherical pellets [13]. The release of drug from micro particles was found to depend on a variety of factors including the carrier used to form the multiparticles and the amount of drug contained in them [14].

A growing interest has been made in the development of matrix pellets formulations using some release retarding materials such as Pectin [15], MCC [16-17] or waxes [18-19] to obtain a sustained release effect. The matrix pellets can be prepared by pH dependent acrylic polymers such as Eudragit S [20] or Eudragit L 100 and S100 [21].

Single unit sustained release formulations of Glipizide are available commercially; however they are associated with the possibility of dose dumping. Therefore, multiple unit SR dosage forms of Glipizide are needed to prolong its duration of action and to improve patient compliance. Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes. Glipizide is a weak acid (pKa = 5.9) practically insoluble in water and highly permeable (class II) drug according to the Biopharmaceutical Classification System (BCS). The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half-life of 2- 4 h. and short biological half-life of 2-5 h. Sustained release formulations that would maintain plasma levels of drug for 8 to 12 h are advantageous, as they allow once a day dosing for Glipizide.

In the present work, we used hydrophilic polymers such as pectin, microcrystaline cellulose and Eudragit L-100 in combination for preparation of release retarding matrix pellets. These studies include the development and *in vitro* evaluation of sustained release matrix pellets of glipizide using different hydrophilic polymers in optimum ratios.

MATERIALS AND METHODS:

MATERIALS:

The Glipizide was obtained from Watson Pvt. Ltd. Mumbai, India; Pectin [Molychem, Mumbai, India], Microcrystaline cellulose PH-101 [Research lab Fine Chem.; Mumbai, India], Eudragit L-100 [Evonik Industries, Germany], Polyvinylpyrrolidone K-30 [S.D. Fines, Mumbai, India] were of labrotary grade and used without purification.

METHODS:

Drug polymer interaction studies:

Physical mixtures of drug and excipients were filled in the prewashed ampoules and sealed. They were kept at 37 ± 0.5°C for 28 days in stability chamber. After 28 days ampoules were removed and performed the drug-excipients compatibility studies by using Infrared spectroscopy (IR) and Differential Scanning Calorimetry (DSC).

Flow properties of drug, polymers and excipients:

Excipients, polymers and drug were characterized for their physical properties such as angle of repose, density, compressibility index, hausner's ratio. The angle of repose was determined by fixed funnel method. The

accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The angle of repose (1) was calculated from the height of the cone (h) and the radius [22].

$$\tan \theta = \frac{h}{r} \qquad (1)$$

Where, h and r are the height and radius of the powder cone.

The loose bulk density (LBD) and tapped bulk density (TBD) of drug, polymers and excipients were determined. 2 gm of powder was introduced into a 10 ml calibrated measuring cylinder. After noting down the initial volume, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 seconds intervals. The tapping was continued until no further change in volume was noted [23].

The compressibility index of all ingredients was determined by equation (2) [23].

$$C\text{arr}'\text{s Index} = \frac{(\text{TBD} - \text{LBD})}{\text{TBD}} \times 100 \qquad (2)$$

Hausner's ratio was determined by equation (3) [22].

$$\text{Hausner's ratio} = \frac{\text{Tapped bulk density}}{\text{Loose bulk density}} \qquad (3)$$

Preparation of matrix pellets:

Eight different formulation of matrix pellets containing Glipizide (4%w/w), Pectin, Microcrystalline cellulose, Eudragit L-100 and polyvinylpyrrolidone K-30 (5%w/w) were prepared by extrusion-spheronization process. The ratios of release retarding hydrophilic polymers are shown in table no.1. The drug Glipizide, the pelletization aid Pectin, MCC and sustained release polymer i.e. Eudragit L-100 were mixed in a mortar and pestle using IPA: water (30:70) and PVP K 30 as a binder solution for 20min to achieve a consistency of the damp mass. The prepared damp mass was immediately passed through a radial basket extruder using 1.2 mm diameter screen and uniform size extrudates were produced at a speed of 15 rpm. The extrudate were then spheronized in a Spheronizer with a rotation plate of regular crosshatch geometry for 15 min at a rotation speed of 800-1200 rpm. The resultant matrix pellets were dried at room temperature [24].

Characterization of pellets:

Flow properties of matrix pellets:

Pellets were characterized for their flow properties such as angle of repose, density, compressibility index, hausner's ratio as earlier.

Physical properties of matrix pellets:

Determination of particle size, roundness, circularity and Pellips:

The pellets were taken for particle size analysis and the average particle size was determined. Particle size of the pellets were measured and analyzed for their average diameter and different shape factors such as roundness, circularity and Pellips factor using a Motic DMWB2-223 digital microscope. The roundness (4), circularity (5) and pellips (6) values of the prepared pellets were determined.

$$\text{Roundness} = \frac{0.9399\text{P}}{4\pi\text{A}} \qquad (4)$$

$$\text{Circularity} = \frac{4\pi\text{A}}{\text{P2}} \qquad (5)$$

$$\text{Pellips} = \frac{\text{P}}{\pi \times \text{Dmax}} \qquad (6)$$

Where, P is the perimeter of the pellet image and A is the area determined by the total number of pixels within the feature. A roundness value of 1 corresponds to the image of a perfect sphere [24-25].

Percent friability:

Accurately weighed 200 mg of matrix pellets (Wi) were placed in the plastic chamber of a Roche Friabilator and subjected to impact testing at 25 rpm for 4 min. The pellets were then screened using a sieve number 40 and the weight of the pellets (Wf) retained on the sieve was measured. The results are expressed as the means of five determinations ± S.D. Percent friable amount was calculated using equation (7).

$$\text{Percent friable amount} = \frac{\text{Wi} - \text{Wf}}{\text{Wi}} \times 100 \qquad (7)$$

Where, Wi indicates initial weight of matrix pellets and Wf indicates the weight retained after 100 revolutions.

Table 1: Composition of different formulations of Glipizide matrix pellets (capsule 250 mg)

Composition in mg	GSR 1	GSR 2	GSR 3	GSR 4	GSR 5	GSR 6	GSR 7	GSR 8
Glipizide	10	10	10	10	10	10	10	10
Pectin	125	125	112.5	112.5	100	75	87.5	125
MCC	65	52.5	52.5	62.5	65	87.5	75	50
Eudragit L- 100	37.5	50	62.5	52.5	62.5	65	65	52.5
PVP K-30	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5

Table 2: Physical properties of drug, polymer and excipients

Ingredients	Parameters				
	Angle of Repose	Loose Bulk Density	Tapped Bulk Density	Hausner's Ratio	Compressibility Index
Glipizide	26.75±1.4	0.26±0.017	0.37±0.02	1.34±0.04	26.20±0.31
Pectin	31.12±1.1	0.82±0.05	1.31±0.05	1.44±0.42	30.85±1.29
Eudragit L-100	28.12±1.3	0.68±0.04	1.12±0.08	1.65±0.31	36.76±1.6
MCC PH-101	26.45±1.2	0.84±0.06	1.32±0.04	1.50±0.32	32.74±1.6

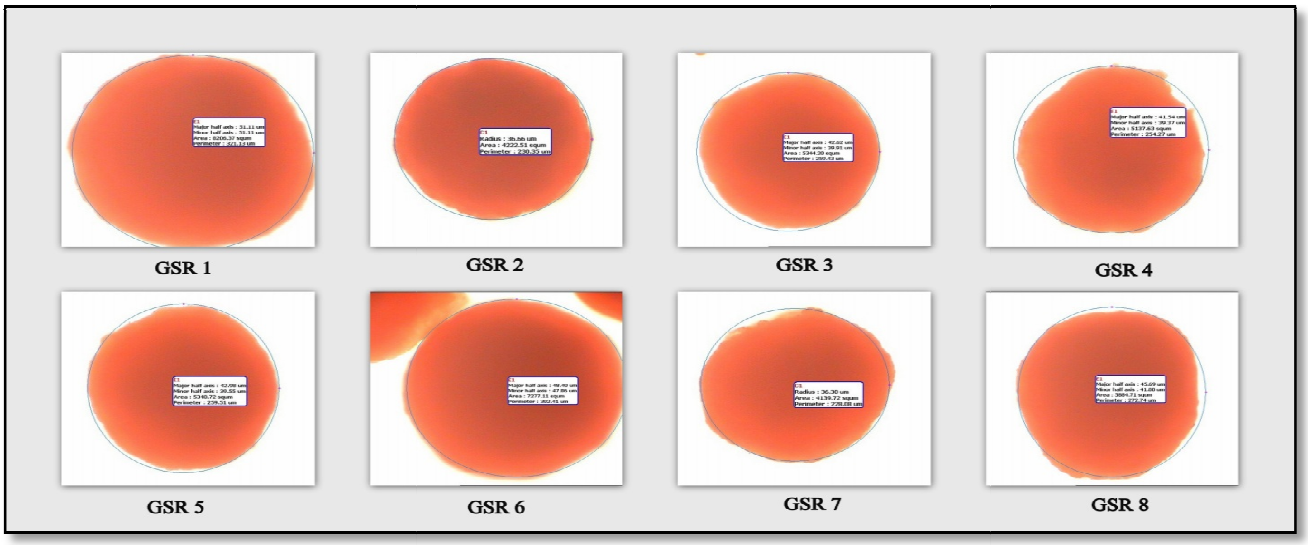

Figure 3: Particle size measurement of matrix pellets of different formulations.

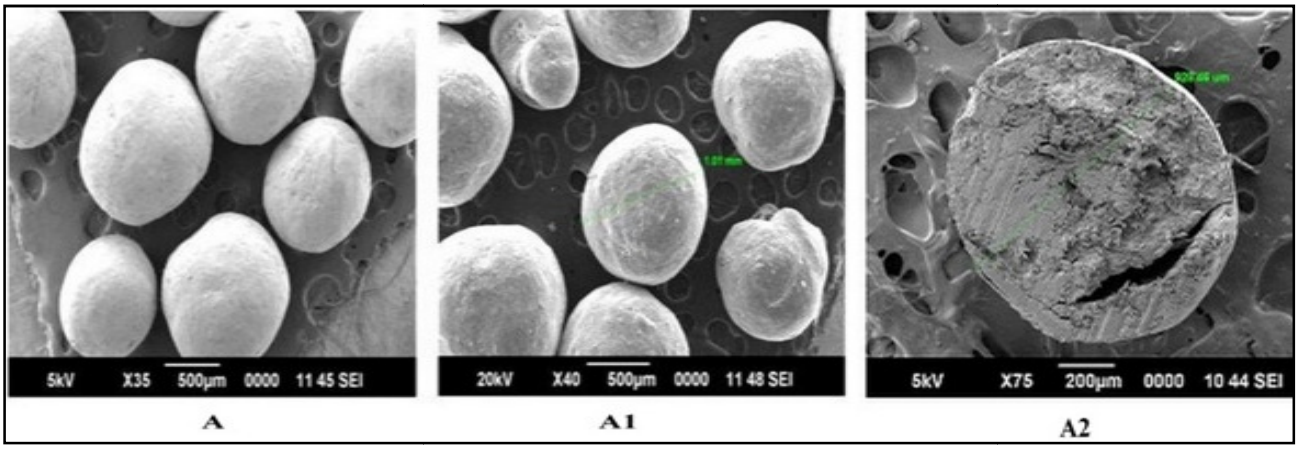

Figure 6: The photomicrograph of SEM studies of optimized formulation (GSR 6) shows surface morphology of matrix pellets (A), measured size of matrix pellet with its total diameter of 1.01 mm (A1) and cross section view of pellets (A2)

Table 3: Flow properties of matrix pellets of various batches

Batch no.	Flow rate (g/sec) ± S.D.	Angle of Repose (°) ± S.D.	Loose Bulk Density	Tapped Bulk Density	Hausner's Ratio± S.D.	Compressibility Index(%) ± S.D.
GSR 1	0.97±0.03	27.66±0.48	0.26±0.01	0.32±0.01	1.22±0.04	18.52±2.46
GSR 2	1.06±0.05	21.10±2.84	0.30±0.01	0.32±0.02	1.07±0.02	7.10±1.72
GSR 3	1.16±0.04	18.36±0.93	0.28±0.01	0.31±0.01	1.08±0.04	8.49±1.18
GSR 4	0.73±0.02	32.49±2.30	0.32±0.01	0.35±0.01	1.12±0.04	11.65±3.8
GSR 5	0.80±0.02	24.81±1.75	0.27±0.01	0.32±0.01	1.17±0.05	15.27±2.91
GSR 6	0.91±0.03	17.15±0.33	0.25±0.01	0.28±0.01	1.11±0.01	10.58±2.46
GSR 7	0.85±0.01	15.68±1.54	0.27±0.01	0.31±0.01	1.12±0.04	11.65±3.8
GSR 8	0.79±0.01	29.19±1.38	0.25±0.01	0.27±0.01	1.07±0.04	7.40± 3.31

Table 4: Particle size analysis of matrix pellets of different formulation

Batch No.	Particle size (mm) ± S.D	Roundness ± S.D	Circularity ± S.D	Pellips ± S.D	Friability (%)	Percent Production yield	% Drug content
GSR 1	1.25±0.11	1.123±0.031	1.004 ± 0.014	1.00± 0.010	1.88±0.16	76.50±1.50	87.52±0.54
GSR 2	1.38±0.19	1.098±0.251	0.992 ± 0.017	0.934 ± 0.072	1.07±0.08	66.20±0.90	88.81±0.86
GSR 3	1.38±0.11	1.118±0.032	0.997 ± 0.031	0.959 ± 0.055	0.73±0.11	61.83±0.27	91.07±0.54
GSR 4	0.87±0.24	0.541±0.020	1.014 ± 0.025	0.984 ± 0.016	1.18±0.10	75.20±0.60	94.40±0.43
GSR 5	0.94±0.19	0.503±0.009	0.996 ± 0.030	0.979 ± 0.021	1.21±0.07	64.93±0.77	92.03±0.22
GSR 6	0.91±0.15	0.538±0.102	0.996± 0.040	0.980 ± 0.013	0.82±0.06	83.76±1.04	95.48±0.64
GSR 7	0.87±0.22	0.560±0.100	0.998 ± 0.010	0.986 ± 0.014	1.10±0.18	71.56±1.44	94.72±0.76
GSR 8	1.01±0.18	0.503±0.138	0.991 ± 0.008	0.954 ± 0.040	1.59±0.17	67.50±0.90	89.02±0.65

Determination of production yield:
The yield of manufactured pellets was calculated using the weight of the final product after screening divided by the initial total weight of the formulation blend (drug and polymers) used for preparation of pellets.

Percent drug content:
250 mg of pellets equivalent to 10 mg of drug was accurately weighed, crushed, and dissolved in 70 mL of methanol for 15 min, diluted to 100 mL with same solvent and filtered. 10 mL of the filtrate was diluted to 100 mL with same solvent. Further dilution was done from 10 mL to 100 mL with methanol. The content of Glipizide was determined spectrophotometrically by measuring the absorbance at 276 nm. The results are expressed as mean values of three determinations ± S.D.

***In vitro* drug release study:**
In vitro drug release study was performed with 250 mg pellets equivalent to 10 mg of Glipizide which was filled in an empty capsule and marketed SR Tablet 10 mg by using type II (paddle) apparatus (Electrolab TDT- 08L plus, Dissolution tester USP Mumbai, India) at 100 rpm in pH 6.8 phosphate buffer at 37±0.5°C. The 5ml sample was withdrawn at predetermined time intervals (0,1,2,3,4,5,6,7,8,9,10,11 and 12 h) and replaced with fresh dissolution media. The withdrawn samples were filtered through membrane filter 0.45 µm and analyzed using UV spectrophotometer (1700, Shimadzu, Japan) at λmax 276 nm. This test was performed in triplicate and mean ± SD was calculated.

Kinetics modeling of drug release and release mechanism:
The data of drug release obtained from dissolution studies were fitted into Higuchi kinetics equation to determine the kinetics of drug release and its mechanism from matrix pellets into the dissolution medium.

FTIR and DSC
Pure drug, physical mixtures and formulation triturate were mixed separately with IR grade KBr and corresponding pellets were prepared and scanned over a wave range of 4000 to 400cm^{-1} using FTIR. Optimized Formulation GSR 6 triturate was mixed with IR grade KBr in the ratio of 1:100 and pellets were prepared by applying 10 metric ton of pressure in hydraulic

press. The pellets were scanned over a wave range of 4000-400 cm^{-1} in FTIR (8400 S Shimadzu).

The melting point of Glipizide was confirmed by DSC at the scanning rate of 10°C/min with 40 ml/min of nitrogen purging. The DSC measurements of formulated pellets of optimized formulation GSR 6 were performed on a differential scanning calorimeter (Mettler Toledo, Switzerland) with a thermal analyzer. Under nitrogen flow of 40 ml/min, 2 mg of samples were placed in a sealed aluminum pan, and heated at a scanning rate of 10°C/min from 35^0C to 400^0C. A sampling (aluminum) pan containing indium was used as reference. Comparison of formulation GSR 6 of sustained release matrix pellets (capsule) with marketed sustained release (Glytop 10 SR) tablet of Glipizide was carried out.

Percent drug content:

250 mg of pellets equivalent to 10 mg of drug were accurately weighed and marketed SR Tablet 10 mg, crushed separately, and dissolved in 70 mL of methanol for 15 min, diluted to 100 mL with same solvent, and filtered. 10 mL of the filtrate was diluted to 100 mL same solvent. Further dilution was done from 10 mL to 100 mL with methanol. The content of Glipizide was determined spectrophotometrically by measuring the absorbance at 276 nm separately. The results are expressed as mean values of three determinations ± S.D.

Surface topography:

The dried pellets of optimized formulation GSR 6 were mounted onto the stages prior to coating with gold to a thickness about 30 nm under vacuum. The morphology of the pellets was then observed under SEM (JSM 6390, India) [24].

Stability studies:

The accelerated stability studies were carried out according to International Conference on Harmonization (ICH) Q1A (R2) guide lines .The optimized matrix pellets GSR 6 powder were packed in amber colored glass vials, sealed with rubber plug and kept under temperature and moisture condition (40 ± 2ºC and 75 ± 5% RH) for a period of 3 months in stability chamber. The samples were withdrawn at 30, 60 and 90 days interval and evaluated for drug content and *in vitro* drug release.

RESULTS AND DISCUSSION

On the basis of above studies the sustained release matrix pellets were prepared and characterized. Figure 1 depicts the IR spectra of pure Glipizide (A) and in the same spectra most interesting bands observed were N-H stretching and C=O stretching in amide group at 3326 cm^{-1} and 1688 cm^{-1} respectively [26]. FTIR spectra were recorded for physical mixtures of Glipizide and pectin (B), Glipizide and MCC PH-101 (C), Glipizide and Eudragit L-100 (D), Glipizide and PVP K-30 (E) (Figure 1).

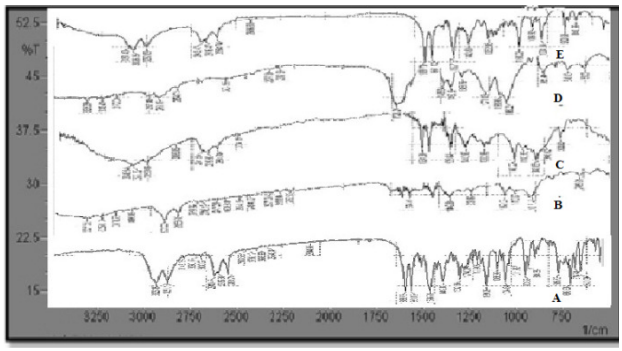

Figure 1: FTIR spectrums of pure drug (A) and different mixtures of Glipizide + pectin (B), Glipizide + MCC (C), Glipizide + Eudragit (D), Glipizide + PVP K-30 (E).

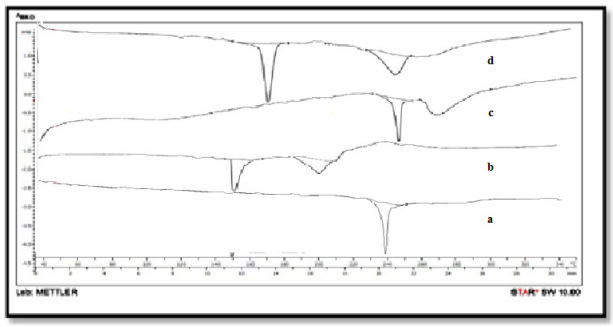

Figure 2: DSC thermogram of pure drug (a) and different physical mixtures of Glipizide + Pectin (b), Glipizide + Eudragit (c), Glipizide + MCC(d)

All the characteristic peaks of drug appear in the spectra of physical mixtures at the same wave number indicating no modification or interaction between drug and the polymers. The melting point of Glipizide was reported at 211°C. It was confirmed with reported melting point of Glipizide (209°C - 211°C) by DSC [26] and thermogram exhibited a sharp melting endothermic peak at 211°C (Figure 2 a). DSC thermogram of physical mixture of Glipizide with Pectin (b), Glipizide with MCC PH-101 (c) and Glipizide with Eudragit L-100 (d) (Figure 2) which elucidated that there was not any major difference in onset temperature and peak temperature, hence there was no interaction

found between drug and polymers in physical mixture. Drug, polymer and excipient were characterized for their physical properties such as angle of repose, loose bulk density, tapped bulk density, hausner's ratio and compressibility index (Table 2). Angle of repose of drug and polymer showed in the range of excellent to good indicating good flow potential for the pellets. However, the percent Carr's index and Hausner's ratio of drug and polymer showed in the range passable to poor, which indicates less compressibility. All eight formulations were also characterized for their physical properties such as angle of repose, loose bulk density, tapped bulk density, hausner's ratio and compressibility index (Table 3). The flow properties were found within limits. The particle size of matrix pellets of different formulations was found in the range of 0.5 to 2.0 mm which matches to standard limits. The roundness, circularity, pellips, percent friability, production yield, and percent drug content values were also within limits (Table 4). In which, GSR1, GSR3, GSR4 and GSR6 batches matrix pellets were found nearly spherical shape with good roundness and circularity values. The percent of pellet formulations that was friable in the range 0.73 ± 0.11 to 1.88 ± 0.16, which was within official limits. The production yield of all formulation was found in the range of 60 to 85%. This may vary due to different excipient ratio, process parameter in extrusion spheronization, binder concentration. The formulation GSR 6 showed drug content within limits (i.e. 95-100%). Particle size of different matrix pellet formulation was measured using a Motic DMWB2-223 digital microscope (Figure 3). Among all formulations, GSR 6 was selected as an optimized formulation based on *in vitro* drug release, which showed prolonged drug release up to 90.07% for 12 h (Figure 4).

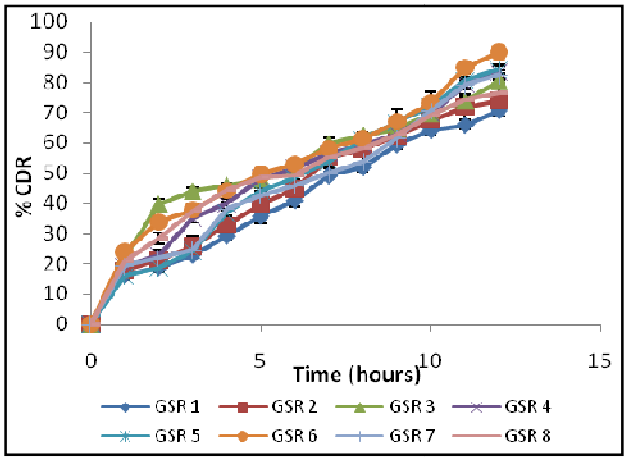

Figure 4: Dissolution profile of sustained release matrix pellets in phosphate buffer (pH 6.8)

The release kinetics of optimized formulation GSR 6 was calculated by applying the *in vitro* dissolution data to Higuchi release kinetics and it was found that the *in-vitro* drug release of Glipizide was best explained by Higuchi kinetics. The Higuchi kinetics were found to be fairly linear as indicated by their high regression value (R^2 = 0.971). Data for optimized formulation GSR 6 showed that passage of drug through rate controlling polymeric membrane was found to be dependent on square root of time and linear relation observed with regression coefficient. *In vitro* drug release study of Glipizide sustained release matrix pellets compared with marketed sustained release Tablet **(Glytop 10 SR®)** by using USP dissolution Type II apparatus (Paddle) and the results of % cumulative drug release of formulation GSR 6 and GSR Tablet (Glytop 10 SR)® was found to be 90.07±0.67 and 98.23±0.88 respectively at 12 h (Figure 5).

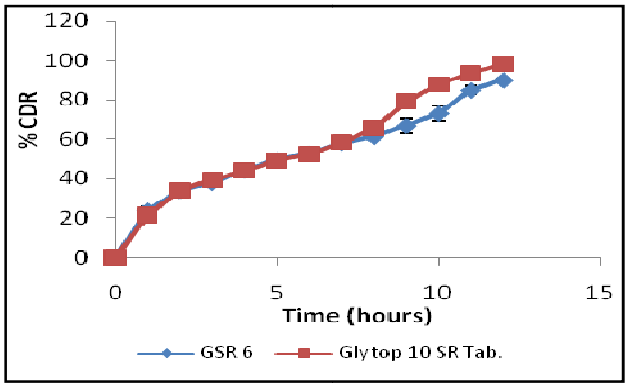

Figure 5: *In vitro* Drug Release of formulation GSR 6 and Glytop 10 SR® Tablet

Comparison Percent drug content for sustained released matrix pellets (capsule) formulation GSR 6 and marketed SR Tab **(Glytop 10 SR®)** was found to be 95.48±0.64 and 98.49±0.54 respectively**.** Both the batch showed drug content within limits. Surface topology, external morphology and cross section of pellets formulations GSR 6 was studied using scanning electron microscopy (Figure 6). The surface diameter of matrix pellets were found within the range of 0.5 to 1.5mm and the images were observed nearly spherical with smooth and regular surface without any fracture and cross section shows uniform distribution of drug in a polymer. Short term Stability studies were performed as per ICH guidelines. Physicochemical parameters determine at the interval of 30, 60 and 90 days and at the end of 90 days the % drug content and % drug release of formulation GSR 6 was found to be 89.99±0.65 and 84.20±0.1 and found that the pellets of

optimized batch (GSR 6) were stable even at exaggerated condition of temperature and humidity.

CONCLUSION

The sustained released matrix pellets of Glipizide were successfully prepared using Pectin, Eudragit L-100, MCC PH-101 as pelletization aid. Pellets of desired size, shape, flow characteristics were obtained. The shape of pellets was found circular and nearly spherical with mean diameter 0.5 mm to 1.5 mm in Motic digital microscope and in scanning electron microscopy. The result of % cumulative drug release of prepared sustained release matrix pellets was found to be 90.07±0.67 at the end of 12 h. This means the study demonstrated that the blending of hydrophilic polymers in optimum ratios could be used as effective release retarding carrier for Glipizide leading to formation of promising potential for oral administration.

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