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Preparation and Characterization of Mucoadhesive Microcapsules of Gliclazide with Natural Gums

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Original Research Article

ABSTRACT

Gliclazide is an oral hypoglycemic agent used in management of non-insulin dependent diabetes mellitus. Among people who are suffering from long term disorders, the major were categorized under diabetes so, a dosage form is needed to provide continuous therapy with high margin of safety & such dosage form can be achieved by microencapsulation. Gliclazide microspheres with sodium alginate (coat material, gum kondagogu, gum guar and xanthan gum (mucoadhesive agents) were prepared by orifice-ionic gelation and emulsification ionic gelation techniques varying concentrations (1:0.25, 1:0.5, 1:0.75 and 1:1). Formulations were then evaluated for surface morphology, particle shape, Carr's index, microencapsulation efficiency, drug release, mucoadhesion studies. Compatibility studies were performed by FTIR, DSC, and XRD techniques and no interactions were found between drug and excepients used. The microspheres were found spherical and free flowing with emulsion ionic gelation technique with a size range 400-600µm. % drug content and encapsulation efficiency found in the range of 55%-68% and, 86.23%-94.46% respectively. All microspheres showed good mucoadhesive property in in-vitro wash of test. *In vitro* drug release studies showed that the guar gum has more potentiality to retard the drug release compared to other gums and concentrations. Drug release from the microspheres was found slow following zero order release kinetics with non-fickian release mechanism stating release depended on the coat: core ratio and the method employed. The concentration of 1:1 of SA: GG (EMG 4) found suitable for preparing the controlled release formulation of gliclazide stating emulsification gelation technique is the best among followed.

***Key words*:** Gliclazide, Natural gums, orifice ionic gelation technique, emulsification ionic gelation technique.

INTRODUCTION

Microsphere carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery (Bentia S., 1984) which can precisely control the release rates and target drugs to a specific body site with enormous impact in formulation and development of novel drug delivery systems. Microspheres form an important part of such delivery systems (Woo *et al.*, 2001, Capan *et al.*, 2003, Gohel *et al.*, 1998) they have varied applications and are prepared using various polymers (Vasir *et al.*, 2003). However; the success of these microspheres is limited due to their short residence time at the site of absorption. It would be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes (Ikeda *et al.*, 1992, Nagai *et al.*, 1984, Illum *et al.*, 1988, Schaefer *et al.*, 2000)

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The present study is aimed to develop microspheres of gliclazide. 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. Gliclazide is well absorbed by the body, approximately 80% is absorbed. One dose of gliclazide has a half-life of 11-12 hours with the peak absorbance occurring at about 4-6 hours. Like most sulphonyl ureas, gliclazide binds primarily to plasma albumin (85-99%), allowing it to be distributed uniformly throughout the body.

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 with 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 with natural gums as mucoadhesive agent were formulated by selected techniques and then characterized by evaluating preformulation and post formulation parameters.

MATERIALS

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

METHODOLOGY

Microspheres of gliclazide were prepared by two methods: Ionic orifice gelation technique and Emulsification ionic gelation technique (RamaKrishna *et al.,* 2008, Kosaraju *et al.,* 2007).

Orifice Ionic Gelation Technique

Gliclazide microspheres were prepared by using different ratios of drug: Sod. Alginate: natural gum as mucoadhesive polymer at concentrations (1:1:0.25, 1:1:0.5, 1:1:0.75, 1:1:1) with every gum (gum kondagogu, gum Xanthan, gum guar) and the batches were named as (OMK1, OMK2, OMK3, OMK4), (OMX1, OMX2, OMX3, OMX4) and (OMG1, OMG2, OMG3, OMG4). The pure drug is dispersed in the solution of sodium alginate and water and to this; the gum was added and stirred to get a viscous aqueous dispersion. Drop wisely the dispersion was extruded through 22# syringe needle and poured in 15% $CaCl_2$ solution by stirring at 50 rpm using a magnetic stirrer (Remi MS-301). The microspheres thus formed are allowed 30min for curing in calcium chloride solution then were decanted and washed with petroleum ether and air dried over night at room temperature.

Emulsification Ionic Gelation Technique

Gliclazide microspheres were prepared by using different ratios of drug: Sod. Alginate: natural gum as mucoadhesive polymer at concentrations (1:1:0.25, 1:1:0.5, 1:1:0.75, 1:1:1) with every gum (gum kondagogu, gum Xanthan, gum guar) and the batches were named as (EMK1, EMK2, EMK3, EMK4), (EMX1, EMX2, EMX3, EMX4) and (EMG1, EMG2, EMG3, EMG4). The pure drug is dispersed in the solution of sodium alginate and water and to this, the gum 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 (Remi MS-301) at 500 rpm to undergo emulsification which then 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 30minutes 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 method by mounting on a clean glass-slide and observed in the microscope (RamaKrishna *et al.*, 2009).

Scanning Electron Microscopy (SEM)

The surface, morphology, microspheres size, microspheres shape etc., were determined by Scanning Electron Microscopy (SEM) (SEM-LEICA, S430, UK).

Bulk Density

Bulk density was determined according to Lehr *et al.*, 1992. (Equation 1)

Bulk density (ϱ_0) = M/V_o **..... (1)**

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

Angle of Repose

Angle of repose was determined according to Lieberman *et al.*, 1990. (Equation 2)

$\Theta = h/r$ **……. (2)**

% Drug Content Evaluation

Microspheres equivalent to 80mg of gliclazide were crushed in a mortar and extracted with 10ml of methanol then volume adjusted up to 100ml with 6.8 pH phosphate buffer. 1ml of the aliquot was taken and made up to the volume 10ml with phosphate buffer 6.8 pH and absorbance was measured at λ_{max} 229 nm using UV visible spectrophotometer (Schimazdu UV-1700-E23). The procedure was repeated with pure gliclazide and %drug content is calculated.

Microencapsulation Efficiency

Microencapsulation efficiency was calculated (Raparla *et al.*, 2010). (Equation 3)

$$\text{Microencapsulation efficiency} = \left[\frac{\text{estimated percentage drug content}}{\text{Theoratical percentage drug content}}\right] \times 100 \quad \text{....3}$$

Determination of Wall Thickness

Wall thickness of microspheres was determined (Lieberman *et al.*, 1990) (equation 4).

$$h = [r\,(1-P)\,d1/3\{Pd2 + (1-P)\,d1\}] \times 100 \quad \text{..... (4)}$$

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 Differential scanning calorimeter (Seiko Japan. DSC model 220C). Samples were sealed in aluminum pans and the DSC thermo grams were reported at a heating rate of 10°C/min from 20°Cto 200°C.

X-Ray Diffraction Studies

Different samples were evaluated by X-ray powder diffraction. Diffraction patterns were obtained by using X-ray diffractometer (XRD-Shimadzu 7000) with a radius of 240mm. The Cu, Ka radiation was Ni filtered. A system of diverging and receiving slits of 1° 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 5-60°.

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**

A piece of intestinal mucosa (2x2 cm) was mounted on to glass slide of (3x1 inch) using elastic bands. About 50 microspheres were spread on each wet tissue specimen and then the slide was hung on to the arm of a USP tablet disintegrating test apparatus. The disintegration machine containing tissue specimen was

adjusted for up and down moment in 6.8pH phosphate buffer at 37°C in a beaker. Number of microspheres still adhering on to the tissue was counted at hourly intervals up to 8 hrs (Raparla *et al.*, 2010).

***In vitro* Release Studies**

Microspheres equivalent to 80mg gliclazide were packed in hard gelatin capsules and subjected to *in vitro* drug release studies in 0.1N HCl for first two hours and then transferred into pH 6.8 phosphate buffer (900ml) using USP XXIV eight-station dissolution test apparatus (Electrolab ETD-209) with a basket stirrer at 100 rpm at 37 ± 0.5°C for 12hrs. Samples were withdrawn at predetermined time intervals and analyzed by UV-spectroscopy at λ_{max} 227nm (0.1N HCl) & 229nm (pH 6.8 phosphate buffer). The data used to determine rate, order and mechanism of drug release (Higuchi *et al.*, 1963, Korsmeyer *et al.*, 1983, Ritger *et al.*, 1987).

RESULT AND DISCUSSION

All formulations were found spherical and free flowing with angle of repose values around 23.2±0.61°-25.7±.0.84°. Carr's index, Hausner's ratio and true density results were found around 96.13±0.51-96.93±0.41, 0.03-0.04 and 0.79±0.4-0.96±0.1 respectively (Table 1a & 1b). The SEM photographs indicated that the microspheres were spherical and completely covered with the coat polymer (Fig. 1). The Microencapsulation efficiency was found around 57.50±0.59%-61.68±0.43% indicating uniformity in drug content (Table 2a & 2b).

Drug release from the microspheres was found slow and controlled and release depended on the composition of the coat and method employed for the preparation (Fig. 2a & 2b). In most of the formulations, the r^2 values (Table 3a & 3b) found higher in zero order models than first order models indicating release followed zero order kinetics and followed non-fickian mechanism with n-value between 0.8965-1.0421. Microspheres containing xanthan gum showed good mucoadhesion and rate was found faster at gastric pH than at intestinal pH indicating good mucoadhesive property in intestinal pH. The wall thickness and permeability coefficient values were found around 4.12±0.46-5.85±0.56μ and 4.067-5.790 respectively (Table 4a & 4b).

IR spectra of gliclazide pure drug showed much number of prominent peaks at different wave numbers indicating presence of functional groups & substituents. Peaks at 1647cm^{-1}, 1597cm^{-1}, and 1473cm^{-1} because of C=C stretching inside the benzyl ring, at 1165cm^{-1}, 1708cm^{-1} because of C=O stretching, at 2387cm^{-1}, 2868cm^{-1}, 2953cm^{-1} because of C=H asymmetric & symmetric stretching in methyl groups, at 721cm^{-1}, 752cm^{-1} because of C-H bending in di-substituted benzene ring. Peaks between 2250-2700cm^{-1} because of N-H asymmetric & symmetric vibrations in amino group. Broad & intense peak appeared at 3275cm^{-1} and 1473cm^{-1} because of N-N stretching in amine linkage and C-N stretching respectively. All these peaks were appeared unchanged in IR spectra of all compositions and data clearly states that drug & excepients were found compatible without interaction (Fig. 3).

The melting point of pure gliclazide was found at 164.67°C following exothermic reaction with on-set and end-set at 160.58°C & 167.23°C respectively with a glass transition lag around 6.67°C & the same found in all compositions with no change in both melting point and glass transition lag. Special peaks were found indicating melting point of sodium alginate at 204.42°C, Guar gum at 105.07°C, Kondagogu gum at 102.04°C, Xanthan gum at 106.93°C. Influence of excepients was found only in changing on's & end's of melting point peak of gliclazide by absorbing heat but not by interactions indicating unchanged crystalline nature of the drug without undergoing polymorphism in all formulations. X-ray diffractogram of gliclazide confirmed its crystalline nature as evidenced from the number of sharp & intense peaks. The diffractogram of gliclazide with polymers showed diffused peaks indicating polymers amorphous nature. Diffraction pattern of samples spectra represent availability of crystalline peaks of drug situated at 16.23, 19.56, 21.12, and 23.56 (2θ) similar to the pure drug. The obtained 2θ values as characteristic peaks were found at the same position in all compositions but the intensities

Table 1a. Physical properties of gliclazide microspheres formulated with natural gums by Orifice ionic gelation technique.

Sl. no	Formulation code	Angle of repose	Bulk density (g/cm3)	Carr's index	Hausner's ratio	True density (g/cm3)	Average particle size
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	OMG1	24.6±0.91	0.60±0.03	96.63±0.49	0.03	0.83±0.5	500±5
6	OMG2	25.2±0.63	0.55±0.02	96.39±0.59	0.04	0.91±0.2	515±6
7	OMG3	24.8±0.74	0.57±0.09	96.25±0.41	0.04	0.93±0.3	525±8
8	OMG4	24.3±0.91	0.62±0.06	96.34±0.51	0.03	0.89±0.1	530±10
9	OMX1	25.7±.0.84	0.61±0.04	96.93±0.41	0.04	0.79±0.4	525±5
10	OMX2	23.2±0.91	0.66±0.06	96.25±0.49	0.03	0.87±0.5	534±8
11	OMX3	25.6±0.71	0.56±0.04	96.33±0.65	0.04	0.94±0.2	545±10
12	OMX4	24.8±0.82	0.59±0.05	96.13±0.51	0.04	0.96±0.1	555±5

*Mean ± S.D (*n*=3)

Table 1b. Physical properties of gliclazide microspheres formulated with natural gums by Emulsion ionic gelation technique.

Sl. no	Formulation code	Angle of repose	Bulk density (g/cm3)	Carr's index	Hausner's ratio	True density (g/cm3)	Average particle size
1	EMK1	25.4±0.61	0.66±0.03	96.46±0.31	0.04	0.90±0.2	490±10
2	EMK2	26.3±0.72	0.63±0.04	96.38±0.46	0.04	0.96±0.4	510±5
3	EMK3	27.2±0.52	0.56±0.05	96.58±0.34	0.03	0.92±0.5	530±8
4	EMK4	25.3±0.73	0.64±0.06	96.28±0.51	0.04	0.94±0.3	528±5
5	EMG1	24.6±0.91	0.60±0.03	96.63±0.49	0.03	0.82±0.5	510±10
6	EMG2	25.2±0.63	0.56±0.04	96.39±0.59	0.04	0.91±0.2	525±5
7	EMG3	24.8±0.74	0.57±0.09	96.25±0.41	0.04	0.93±0.3	528±8
8	EMG4	24.3±0.91	0.60±0.07	96.34±0.51	0.03	0.89±0.1	531±6
9	EMX1	25.7±.0.84	0.61±0.04	96.58±0.43	0.04	0.79±0.4	500±10
10	EMX2	23.2±0.61	0.68±0.06	96.25±0.49	0.03	0.87±0.5	498±12
11	EMX3	25.6±0.71	0.56±0.04	96.33±0.65	0.04	0.94±0.2	506±10
12	EMX4	24.8±0.82	0.59±0.05	96.15±0.51	0.04	0.96±0.1	512±8

*Mean ± S.D (*n*=3)

Table 2a. % Drug content and encapsulation efficiency of microspheres prepared by orifice ionic gelation technique.

Sl. No	Formulation code	D/P ratio	% Drug content	Encapsulation efficiency (%)
1	OMG1	1:0.25	31.91±0.64	72.05±0.48
2	OMG2	1:0.5	28.03±0.68	70.05±0.51
3	OMG3	1:.75	24.63±0.58	67.79±0.83
4	OMG4	1:1	23.11±0.56	69.33±0.40
5	OMX1	1:0.25	29.09±0.85	60.69±0.53
6	OMX2	1:0.5	23.04±0.79	57.50±0.59
7	OMX3	1:.75	21.37±0.68	58.80±0.41
8	OMX4	1:1	19.96±0.48	59.90±0.43
9	OMK1	1:0.25	26.32±0.56	59.22±0.61
10	OMK2	1:0.5	22.48±0.57	56.21±0.52
11	OMK3	1:.75	20.02±0.59	55.09±0.56
12	OMK4	1:1	19.50±0.62	55.89±0.51

*Mean ± S.D (*n*=3)

Table 2b. % Drug content and encapsulation efficiency of microspheres prepared by emulsion ionic gelation technique.

Sl. No	Formulation code	D/P ratio	% drug content	Encapsulation efficiency (%)
1	EMG1	1:0.25	32.15±0.54	72.55±0.58
2	EMG2	1:0.5	28.83±0.48	71.05±0.41
3	EMG3	1:.75	25.13±0.68	68.73±0.63
4	EMG4	1:1	24.21±0.46	70.33±0.50
5	EMX1	1:0.25	30.09±0.65	61.68±0.43
6	EMX2	1:0.5	24.04±0.49	58.5±0.69
7	EMX3	1:.75	22.37±0.58	59.8±0.51
8	EMX4	1:1	20.96±0.68	60.9±0.63
9	EMK1	1:0.25	27.32±0.76	59.82±0.41
10	EMK2	1:0.5	23.48±0.57	58.2±0.62
11	EMK3	1:.75	20.08±0.49	56.09±0.86
12	EMK4	1:1	21.50±0.55	57.89±0.61

*Mean ± S.D (*n*=3)

Table 3a. Release kinetics data of formulations prepared by orifice ionic gelation technique.

Formulation code	Zero order	First order	Higuchi	Korsemeyer- Peppas	
	r^2	r^2	r^2	r^2	n
OMG1	0.9824	0.9387	0.9401	0.9864	1.1485
OMG2	0.9922	0.9444	0.9334	0.9945	1.1106
OMG3	0.9816	0.9481	0.9381	0.9889	1.0841
OMG4	0.9917	0.9673	0.9453	0.9952	0.9782
OMX1	0.9871	0.7337	0.9213	0.9916	0.9922
OMX2	0.9901	0.9584	0.9476	0.9977	0.9457
OMX3	0.9872	0.8497	0.9241	0.9874	0.8965
OMX4	0.9872	0.9439	0.9335	0.9892	0.9521
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

Table 3b. Release kinetics data of formulations prepared by emulsion ionic gelation technique.

Formulation code	Zero order	First order	Higuchi	Korsemeyer- Peppas	
	r^2	r^2	r^2	r^2	n
EMG1	0.9899	0.9387	0.925	0.9928	1.0220
EMG2	0.9908	0.945	0.9291	0.9900	1.0167
EMG3	0.9905	0.9518	0.9307	0.9930	1.0066
EMG4	0.9911	0.9617	0.9349	0.9940	0.9778
EMX1	0.9934	0.7172	0.9375	0.9952	1.0413
EMX2	0.9930	0.8041	0.9356	0.9944	1.0421
EMX3	0.9927	0.8685	0.9318	0.9933	1.0305
EMX4	0.9917	0.8601	0.9284	0.9941	1.0421
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	1.020

Table 4a. Wall thickness, release rate constant and permeability coefficient of microspheres prepared by orifice ionic gelation technique.

Sl. No	Formulation code	Wall thickness (μ)	Release rate constant (mg/hr) ko	Permeability coefficient
1	OMG1	5.98±0.34	0.9824	5.875
2	OMG2	5.138±0.56	0.9922	5.098
3	OMG3	4.23±0.49	0.9816	4.152
4	OMG4	3.68±0.51	0.9917	4.403
5	OMX1	5.65±0.49	0.9871	5.577
6	OMX2	5.42±0.51	0.9901	5.366
7	OMX3	4.65±0.41	0.9872	4.590
8	OMX4	4.12±0.46	0.9872	4.067
9	OMK1	4.85±0.56	0.9774	4.740
10	OMK2	4.685±0.59	0.9695	4.542
11	OMK3	4.434±0.55	0.9561	4.239
12	OMK4	4.21±0.51	0.9685	4.077

*Mean ± S.D (*n*=3)

Table 4b. Wall thickness, release rate constant and permeability coefficient of microspheres prepared by emulsion ionic gelation technique.

Sl. No	Formulation code	Wall Thickness (μ)	Release Rate Constant (mg/hr) ko	Permeability Coefficient
1	EMG1	6.12±0.41	0.993	6.0796
2	EMG2	5.63±0.46	0.990	5.5737
3	EMG3	4.63±0.51	0.992	4.5962
4	EMG4	4.04±0.4	0.992	4.0077
5	EMX1	5.85±0.56	0.989	5.7909
6	EMX2	5.68±0.51	0.990	5.6277
7	EMX3	4.85±0.46	0.990	4.8039
8	EMX4	4.44±0.50	0.990	4.3956
9	EMK1	5.12±0.41	0.993	5.0852
10	EMK2	5.25±0.48	0.987	5.1833
11	EMK3	4.65±0.51	0.987	4.5914
12	EMK4	4.43±0.48	0.984	4.3609

*Mean ± S.D (*n*=3)

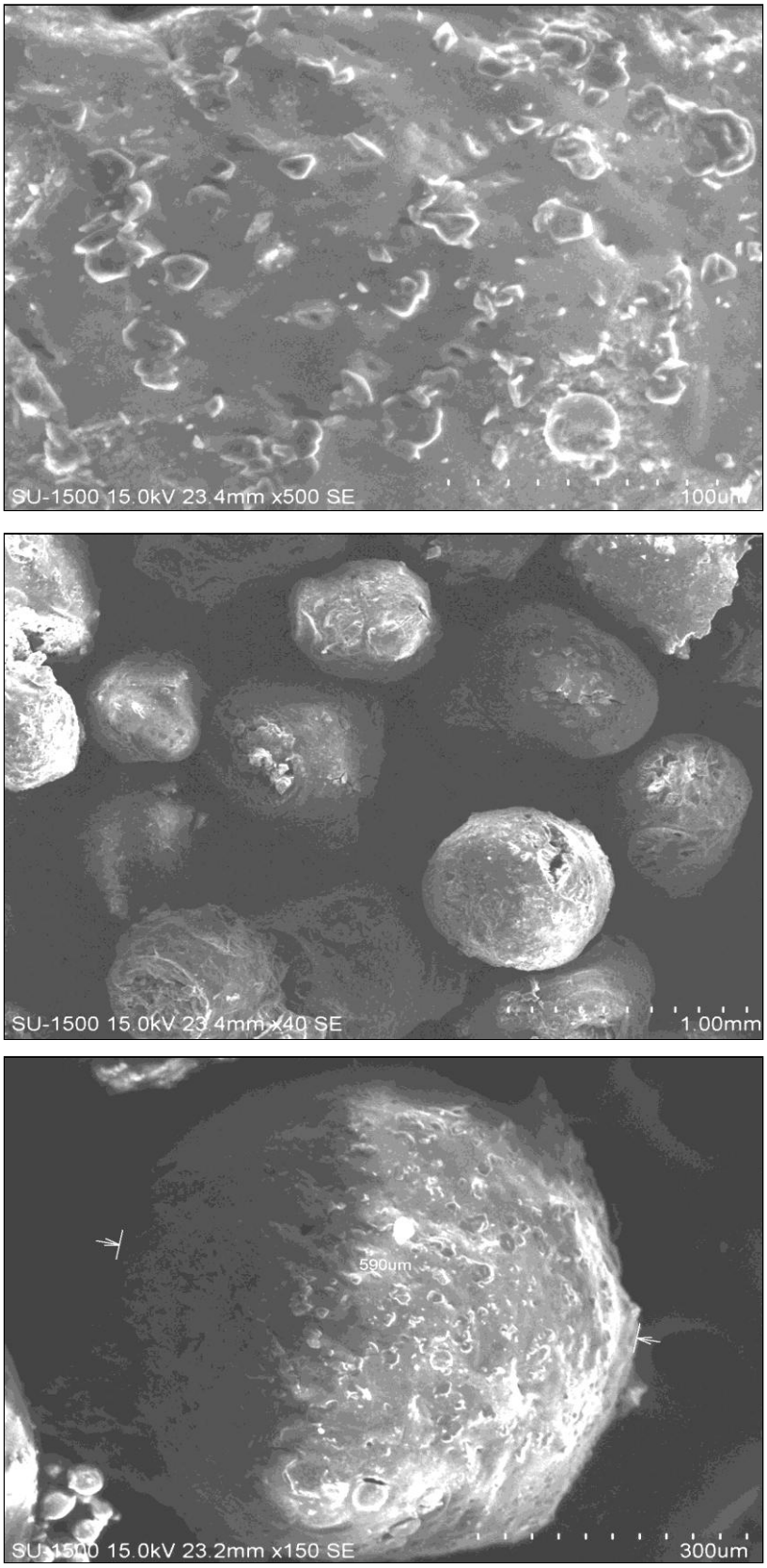

Figure 1. SEM Pictograms of gliclazide microcapsules formulated with xanthan gum by Ionic orifice Gelation Technique and Emulsion Ionic gelation techniques.

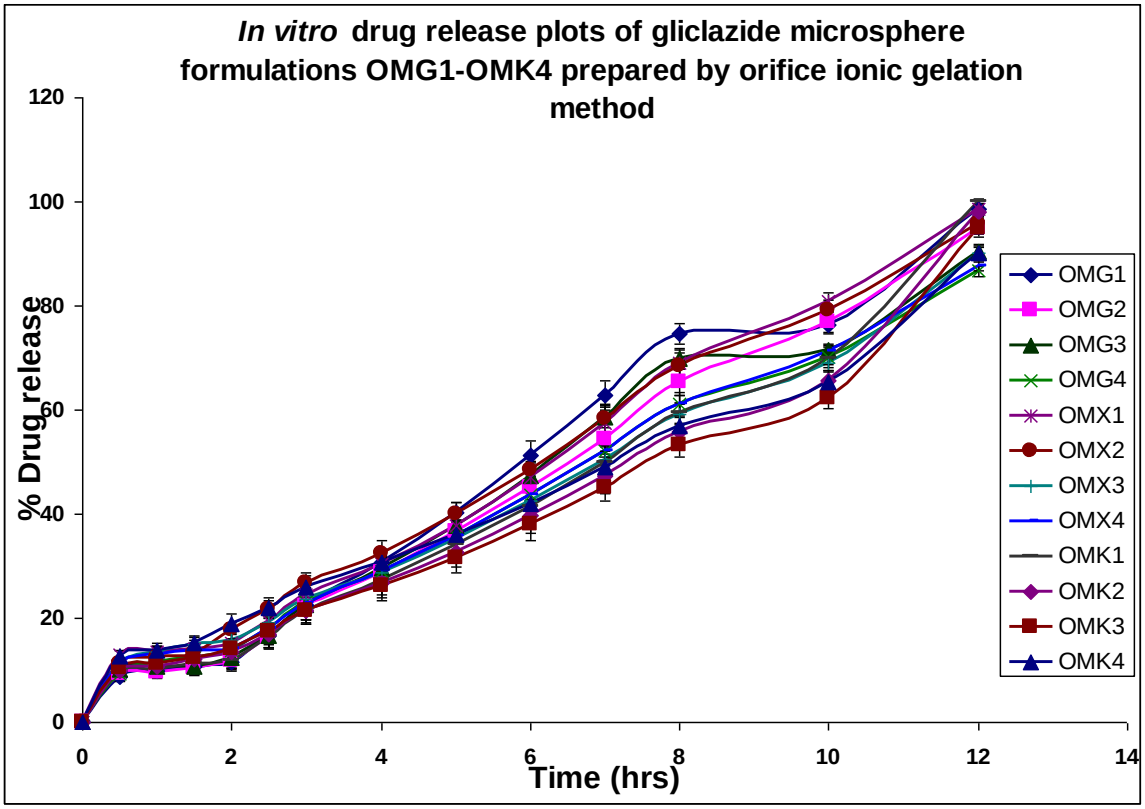

Figure 2a. *In vitro* drug dissolution profiles of mucoadhesive microcapsules prepared by orifice ionic gelation method.

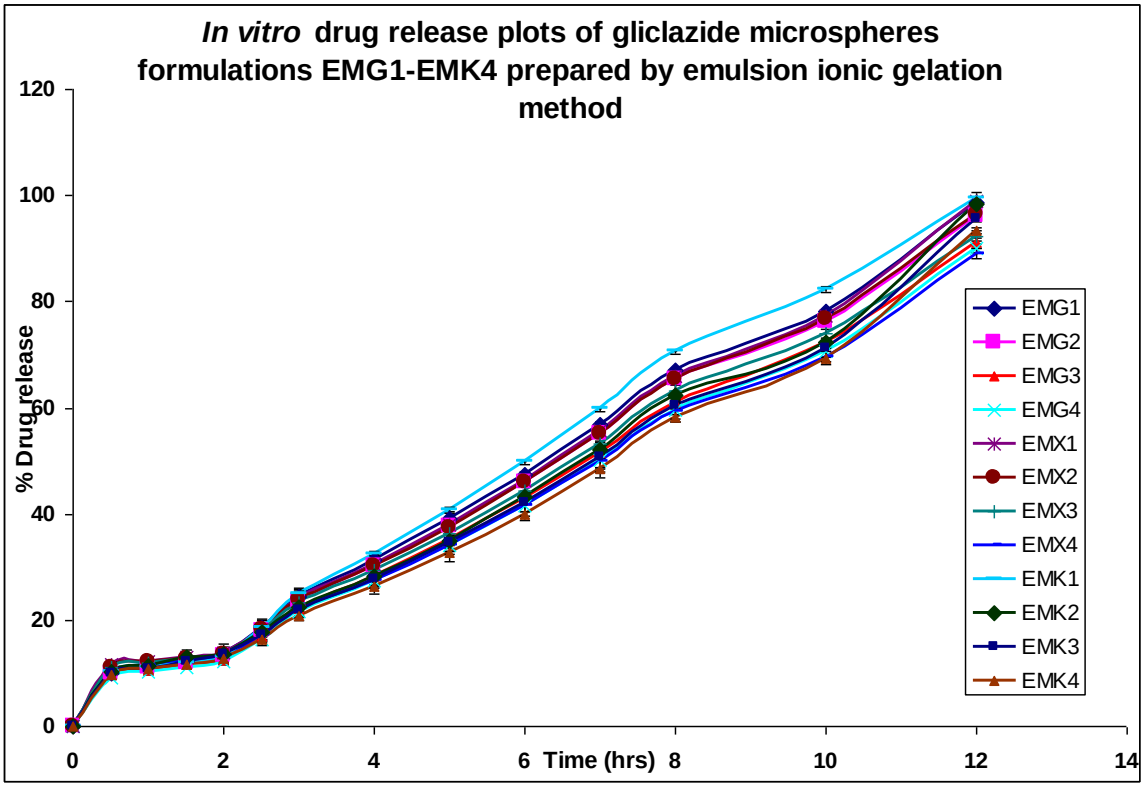

Figure 2b: *In vitro* drug dissolution profiles of mucoadhesive microcapsules prepared by emulsion ionic gelation method.

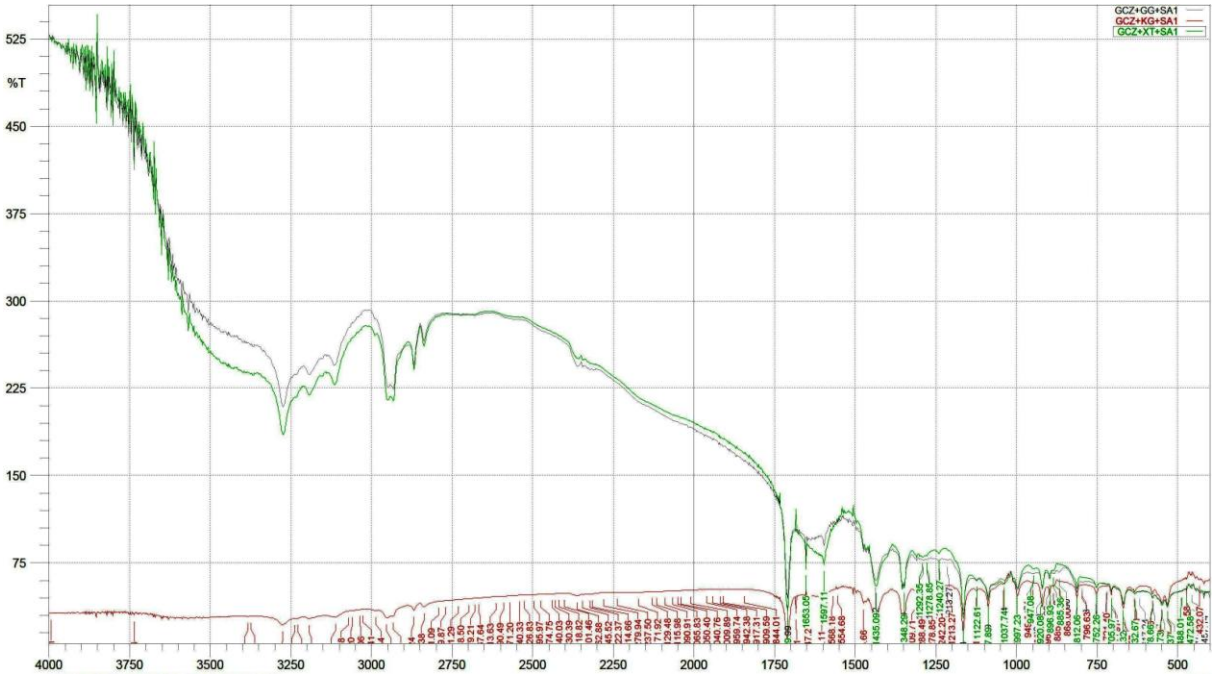

Figure 3. FTIR overlay spectra of gliclazide pure drug and gliclazide with sodium alginate and natural gums.

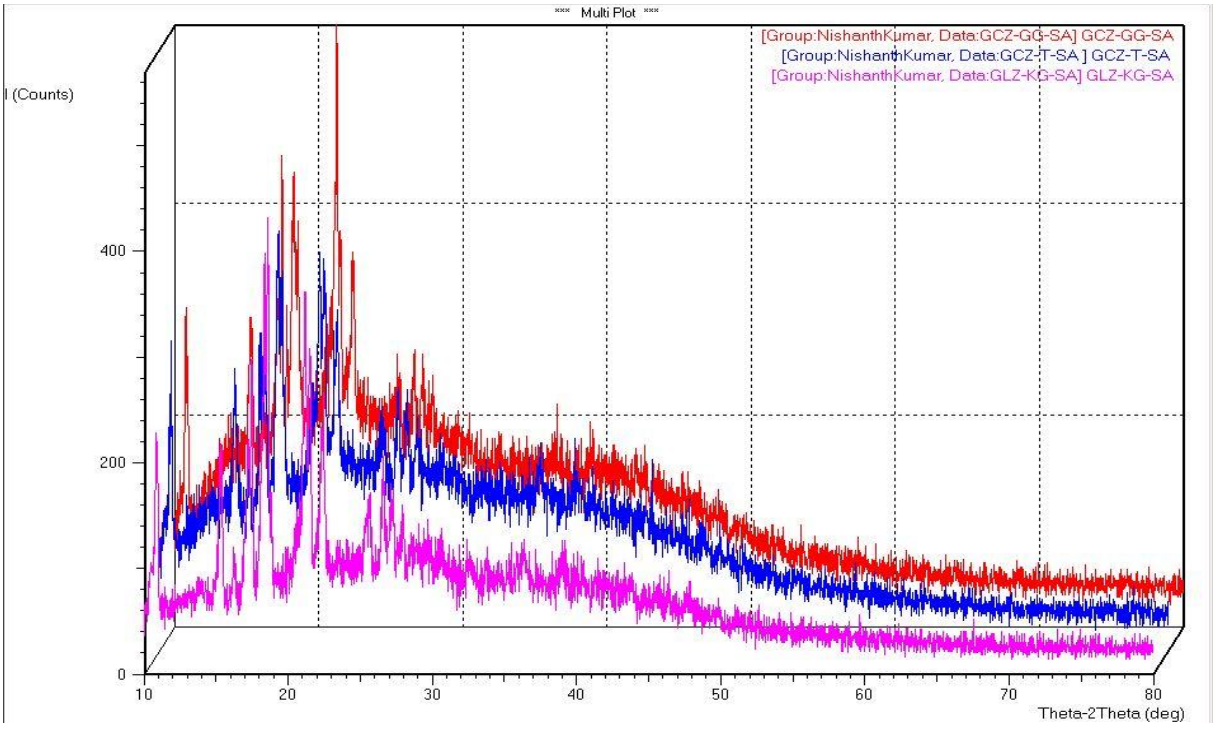

Figure 4. XRD overlay spectra of pure drug gliclazide and gliclazide with sodium alginate and natural gums.

got reduced because of diffused peaks & more orientation in case of polymers. The DSC and XRD data states that the crystallinity of pure drug found unchanged & stable, and indirectly determines the compositions are compatible (Fig. 4, 5).

CONCLUSION

The formulation OMX 4 containing drug: polymer ratio 1:4 was found to be the best formulation prepared by 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 depending on composition of the coat material. Drug release followed diffusion controlled with zero-order kinetics. These mucoadhesive microspheres are thus, suitable for oral controlled release of gliclazide.

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