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Research Article

DESIGN AND DEVELOPMENT OF ORAL CONTROLLED RELEASE FORMULATIONS OF GLICLAZIDE USING NATURAL POLYMERS

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ABSTRACT

Gliclazide is an oral hypoglycemic agent used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). Among the people who are suffering from long term disorders, the major had been categorized under the people who are suffering from diabetes and a dosage form is needed for them that should provide continuous therapy and should have a high margin of safety. Microencapsulation plays a great role in providing such a kind of dosage form. Gliclazide microspheres with a coat consisting of alginate and gum konda gogu were prepared by orifice-ionic gelation method and emulsification gelation technique. The prepared gliclazide microspheres were evaluated for surface morphology and particle shape, Carr's index, microencapsulation efficiency, drug release characteristics, compatibility studies rheological studies. The microspheres were found discrete, more spherical and free flowing with emulsion ionic gelation technique. The microsphere size was found in the range 420-585µm. Sharp endothermic peaks were found from the microspheres formulated with polymers indicating the compatibility between the drug and the polymer gum konda gogu. The encapsulation efficiency was found around 86.23%±0.56 to 94.46% ±0.86 and percentage drug content is in the range of 55±0.65% - 68±0.86%. Drug release from the microspheres was found slow, followed zero order release kinetics with non-fickian release mechanism stating release depended on the coat: core ratio and the method employed in the preparation of microspheres. Among two techniques emulsification gelation technique was found to be more suitable for slow and complete release over a long period. These microspheres showed good mucoadhesive property in the *in vitro* wash of test.

KEYWORDS: Gliclazide, gum Konda gogu, ionic orifice gelation technique, emulsification gelation technique.

INTRODUCTION

Microsphere carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. Recently dosage forms that can precisely control the release rates and target drugs to a specific body site have created enormous impact in formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems.[1-3] They have various applications and can be prepared using various polymers.[4] However, the success of these microspheres is limited due to their short residence time at the site of absorption. It would be more advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes in the form of mucoadhesive formulations.[5-8] Gliclazide, a second generation sulphonylurea derivative and is preferred in therapy because of its selective inhibitory activity towards pancreatic K+ ATP channels, antioxidant property, low incidence of producing severe hypoglycemia and other haemobiological effects. The daily dose, which is given in two fractions, is generally between 40 and 80 mg at the beginning of treatment, but the dose can be increased also at severe conditions. Gliclazide is well absorbed from GIT, approximately 80% is absorbed. One

dose of gliclazide has a half-life less than 10 hours with the peak absorbance occurring at about 4-6 hours. Like most sulphonylureas, gliclazide binds primarily to plasma albumin (85-99%), allowing it to be distributed uniformly throughout the body. Thus, an attempt is made in the present investigation to use gum Konda gogu as a mucoadhesive polymer and prepare microspheres to enhance the gastro-intestinal residence time.

Objective of the Work

The main objective of present study is to provide needed therapy for the treatment of NIDDM because, among the people who are suffering from long term disorders, the major were categorized under the people who are suffering from diabetes. A special dosage form is needed for them that can provide continuous therapy and have a high margin of safety. However, there are numerous drugs for treating type II diabetes, sulphonylureas and biguanides are used commonly by a wide section of patients. The microspheres of gliclazide were formulated by selected techniques and polymers then characterized by evaluating preformulation and post formulation parameters.

MATERIALS AND METHODS

Gliclazide was obtained as a gift sample from Aurobindo pharmaceuticals, Hyderabad, India). Gum Konda gogu was obtained as gift sample from Girizan Co-operative Corporation Ltd (Vishakhapatnam, India). Sodium alginate and calcium chloride, heavy liquid paraffin were procured from Central Drug House (CDH, Mumbai, India). All other reagents used were of analytical grade.

Microspheres of gliclazide were prepared by two methods

1. Ionic orifice gelation technique and
2. Emulsion ionic gelation technique

Method I: Gliclazide microspheres were prepared by Ionic orifice gelation technique by using different ratios of drug: Sod. Alginate: konda gogu polymer at concentrations (1:1:0.25, 1:1:0.5, 1:1:0.75, 1:1:1) and the batches were named as OMK1, OMK2, OMK3, OMK4. The pure drug is dispersed in the solution of sodium alginate and water and to this, the polymer was added and stirred to get a viscous aqueous dispersion. Drop wisely the dispersion was poured in 15% $CaCl_2$ solution using 22# needle by stirring at 50 rpm. The microspheres thus formed are allowed 30 min for curing in calcium chloride solution then were decanted and washed with petroleum ether and air dried over night at room temperature.

Method II: Gliclazide microspheres were prepared by Emulsion gelation technique by using different ratios of drug: Sod. Alginate: konda gogu polymer at concentrations (1:1:0.25, 1:1:0.5, 1:1:0.75, 1:1:1) and the batches were named as EMK1 , EMK2 , EMK3 , EMK4. The pure drug is dispersed in the solution of sodium alginate and water and to this, the polymer was added and stirred to get a viscous aqueous dispersion which was then extruded through a syringe needle 23# into light liquid paraffin containing 1.5% span-80 and 0.2% glacial acetic acid being kept under magnetic stirring at 500 rpm to undergo emulsification which hen leads to form spheres dispersed. Needed amount of 15% w/v calcium chloride solution is poured by continuing stirring, by which the formed spheres are exposed towards the calcium chloride. The formed spheres were allowed to keep as such for 30 minutes to finish curing process. The microspheres were decanted and washed with petroleum ether to remove liquid paraffin and water. They were collected by decantation and the product thus separated was washed with chloroform to remove the traces of paraffin oil and dried.

EVALUATION OF MICROSPHERES

Particle Size Analysis

The mean diameter of drug loaded microspheres was determined by optical microscopy by mounting the on a clean glass-slide and observed in the microscope. The eyepiece of the microscope fitted with a micrometer of calibrated for 1 unit was equal to 1/30mm (33.33 µm). All the three dimensions (lxbxh) of the microspheres were measured and average mean particle size is determined.

Scanning Electron Microscopy (SEM)

The surface, morphology, microspheres size, microspheres shape etc., were determined by Scanning Electron Microscopy (SEM). Dry microspheres were placed on an electron microscope brass

stub that is coated with gold in an ion sputter. Picture of micro particles were taken by random scanning ofthestub.

Bulk Density

Accurately weighed microspheres (Wm) were transferred into a 100-mL graduated cylinder to obtain the apparent volumes (V) of between 50 and 100 ml. The bulk density was calculated in gram per milliliter by the following formula:

$$\text{Bulk density } (\rho_0) = M/V_o$$

Where, M = mass of the powder, Vo = volume of the powder

Angle of Repose

A funnel was fixed in a stand in such a way the top of the funnel was at a height of 6cm from the surface. The microspheres were passed from the funnel so that they form a pile. The height and the radius of the heap were measured and the angle of repose was calculated using the equation.

$$\Theta = \quad h/r$$

% Drug Content Evaluation

Gliclazide microspheres were estimated by UV spectroscopic method based on the measurement of absorbance at 229 nm in phosphate buffer of pH 6.8. Microspheres containing equivalent to 80 mg of gliclazide were crushed to fine powder in a mortar, extracted with 10 ml of methanol, and made up to 100 ml with 6.8 pH. One ml of the sample solution was taken and made up to the volume to 10 ml with phosphate buffer 6.8 pH and the absorbance was measured at 229 nm. The procedure was repeated with pure gliclazide. The absorbance values from the pure drug and gliclazide were treated and %drug content is calculated. The absorbance values were not differed significantly (p.0.1) indicating no interface of konda gogu in the estimation of gliclazide. The method was validated for linearity, accuracy and precision.

Microencapsulation Efficiency

Microencapsulation efficiency was calculated using the following formula.

$$\text{Microencapsulation efficiency} = \left[\frac{\text{estimated percentage drug content}}{\textit{Theoratica l} \ \text{percentage drug content}} \right] \times 100$$

Determination of Wall Thickness

Wall thickness of microspheres was determined by using equation.

$$h = [r\,(1-P)\,d1/3\{Pd2 + (1-P)\,d1\}] \times 100$$

Where, h= wall thickness, r = arithmetic mean radius of microspheres, d1 and d2 are densities of core and coat material respectively, P is the proportion of medicament in microspheres. All the experimental units were studied in triplicate (n=3).

Differential Scanning Calorimetry (DSC)

DSC was performed on gliclazide drug loaded microspheres using Seiko (Japan) DSC model 220c. Samples were sealed in aluminum pans and the DSC thermo grams were reported at a heating rate of 10°/min from 20°to 200°.

X-Ray Diffraction Studies

Different samples were evaluated by X-ray powder diffraction. Diffraction patterns were obtained by using X-ray diffractometer with a radius of 240mm. The Cu Ka radiation was Ni filtered. A system of diverging and receiving slits of 1^o and 0.1mm respectively was used. The pattern was collected with 40 Kv of tube voltage and 30 mA of tube and scanned over the 2Θ range of $5\text{-}60^0$.

FT-IR Studies

Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, carrier and drug-loaded microspheres formulations were obtained using a Perkin- Elmer system 200 FT-IR spectrophotometer. The pellets were prepared on KBr-press under hydraulic pressure of 150kg/cm^2; the spectra were scanned over the wave number range of 4000 to 400 cm^{-1} at the ambient temperature.

***In Vitro* Wash-Off Test For Mucoadhesive Microspheres**

The mucoadhesive property of the microspheres was evaluated by an *in vitro* adhesion testing method known as wash-off method. A piece of intestinal mucous (2x2 cm) was mounted on to glass

slides of (3x1 inch) with Elastic bands. Glass slide was connected with a suitable support. About 50 microspheres were spread on to each wet tissue specimen and there after the support was hung on to the arm of a USP tablet disintegrating test machine. The disintegration machine containing tissue specimen was adjusted at slow, regular up and down moment in a test fluid at 37 ^{o}C taken in a beaker. AT the end of 1 hr and later at hourly intervals up to 8 hrs, the machine was stopped and the number of microspheres still adhering on to the tissue was counted. The test was performed in phosphate buffer of pH 6.8.

***In Vitro* Release Studies**

Microspheres containing equivalent to 80 mg of gliclazide were packed in hard gelatin capsule and subjected to *in vitro* drug release studies. Release of Gliclazide form microspheres was studied in 0.1 N HCl for first two hours and then transferred into Phosphate buffer of pH 6.8 (900 ml) using USP XXIV eight-station Dissolution rate test apparatus with a basket stirrer at 100 rpm at 37 ± 0.5^{o}C. 5 ml of aliquots was withdrawn at predetermined time intervals by replacing a fresh sample of dissolution medium. The absorbance of the collected samples measured using UV-spectrophotometer at λ_{max} 227 nm (0.1 N HCl) & 229 nm (Phosphate buffer of pH 6.8) nm. The release data fitted to zero order, first order, higuchi, and Korsmeyer peppas equations to determine the corresponding release rate and mechanism of drug release from the microspheres.

RESULTS & DISCUSSION

Gliclazide microspheres were prepared by ionic gelation process and emulsification gelation process employing gum konda gogu as the polymer. These microspheres were found to be discrete spherical and free flowing and the ability as indicated by angle of repose where the values are ranged around 25.3.^{O}-27.2^{O}, and the Carr's index, Hausner's ratio and true density results were found around 96.28-96.68, 0.03-0.04 and 0.90-0.96 respectively data showed in Table No 1. The SEM photographs indicated that the microspheres were spherical and completely covered with the coat polymer showed in Figure No 2. Low coefficient of variation (< 2.0%) was found in percent drug content indicated uniformity of drug content in each batch of microspheres. The Microencapsulation efficiency were found in the range of 55.09%-59.82% data showed in Table No 3. Gliclazide release from the microspheres was studied in phosphate buffer (pH 7.4) for 12 hours as prescribed for gliclazide tablets in USP XXIV. Gliclazide release from the microspheres was found slow which was controlled over extended period and release was found to be depended on the composition of the coat and method employed for the preparation of microspheres showed in Figure No 1. The model that best fits the release data was evaluated by correlation coefficient (r^2) showed in Table No 4. In most of the formulated microspheres, the r^2 values were higher in zero order models than that of first order model indicating the drug release from the most of the microspheres was according to zero order kinetics. The drug release mechanism from the microspheres was non-fickian transport as n value is in between 0.64-1.015. Microspheres with a coat consisting of alginate and gum Konda gogu exhibited good mucoadhesive properties in the *in vitro* wash-off test. The wash-off rate was faster at gastric pH than at intestinal pH. The results of the wash-off test indicated that the microspheres had good mucoadhesive properties. The wall thickness and permeability coefficient values are found in the desired range around 4.21-5.25 microns and 4.074 to 5.18 respectively data showed in Table No 2. In FT- IR spectra of gliclazide pure drug has many number of peaks were formed prominently at different wave numbers indicating the presence of functional groups & substituents like peaks at 1647 cm^{-1},1597 cm^{-1},1473 cm^{-1} wave number due to C=C stretching inside the benzyl ring ,prominent peaks at 1165 cm^{-1} ,1708 cm^{-1} due to C=O stretching , prominent peaks appeared at 2387 cm^{-1},2868 cm^{-1},2953 cm^{-1} wave number are due to CH asymmetric & symmetric stretching , in methyl group indicates the presence of methyl groups in the structure , peak 721 cm^{-1},752 cm^{-1} wave number are due to CH bending indicates the disubstituted benzene ring. Number of noise peaks in between 2250-2700 cm^{-1}wave number is, due to NH asymmetric & symmetric vibrations. This indicated the presence of amino group in the structure. Broad & intense peak appeared at 3275 cm^{-1} wave number due to N-N stretching indicates amine linkage in structure & peak at 1473 cm^{-1} wave number also indicates the presence of CN stretching and all these peaks were appeared unchanged in IR spectra of combinations gliclazide+ sodium alginate + gum Konda gogu. The data clearly states that there is no

interaction between the pure drug gliclazide & other excipients. Therefore, it can be said that the drug & excipients are compatible showed in Figure No 3.

In DSC thermograms the melting point of pure gliclazide was found at 164.67^{o}C & followed exothermic type of reaction where onset was started 160.58^{o}C & ends with 167.23^{o}C. the glass transition lag was found around 6.67^{o}C & the same exothermic type of reactions was found in combination of Gliclazide+ sodium alginate + gum Konda gogu. & no change was found in melting point as well as glass transition lag but special peaks were found indicating melting point of sodium aliginate at 204.42^{o}C, Konda gogu at 102.04^{o}C, & the influence of excipients were found only in changing intensity of melting point peak of gliclazide by absorbing heat but not by interactions. The above interpretational data clearly indicates that the crystalline nature of the drug had not been change & it doesn't under went any polymorphism because of no interaction which has proved by seeing its unchanged melting point in all combinational spectra.

Finally, by DSC data it is said that the drug & polymers are compatible. In XRD spectra, also the peaks that are appeared at specific 2Ǿ values in pure drug were also found in the spectra of sample showed in Figure No 4, 5.

CONCLUSION

The formulation OMK 4 containing drug: polymer ratio 1:4 was found to be the best formulation and the best technique orifice ionic gelation technique, regarding all properties evaluated in order to achieve objective of this study. The novel formulation design facilitated the optimization and successful development of gliclazide microspheres. Gliclazide release from the mucoadhesive microspheres was slow and extended over longer periods and depended on composition of the coat. Drug release was diffusion controlled and followed zero-order kinetics. These mucoadhesive microspheres are, thus, suitable for oral controlled release of gliclazide.

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Table 1: Physical properties of gliclazide microspheres formulated with Different Polymers by Orifice ionic gelation technique, mean ± S.D (n=3)

S.NO	FORMULATION CODE	ANGLE OF REPOSE	BULK DENSITY (g/cm^3)	CARR'S INDEX	HAUSNER'S RATIO	TRUE DENSITY (g/cm^3)	AVERAGE PARTICLE SIZE (µ)
1	OMK1	25.4±0.61	0.66±0.03	96.46±0.31	0.04	0.90±0.2	420±10
2	OMK2	26.3±0.72	0.63±0.04	96.35±0.46	0.04	0.96±0.4	460±18
3	OMK3	26.5±0.81	0.56±0.05	96.68±0.56	0.03	0.92±0.5	480±20
4	OMK4	25.3±0.73	0.64±0.06	96.28±0.51	0.04	0.94±0.3	485±10
5	EMK1	25.4±0.61	0.66±0.03	96.46±0.31	0.04	0.90±0.2	490±10
6	EMK2	26.3±0.72	0.63±0.04	96.38±0.46	0.04	0.96±0.4	510±5
7	EMK3	27.2±0.52	0.56±0.05	96.58±0.34	0.03	0.92±0.5	530±8
8	EMK4	25.3±0.73	0.64±0.06	96.28±0.51	0.04	0.94±0.3	528±5

Table 2: Wall thickness, release rate constant and permeability coefficient of microspheres prepared by various techniques.

S. NO	FORMULATION CODE	WALL THICKNESS (µ)	RELEASE RATE CONSTANT (mg/hr) ko	PERMEABILITY COEFFICIENT
1	OMK1	4.85±0.56	0.9774	4.740
2	OMK2	4.685±0.59	0.9695	4.542
3	OMK3	4.434±0.55	0.9561	4.239
4	OMK4	4.21±0.51	0.9685	4.077
5	EMK1	5.12±0.41	0.993	5.0852
6	EMK2	5.25±0.48	0.987	5.1833
7	EMK3	4.65±0.51	0.987	4.5914
8	EMK4	4.43±0.48	0.984	4.3609

***Mean ± S.D (n=3)**

Table 3: % Drug content and encapsulation efficiency of microspheres prepared by various techniques

SL. NO	FORMULATION CODE	D/P RATIO	% DRUG CONTENT	ENCAPSULATION EFFICIENCY (%)
1	OMK1	1:0.25	26.32±0.56	59.22±0.61
2	OMK2	1:0.5	22.48±0.57	56.21±0.52
3	OMK3	1:.75	20.02±0.59	55.09±0.56
4	OMK4	1:1	19.5±0.62	55.89±0.51
5	EMK1	1:0.25	27.32±0.76	59.82±0.41
6	EMK2	1:0.5	23.48±0.57	58.2±0.62
7	EMK3	1:.75	20.08±0.49	56.09±0.86
8	EMK4	1:1	21.5±0.55	57.89±0.61

***Mean ± S.D (n=3)**

Table 4: Release kinetics data of formulations prepared by orifice ionic gelation technique Method for all formulations

Formulations	Zero order	First order	Higuchi	Korsemeyer- Peppas	
	r^2	r^2	r^2	r^2	n
OMK1	0.9774	0.9037	0.8597	0.9037	0.8013
OMK2	0.9695	0.9322	0.8519	0.9113	0.7559
OMK3	0.9561	0.9056	0.8286	0.9056	0.8013
OMK4	0.9685	0.9322	0.9064	0.9322	0.6424
EMK1	0.9932	0.9675	0.9058	0.9932	1.077
EMK2	0.9873	0.7432	0.8853	0.9901	1.004
EMK3	0.9874	0.7628	0.8834	0.993	1.015
EMK4	0.9844	0.7907	0.8753	0.9911	1.02

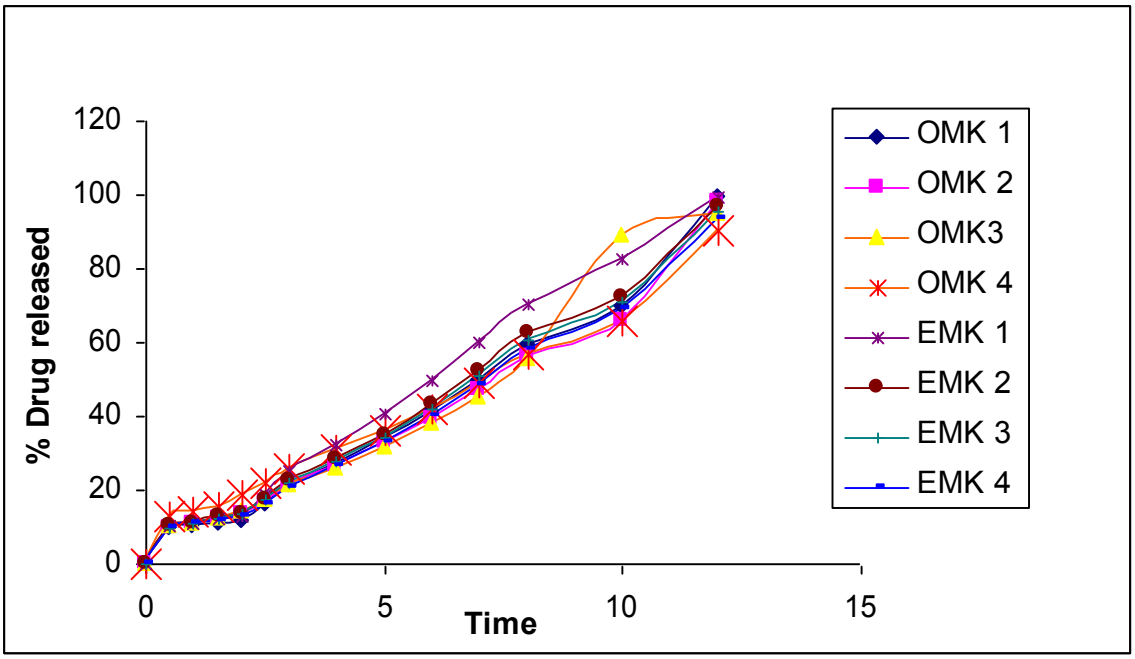


Figure 1: *In vitro* drug dissolution profiles of mucoadhesive microcapsules prepared by various techniques

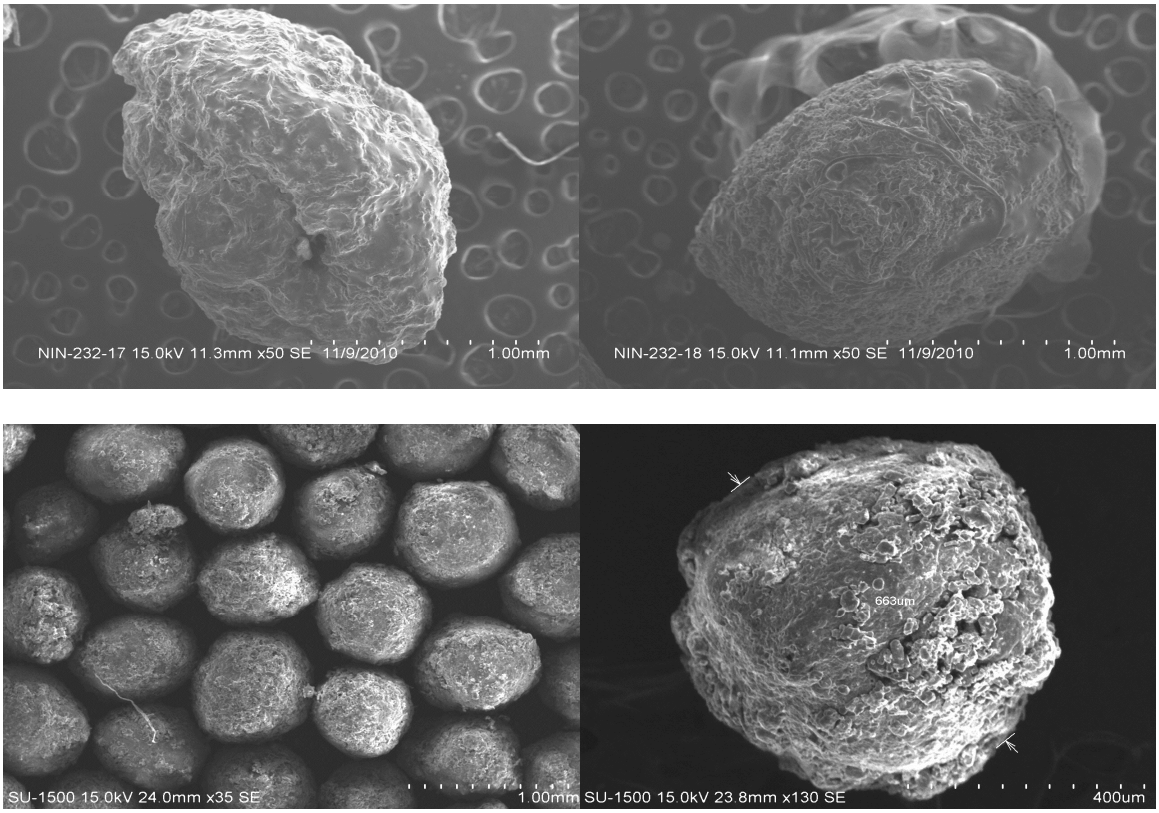
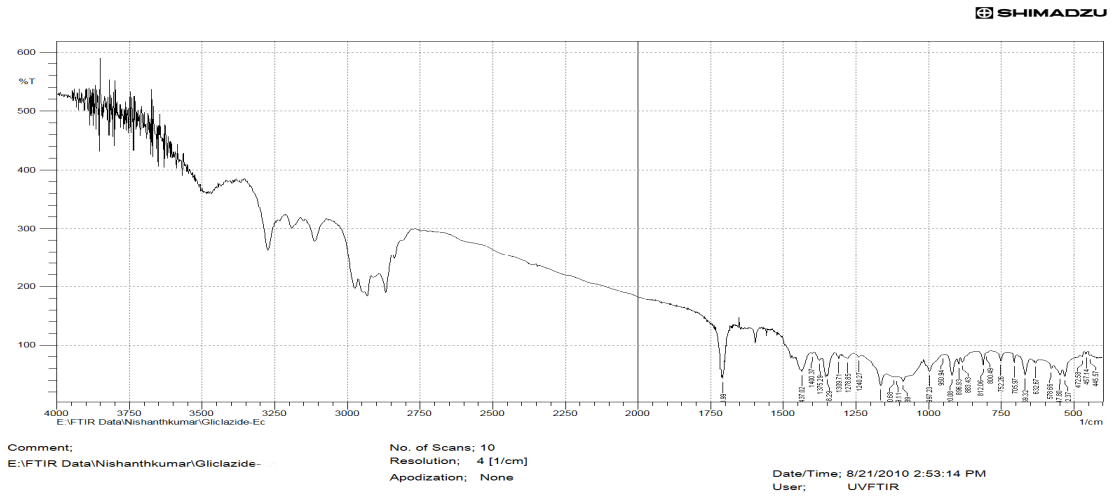


Figure 2: SEM Photograph of Gliclazide Microcapsules Formulated with Gum Konda gogu by Ionic orifice Gelation Technique and Emulsion Ionic gelation techniques



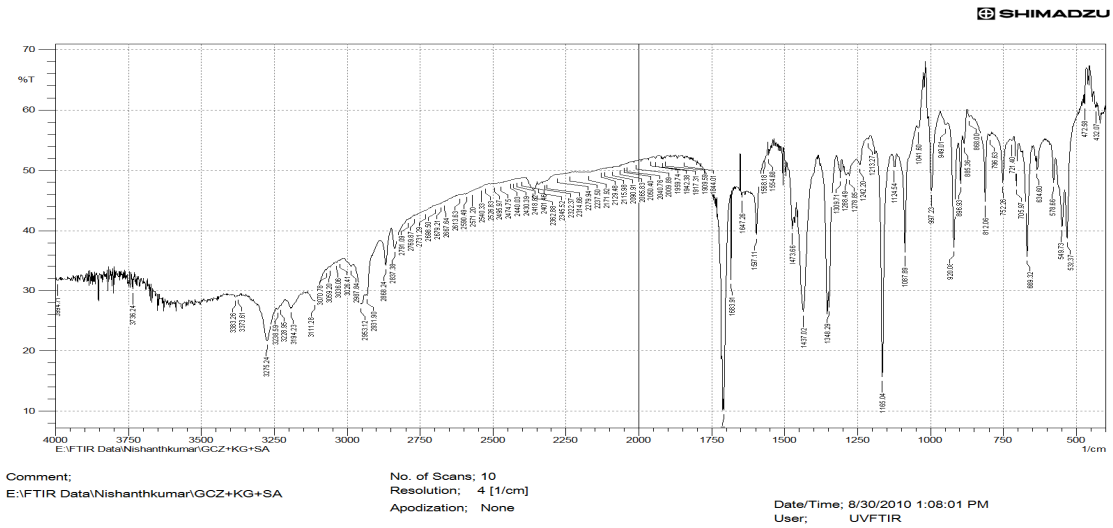


Figure 3: FTIR spectra of Gliclazide Pure drug and Gliclazide with Sodium alginate and Gum Konda gogu.

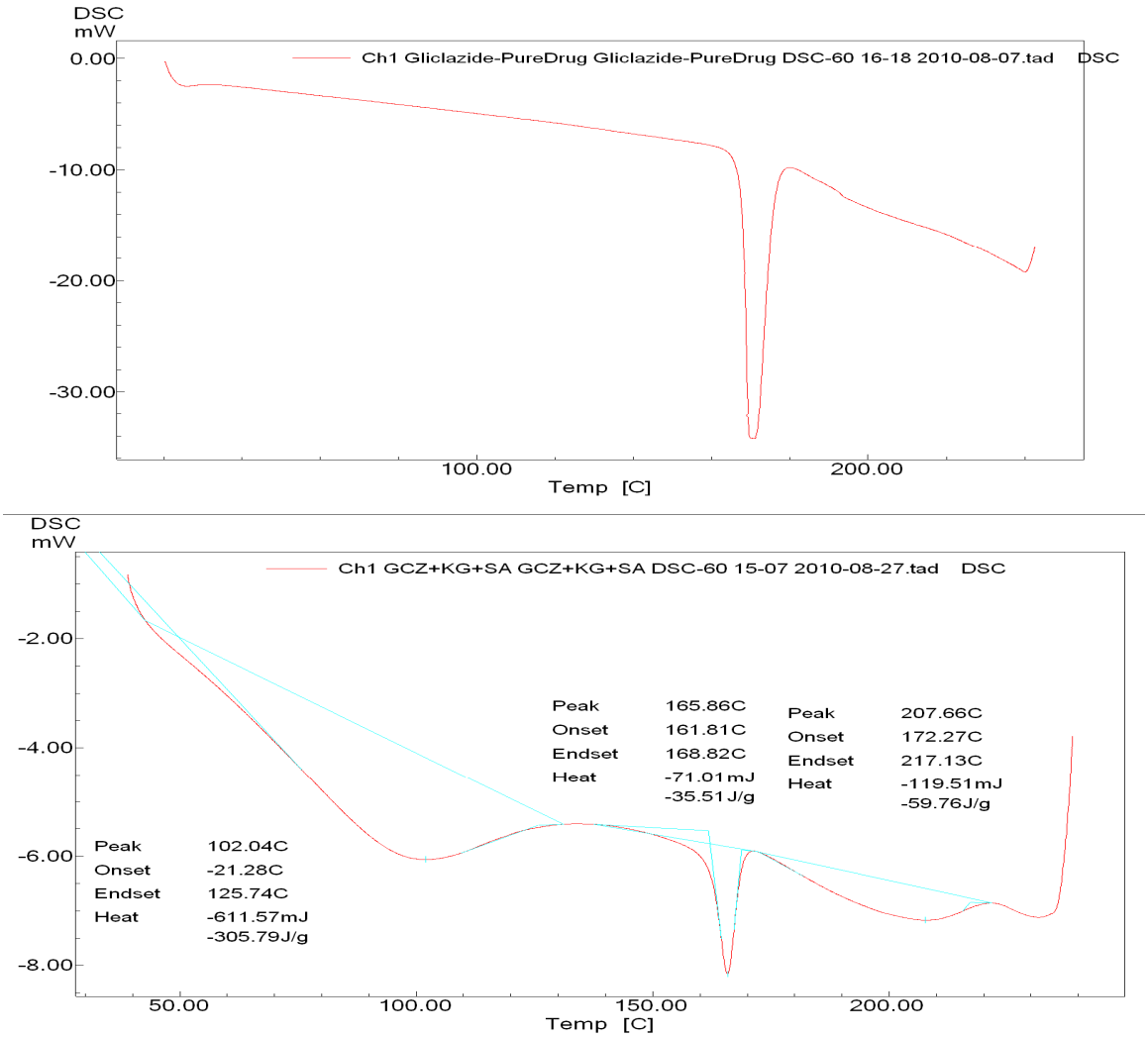


Figure 4: DSC thermogram of Gliclazide pure drug and gliclazide with sodium alginate and gum Konda gogu.

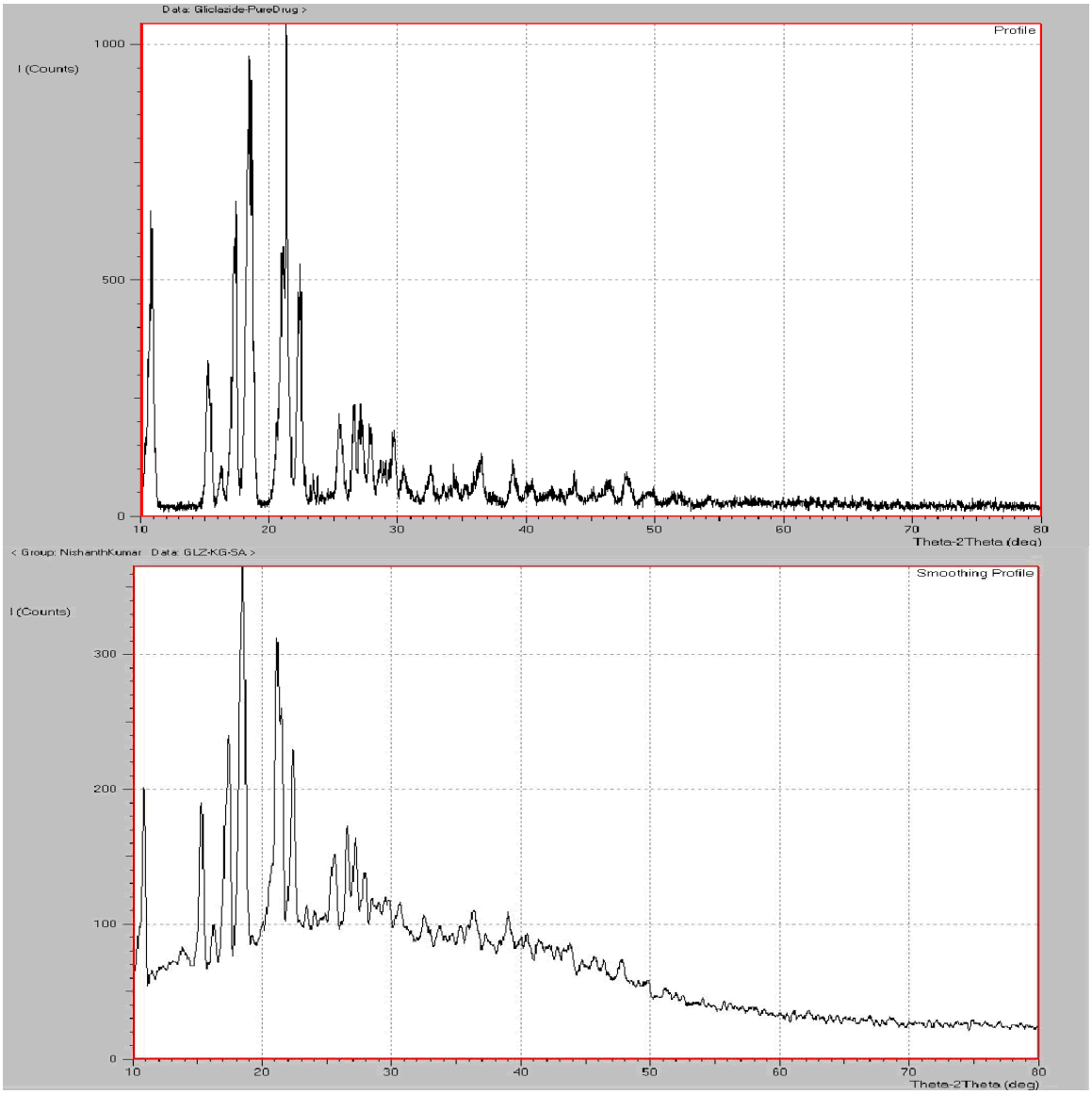


Figure 5: XRD spectrum of pure drug Gliclazide and gliclazide with sodium alginate and gum Konda gogu.

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