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"FORMULATION AND EVALUATION OF NANOPARTICLES CONTAINING GLIPIZIDE"

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ABSTRACT
Nowadays, nanotechnology has grown to be an important research field in all areas including medicinal chemistry. The size, orientation and physical properties of nanoparticles have reportedly shown to change the performance of any material. The development of new delivery systems for the controlled release of drugs is one of the most innovative fields of research in pharmaceutical sciences. Nanoparticles specially designed to release the drug in the vicinity of target sites. The aim of this study was to formulate and evaluate the Glipizide nanoparticles is to minimize the dosing frequency, taste masking and toxicity and to improve the therapeutic efficacy by formulating Glipizide nanoparticles. Glipizide is low soluble, high permeable and short half-life antidiabetic drug. Glipizide nanoparticles were formulated by ionotropic gelation method using polymer chitosan gel (1mg/ml) with seven different formulations. Nanoparticles were characterized by determining it Drug content, Fourier Transform Infra-red Spectroscopy (FT-IR) analysis, *In vitro* release studies, Entrapment efficiency (EE), Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), Zeta Potential, X-ray diffraction, Stability studies. Drug entrapment efficacy was > 99%. The in-vitro release of nanoparticles were carried out which exhibited a sustained release of Glipizide from nanoparticles up to 24hrs. The results showed that nanoparticles can be a promising drug delivery system for sustained release of Glipizide.

KEYWORDS: Glipizide, Calorimetry, ionotropic.

INTRODUCTION
In recent years, the number of active agents having low aqueous solubility increased significantly. Oral delivery of poorly water soluble drugs often results in low bioavailability since the rate-limiting step for absorption from the gastrointestinal tract is a significantly slower dissolution rate.[1] Among the five key physico-chemical properties in the early compound screening including pka, solubility, permeability, stability and lipophilicity, poor solubility tops the list of undesirable compound properties.[2] Compounds with insufficient solubility carry a higher risk of failure during discovery and development, since it may compromise other properties of compound and add undesirable properties, can influence both pharmacokinetic and pharmacodynamics properties of the compound and finally may affect the bioavailability.[3,4] Nanoparticles are solid colloidal particles with diameters ranging from 1 - 1000 nm.[5] Nanoparticulate drug delivery system (1-1000 nm) is usually intended for oral, parenteral or topical rout with the ultimate objective being the alteration of the pharmacokinetic profile of the active molecule.[6] To overcome all this, a new drug delivery system called nanoparticles can be employed without facing above mentioned problems.[7,8] The reason why these nanoparticles are attractive for medical purposes is based on their important and unique features, such as their surface to mass ratio that is much larger than that of other particles, their quantum properties and their ability to absorb and carry other compounds. Nanoparticles have a relatively large (functional) surface which is able to bind, adsorb and carry other compounds such as drugs.[8,9] Nanoparticles may partially protect the entrapped drug or gene from degradation and improve cellular uptake through endocytosis. While a variety of polymers and lipids have been employed to form drug loaded nanoparticles, one biodegradable polymer that has received a good deal of recent attention as a component of oral drug and gene delivery systems is chitosan.[10,11]

An oral hypoglycemic agent Glipizide is second generation sulfonyl urea used for the treatment of non-insulin dependent diabetes mellitus. It acts by stimulating the release of insulin from the pancreas. Bio pharmaceutically Glipizide is a class II drug, which has low solubility and high permeability. Its short biological half-life (3.4±0.7 hours) necessitates that it be administered in 2 or 3 doses of 2.5 to 10 mg per day.[12,13] Thus it is a potential candidate for the development of extended release formulations. Extended release

formulations released the drug slowly for maximum period of time may improve the therapeutic effect, bioavailability and drug stability. It also reduces side effects of respective drugs and dosing frequency.[14] Administration of conventional tablets of Glipizide has been reported to exhibit fluctuations in the plasma drug levels, resulting in manifestation of side effects or reduction in drug concentration at the receptor site. In this present study an attempt was made to formulate the Glipizide loaded into chitosan nanoparticles. The optimized batch depending on encapsulation efficiency was characterized for Field- Emission Scanning Electron Microscopy, Fourier Tansform Infrared Spectroscopy, X-ray Diffraction analysis, *In-vitro* dissolution study, and *In-vivo* study.[15]

MATERIAL AND METHODS

Glipizide was a gift sample from Novans Pvt. Ltd Mumbai. Chitosan, glacial acetic acid and sodium tripolyphosphate were purchased from Lova Chemicals Ltd, India. All other chemical used were of analytical grade.

Preparation of 1.0% w/v of 150cps Chitosan Gel

150cps Chitosan and sodium chloride were dissolved in 3% glacial acetic acid and stirred with slight warming. Then, the solution was kept overnight for air drying under room temperature to obtain a clear gel of 1.0% w/v of 150cps chitosan.[16]

Preparation of Glipizide nanoparticles by inotropic gelatins method

The preparation of nanoparticle was done by taking different concentration of chitosan in 5% glacial acetic acid and stirred for more than 4 hours continuously and kept overnight to get chitosan after stabilization 9. The formulation of nanoparticle was done by inotropic gelation method. The different concentration of chitosan gel (1mg/ml) was taken in 5ml of 0.5% TPP which is acting as cross linking agent. Both the solutions were kept under high speed stirring (3000 rpm) using high speed stirrer. The final solution of chitosan suspensions were centrifuged for 20 minutes. The above mentioned method used for different formulations with various proportion of polymer concentration.[16]

RESULTS

CHARACTERIZATION OF GLIPIZIDE NANOPARTICLES

Average particle size and size distribution

The average particle size and size distribution was measured by dynamic light-scattering method (Zeta potential/particle sizer NIOCOMP 380 ZLS, USA) at 25°C with a detection angle of 90° using NUMBER-WT NIOCOMP distribution. In order to analyze, 1 ml of the nanosuspension was diluted to 10 ml with distilled water.[17]

Entrapment efficiency (EE)

The prepared SLN dispersion was centrifuged at 15000 rpm for 30min at 0^0 C using REMI cooling centrifuges. Then the supernatant is analysed for the free drug content.[18]

EE= (total drug content-free drug content/ total drug content) X 100

Zeta Potential

The Zeta potential of the formulations was measured by using Malvern Zeta-sizer and it was found to be ranging from 26.2±0.2, 27.8±0.4, 27.9±0.6, 28.12±0.3, 28.30±0.1, 29.4±0.7 and 31.3±0.4. The results were shown in Table No.2 and Figure No.5.[19]

Drug content

Drug content was determined by centrifugation method. The redispersed nanoparticles suspension was centrifuged at 15,000 rpm for 40 min at 25° to separate the free drug in the supernatant. Concentration of Glipizide in the supernatant was determined by UV-Vis spectrophotometyrically at 275.5 nm after suitable dilution.[19]

Fourier Transform Infra-red Spectroscopy (FT-IR) analysis

The samples were homogeneously mixed with potassium bromide and infrared spectrums were traced in the region of 4000-400 cm-1 by using an infrared spectrophotometer (IR- 8400, Shimadzu Co. Ltd., Singapore).[19]

In vitro release studies

Accurately weighed samples were suspended in 100 ml phosphate buffer saline (pH 7.4). The solution was stirred at 50 rpm with temperature adjusted to 37±1°C. At planned time intervals 1 ml samples were withdrawn and make the volume up to 10 ml. Centrifuged this solution at 20,000 rpm for 30 min. Aliquots of supernatant were examined by a UV spectrophotometer at 275.5 nm. The settled nanoparticles in centrifuge tube were re-dispersed in 1 ml fresh phosphate buffer saline (pH 7.4) and returned to the dissolution media.[19]

Scanning Electron Microscopy (SEM)

The SEM analysis of prepared nanoparticles was performed for morphological studies. The formulations are poured in to circular aluminum stubs using double adhesive tape and coated with gold in HUS -5GB vaccum evaporator and observed in Hitachi S-3000N SEM at an acceleration voltage of 10 Kv and a magnification of 5000X.[18]

Differential Scanning Calorimetry (DSC)

DSC analysis was performed in order to investigate the melting and recrystallization behavior of crystalline materials like nanoparticles. The samples were sealed in aluminum pans and measurements were recorded using DSC instrument. The samples were heated from 25 to

2000 C at a heating rate of 100 C /min under nitrogen atmosphere.[20]

Stability studies

The physical stability of Glipizide loaded chitosan nanoparticles was evaluated after storage for 3 months under different temperature conditions. Nanoparticles (**F5 and F7**) were stored in polyethylene plastic bottles with droppers and placed at 25° ± 2°C or at 40° ± 2°C away from light. Benzalkonium chloride (0.02%) was added to each sample as preservative to prevent the microbial growth during the storage period. At 1, 2 and 3 months, samples were withdrawn and tested for drug content, pH, viscosity and particle size. The encapsulating efficiency was tested after 3 months.[17]

pH

The pH of the prepared nanoparticles was measured using pH meter 3510 Jenway.[17]

XRD (X-ray diffraction) measurement

X-ray diffraction of samples was carried out using Model-D8 Advance, Brucker AXS GmbH, Germany diffractometer. A Cu Kα source operation (40 kV, 40 mA) was employed. The diffraction pattern was recorded over a 2θ angular range of 3-50o with a step size of 0.02o in 2θ and a 1 Sec counting per step at room temperature.[20]

Table No.1: Formulation of Nanoparticles

S.No	Formulation	Amount of drug (mg)	Amount of polymer (mg)
1	FGN- 1	10	50
2	FGN- 2	10	100
3	FGN- 3	10	150
4	FGN- 4	10	200
5	FGN- 5	10	250
6	FGN- 6	10	300
7	FGN- 7	10	350

Table No.2: Characterization of Nanoparticles

S.No	Formulation	Entrapment efficiency (%)	Particle size (nm)	Zeta potential (mv)	pH of formula	Drug Content (%)
1	FGN- 1	55.5±2.4	460±42	26.20±0.2	5.2	57.24+0.03
2	FGN- 2	73.6±0.8	360 ±12	27.80±0.4	5.5	65.0 + 0.06
3	FGN- 3	85.3±0.8	480±78	27.90±0.6	6.5	70.7 + 0.02
4	FGN- 4	84.3±3.6	520±76	28.12±0.3	7.3	64.62+0.03
5	FGN- 5	85.3±2.9	625±55	28.30±0.1	6.2	57.23+0.02
6	FGN- 6	85.6±1.2	710±82	29.40±0.7	5.9	65.24+0.03
7	FGN- 7	84.9±1.4	814±62	31.30±0.4	6.1	53.31+0.07

Table No.3: Dissolution study of different batches

S.No	Time in hours	% Drug release of FGN- 1	% Drug release of FGN- 2	% Drug release of FGN- 3	% Drug release of FGN- 4	% Drug release of FGN- 5	% Drug release of FGN- 6	% Drug release of FGN- 7
1	0	0	0	0	0	0	0	0
2	3	32.871	37.551	36.744	27.545	29.804	34.640	38.842
3	6	42.555	48.709	45.395	43.501	45.868	51.390	51.540
4	9	51.303	59.746	54.541	54.695	54.387	59.010	60.093
5	12	59.599	70.896	62.762	62.762	66.071	70.444	72.101
6	15	66.033	79.428	72.284	67.819	70.498	74.517	83.149
7	18	71.854	84.794	82.441	78.030	80.236	82.00	87.440
8	21	77.950	90.005	86.665	82.307	87.826	84.922	93.055
9	24	86.742	95.062	91.189	90.902	90.759	90.328	97.931

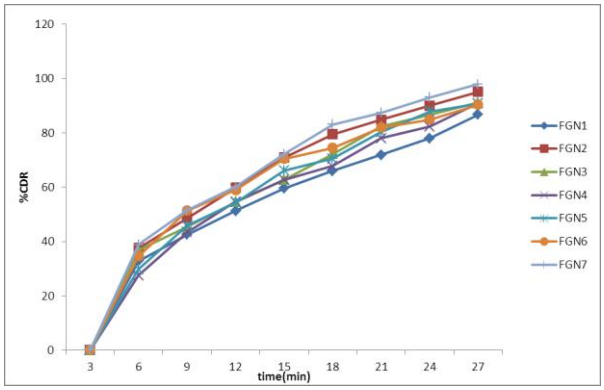

Figure No.2: Dissolution study of different batches

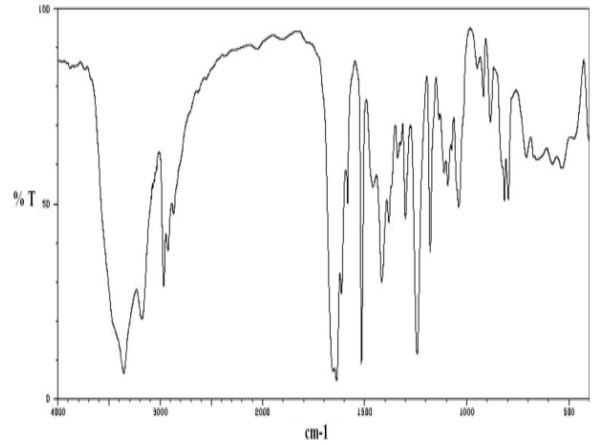

Figure No.2: FT-IR spectra of pure Glipizide.

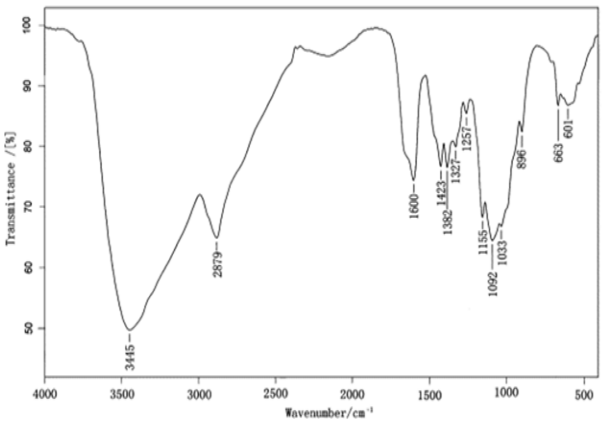

Figure No.2: FT-IR spectra of pure Chitosan

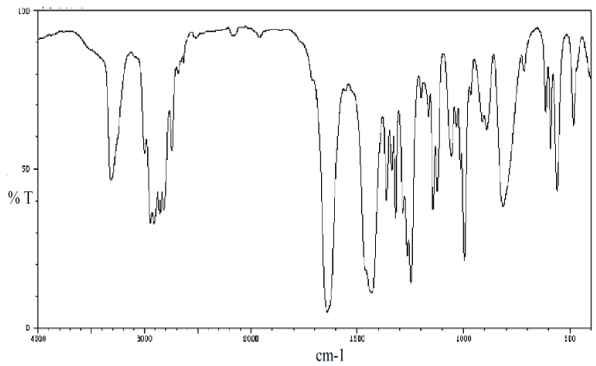

Figure No.3: FT-IR spectra of Formulation-7(FGN-7)

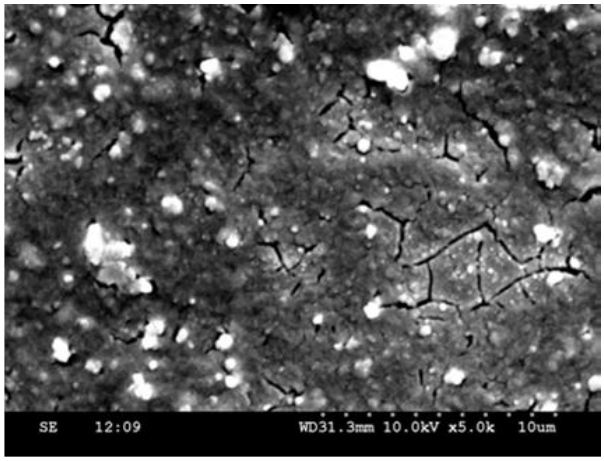

Fig.No.4 SEM Photographs

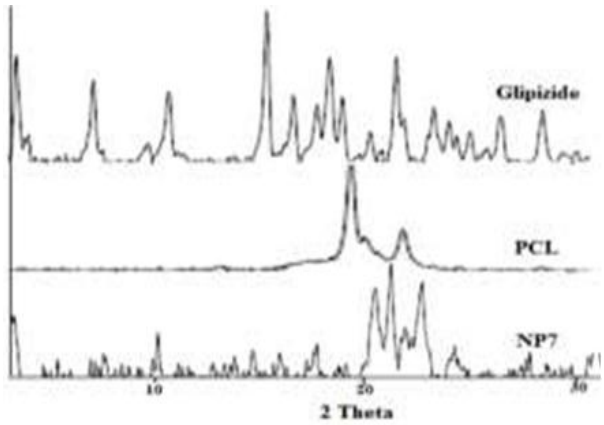

Fig. 5: X-Ray Diffraction pattern of glipizide, Chitosan and batch FGN-7.

CONCLUSION

The Glipizide nanoparticles was prepared by inotropic gelatins technique and evaluated for various evaluation parameters like particle size, drug polymer compatibility, entrapment efficiency, *in vitro* drug release. The results were conclude that FGN-7 can be considered as an optimized formula for sustaining the release of drug for over 24 hours and the formulation can be considered as best alternate to sustained release tablets for the treatment of non-insulin dependent diabetes mellitus and can be best used with minimal or without any major side effects associated with sustained release tablets.

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