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ENHANCEMENT OF SOLUBILITY OF AN ORAL HYPOGLYCAEMIC DRUG, GLIMEPERIDE BY THE TECHNIQUE COCRYSTALLISATION

Preeta Bose [1], Srikanta Chandra [2], Avik Das [3], Tathagata Roy [*1], Susanta Paul [1] and Lucky Mukherjee [4]

Department of Pharmaceutical Technology [1], JIS University, Kolkata - 700109, West Bengal, India.
Jakir Hossain Institute of Pharmacy [2], Miapur, Murshidabad - 742225, West Bengal, India.
Gupta College of Technological Sciences [3], Asansol - 713301, West Bengal, India.
Sister Nivedita University [4], Kolkata - 700156, West Bengal, India.

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Correspondence to Author:
Tathagata Roy

Assistant Professor,
Department of Pharmaceutical Technology, JIS University, Kolkata - 700109, West Bengal, India.

E-mail: troy@jisuniversity.ac.in

ABSTRACT: Co-crystallization is one of the most reliable alternative approaches to increase the solubility of poorly water-soluble drugs without affecting their physicochemical properties. Pharmaceutical cocrystals are neutral organic compounds connected to the API preferentially by loosely formed bonds as dipole-dipole interaction. Our present study aims at improving the solubility of an effective oral hypoglycemic, Glimepiride, a sulphonylurea class of drug that often lacks water solubility. In the process of enhancing its solubility, four different co-formers were used as Anthranilic acid, Succinic acid, Salicylic acid, Benzoic acid, and Gallic acid in different stoichiometric ratios like 1:2 and 1:3. The technique opted for the making is slow evaporation and prepare the nanoparticle by using Chitosan and gelatin polymeric matrix with aldehydic oxidized Xanthan gum as crosslinking agent. Initial confirmation was made through melting point determination. Later structure elucidation of co-crystals was carried out by several analytical methods, such as FTIR, X-ray Diffraction. In FTIR spectra, a sharp decrease in the intensity of N-H peak of salicylic acid and succinic acid was observed in 1:2 ratio, which in turn indicates the formation of the hydrogen bond. PXRD indicates crystallinity by the formation of a sharp, high intense peak in drug: salicylic acid in 1:2 ratios. The nanoparticle was evaluated on the basis of size determination, DEE, and *in-vitro* release study, which gives promising results that release for a prolonged period of time. In the future, *in-vivo* and other physicochemical properties were evaluated.

INTRODUCTION: The successful delivery of any pharmaceutical ingredient to patients requires the ability to manufacture effective drug products. But the common problem which occurs during the delivery of the drug is a challenge that is associated with solubility, permeability, stability, organoleptic properties, and bioavailability [1].

Over the past number of years, the fraction of new chemical entities approaching the marketplace are very frequent and steadily decreasing. For the successful development and commercialization of new drug entities, it requires that API should possess adequate stability, solubility, permeability, and bioavailability [2].

These problems occur mostly in the oral route because most of the drug is pass through Fast Pass Metabolism (FPM), which leads to low bioavailability, and the oral route of drug administration is the most important method for administering drugs for systemic effects. The development of dosage forms, especially for the

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prolonged release purpose, has been a challenge to formulation scientists because of many independent factors governing the absorption of the drug from the gastrointestinal tract [3]. It is seen that most of the drug insoluble or poorly water-soluble and comes under BCS class II and IV where solubility is a major problem, so to overcome this problem, various techniques are there like salt formation, complexation, hydrography, solid dispersion, miceller solubilization, and lastly co-crystallization.

Co-crystallization is one of the emerging crystal engineering techniques for modulating pharmaceutical performance through controlling solid-state properties of Active Pharmaceutical Ingredient. Over the last 15 years, the concept of pharmaceutical co-crystal engineering has gained a tremendous increase. These are multicomponent systems composed of two or more molecules are held together in a suitable stoichiometric ratio by hydrogen bonding or other non covalent bonds which is responsible for improving the physical properties like dissolution profile, solubility and bioavailability of the drug [4]. Crystal engineering is generally considered to be the design and growth of crystalline molecular solids with the aim of impacting material properties. A principal tool is the hydrogen bond, which is responsible for the majority of directed intermolecular interactions in molecular solids. Co-crystals are multi-component crystals based on hydrogen bonding interactions without the transfer of hydrogen ions to form salts; this is an important feature since Bronsted acid-base chemistry is not a requirement for the formation of a co-crystal. Co-crystallization is a manifestation of directed self-assembly of different components. Co-crystals have been described of various organic substances over the years and given various names, such as addition compounds molecular complexes and hetero molecular co-crystals. An alternative approach is there by which the solubility was enhanced without modifying the pharmacophore structure of API is to develop new crystalline form such as co-crystal.

Pharmaceutical cocrystals are organic compound which consist of two or more neutral organic compound within same crystal lattice in a defined stoichiometric ratio with covalent interaction. These are mainly used to improve physicochemical properties of API without changing their chemical structure such as solubility, dissolution rate, melting point, stability, bioavailability. Co formers are mainly used as additives should have at least one functional group amine, amide, ketone, carboxylic acid, ester, carbonyl group. It is mainly a neutral compound [5].

So, in this study forecast, the co-crystallization technique has been conducted by using a poorly water soluble drug with different co-formers.

Drug used in the Study: Glimepiride was used in this study as practically insoluble in water, so we select the drug so that we can try to increase the water solubility by co-crystallization technique. It is a second-generation sulphonylurea class of drug and commonly used for a diabetic patient having type II diabetic mellitus [6].

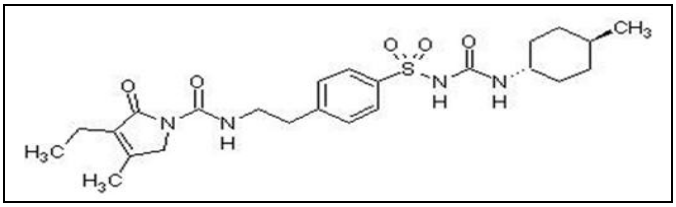

FIG. 1: MOLECULAR STRUCTURE OF GLIMEPIRIDE

Chemistry:

IUPAC Name: 1-[{p-(2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl)phenyl sulphonyl]-3-(trans-4-methylcyclohexyl) urea.

Molecular Formula: $C_{24}H_{34}N_4O_5S$.

Molar Mass: 490.617 g/mol.

Physical Properties:

Solubility: Practically insoluble in water. Water solubility is 0.0347 mg/ml,

Melting Point: 207 °C.

Mechanism of Action: It provokes a brisk release of insulin from the pancreas. It acts on the pancreatic β-cell membrane, which cause depolarization by reducing the conductance of ATP-sensitive K+ channels. This enhances Ca+ influx results in degranulation. Then the rate of insulin secretion at any glucose concentration is increased [7].

Pharmacokinetics:

Absorption: Well absorbed throughout gastro-intestinal tract. 99.5% bound to plasma protein.

Metabolism: Firstly metabolize through hepatic route *via* CYP2C9 enzyme.

Excretion: About 65% excrete through urine and remain through feces.

Interaction:

Drugs that Enhances Activity of Glimepiride: Phenylbutazone, Cimetidine, salicylates, β-blockers *etc*.

Drugs that Decrease Glimepiride: Pheno-barbitone, Phenytoin, thiazides, furosemide, oral contraceptives, *etc*. [8]

Adverse Effects:

Hypoglycemia: It is a common problem, may occasionally be severe and rarely fatal. It is more common in elderly, liver, and kidney disease patients and when potentiating drugs are added.

Nonspecific Side Effect: Nausea, vomiting, headache, transient leukopenia, and different hypersensitivity reaction like photosensitivity, rashes, *etc*.

Polymers used in the Study:

Chitosan: Chitosan is the second abundant polysaccharide and a cationic polyelectrolyte present in nature. It has shown favorable biocompatibility well as the ability to increase membrane permeability, both *in-vitro* and be degraded by lysozyme enzyme in serum. From a biopharmaceutical point of view, Chitosan has the potential of serving as an absorption enhancer across intestinal epithelial for its mucoadhesive and permeability property. Chitosan is a cationic polysaccharide, is commercially available in a range of grades with different molecular weights and degrees of deacetylation. chitin, by a deacetylation process involving alkaline hydrolysis.

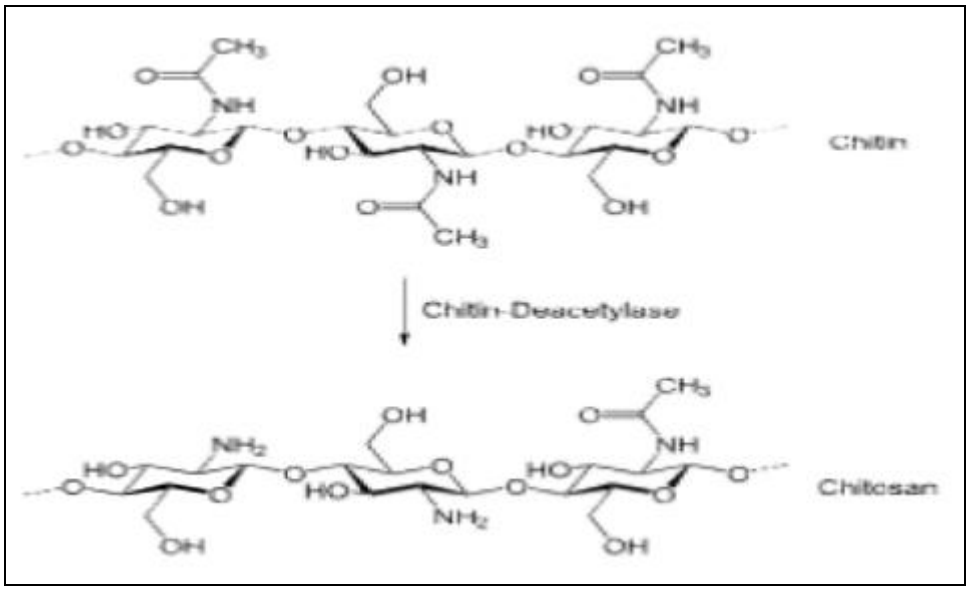

FIG. 2: STRUCTURE OF CHITIN AND CHITOSAN

Chitosan has been used as a nanoparticle material owing to its versatility, biodegradability, biocom-patibility, and natural origin. Its hydrophilicity and solubility permit the design of Nanoparticles capable of protecting the loaded drug and controlling its release. The drug is dissolved, entrapped, encapsulate or attached to a nano-particles matrix. Submicron particles possess a very high surface volume rate [9]. Most nanoparticles prepared from water-insoluble polymers are involved heat, organic solvent or high shear force that can be harmful to the drug stability. In contrast, water-soluble polymers offer mild and simple preparation methods without the use of organic solvent and high shear force. Among water-soluble polymers, chitosan is the most expensively studied [10]. This is because chitosan possesses some ideal properties of polymeric carriers for nano-particles. It also possesses a positively charge and exhibits an absorption enhancing effect. These properties render Chitosan a very attractive material as a drug delivery carrier.

Gelatin: Gelatin is a naturally occurring polymer with relatively low antigenicity and is extensively used in the food and medical products. In addition,

its biodegradability, biocompatibility, nontoxicity, ease of chemical modification, and cross-linking make gelatin-based nanoparticles an efficient carrier in the delivery and controlled release of the drugs. It is known that the mechanical properties such as swelling behavior and thermal properties of gelatin NPs depend significantly on the degree of cross-linking between cationic and anionic groups [11].

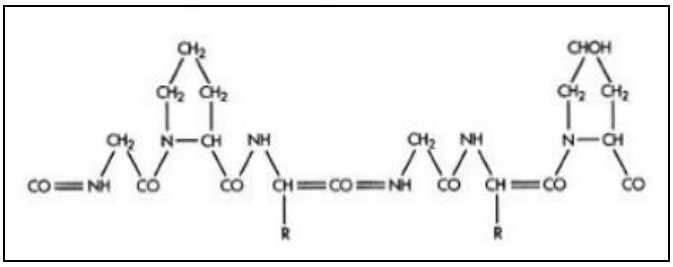

FIG. 3: STRUCTURE OF GELATIN

Xanthan Gum: Xanthan gum is a natural polysaccharide and an important industrial biopolymer. It was discovered in the 1950s at the Northern Regional Research Laboratories (NRRL) of the United States Department of Agriculture. The polysaccharide B1459, or xanthan gum, produced by the bacterium *Xanthomonas campestris* NRRL B-1459 was extensively studied because of the properties that would allow it to supplement other known natural and synthetic water-soluble gums. Xanthan gum is a hetero-polysaccharide with a primary structure consisting of repeated pentasaccharide units formed by two glucose units, two mannose units, and one glucuronic acid unit, in the molar ratio 2.8:2.0:2.0 [12].

Here, we use Xanthan gum as a cross-linking agent by reacting Xanthan gum with sodium periodate as it is a natural product and non-toxic in nature. The chemical cross-linker like methylenebisacrylamide, ethylene glycol di(methyl)acrylate, formaldehyde, gluteraldehyde had certain disadvantages *i.e.* toxic in nature and cause certain irritation for that reason here we use modified Xanthan gum. The major problem is associated with phase separation. In recent years, dialdehyde polysaccharides have received increasing attention as an ideal crosslinking agent whose aldehyde groups can crosslink with 3-amino groups of lysine or hydroxyl side groups of protein by Schiff's base formation. In the presence of sodium periodate, the oxidation of xanthan gum is characterized by the specific cleavage of the C2-C3 bond of residues, resulting in the formation of aldehyde groups. On this basis, introducing oxidized xanthan gum into gelatin films is not only a way to improve the properties of gelatin-based films but also an ideal method to restrict phase separation [13].

Procedure:

Different Techniques Used for the Preparation of Co-crystals:

Hot Melt Extrusion Method: It is an emerging technology for co-crystal formation. It is a process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape. It is believed that extrusion offers highly intensive mixing, shear, and close material packing that improves surface contact between drug-coformer blends leading to the formation of co-crystals without using any solvents presented the effect of processing parameters such as screw speed, barrel temperature and screw configuration on extruded co-crystals agglomerates [14].

Mechanochemical Grinding: It is also known as dry grinding or solid-state grinding, which was the most widely used method. Here co-crystals are formed via a mechanochemical reaction by the formation of mechanical energy [15].

Liquid Assisted Grinding: In spite of the method's many advantages, one huge drawback with mechanochemical grinding in the solid-state is that, with no heating stage involved in the process, there are numerous cases where the energy required to complete the co-crystallization of the compound is lacking. The importance of temperature is well known in the field of co-crystals, which cannot be produced through mechanochemical grinding alone. One method to overcome this is the induction of a small amount of water or a solvent to the ball milling mechanism, which acts as a catalyst assisting the process is known as Liquid-assisted grinding. It is also known as solvent drop grinding method or wet granulation, which is mediated by a liquid phase, acts as a catalyst during co-crystallization technique [16].

Spray Drying: This method is widely used to develop particle properties such as shape, size,

density, surface properties, porosity, and crystal habit. By spraying a range of co-crystals under different solvents and saturation conditions, the finding showed that the operating temperature had a significant influence on the co-crystal's solubility [17].

Antisolvent Co-crystallization: It is an important technique for the synthesis of high-quality co-crystals. Generally, during the process super saturation is generated by adding a second liquid to a solution of drug coformer to be crystallized, which is miscible with the solvent and in which the co-crystals is insoluble or sparingly soluble. However it is seen in many cases, coformer solution to facilitate co-crystallization.

Slow Solvent Evaporation Technique: It is the most widely used technique in the preparation of co-crystals where the drug-co former mixture was mixed with a solvent, and then the solvent was evaporated at room temperature [18].

Characterization of Co-crystals: It was seen in case of evaluation of co-crystals several researchers perform certain characterization and we get certain information like;

PXRD: It is mainly used for the structural characterization of Co-crystals. If PXRD of solid materials is performed after co-crystallization, it shows different results that differ from the reactants, indicating a new solid phase formed, which is characterized by a generation of the sharp peak. Chadha *et al*., reported that Chrysin-cytosine co-crystal shows a new peak at 23.68°, which is absent in chrysin and cytosine reflection pattern [19].

FTIR: It is mainly used to characterize the crystalline form by measuring the intensity and location of the characteristic peak. It also indicates which bond participates in the co-crystal formation. Chadha *et al.* reported that after the co-crystallization, the OH stretch shifted from 3080 cm^{-1} to 3089 cm^{-1} [20].

DSC: It indicates the formation of a new solid phase by giving a peak; it is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Chadha *et al*., reported that in DSC scanning, the chrysin-cysteine and chrysin-thiamine cocrystals shows a sharp and single endothermic peak with corresponding their melting point 263.87 °C and 226.84 °C [21].

Particle Size Analysis: From the particle size analysis, the co-crystals are characterized the nano co-crystals by determining the Z average size and poly disparity index [22].

Nano-technology for Delivery of Co-crystal: Controlled drug delivery systems offer numerous advantages over conventional dosages forms, including improved efficacy, reduce toxicity, and improved patient compliance, and can be utilized in the form of nanocarriers in drug delivery. Nanoparticles are solid colloidal particles with diameters ranging from 1-1000 nm. They consist of macromolecular materials in which the active ingredient is dissolved, entrapped, encapsulated, adsorbed or chemically attached. They may be prepared from a variety of materials such as proteins, polysaccharides, and synthetic polymers.

The selection of materials is dependent on many factors, including:

- **a.** Size of nanoparticles required,
- **b.** Inherent properties of the drug, *e.g.,* solubility and stability,
- **c.** Surface characteristics such as charge and permeability,
- **d.** Degree of biodegradability, biocompatibility, and toxicity; and
- **e.** Drug release profile desired.

However, many drugs are not suitable for oral administration due to poor solubility, stability, and/or bioavailability. Encapsulating these drugs in nanoparticles can overcome these limitations, as well as allowing the potential for targeted, sustained delivery in the GI tract. Over the past few decades, there has been considerable interest in developing biodegradable polymer-based nano-spheres as effective drug delivery devices. Various polymers have been used in drug delivery research as they can effectively deliver the drug to a target site and thus increase the therapeutic benefit while minimizing side effects. The controlled release of pharmacologically active agents to the specific site of action at the therapeutically optimal rate and dose regimen has been a major goal in designing

such devices. Biodegradable nanoparticles have been used for site-specific delivery of drugs, vaccines, and various other biomolecules [23].

Different Methods for Preparation of Nano-particle:

Membrane Dialysis Technique: Dialysis offers a simple and effective method for the preparation of small, narrow distributed nanoparticles. Polymer is dissolved in an organic solvent and placed inside a dialysis tube with proper molecular weight cut-off. Dialysis is performed against a non-solvent. The displacement of the solvent inside the membrane is followed by the progressive aggregation of polymer due to a loss of solubility and the formation of homogeneous suspensions of nanoparticles [24].

Nano Precipitation: The nanoprecipitation method is also called as solvent displacement method. The basic principle of this technique is based on the interfacial deposition of a polymer after displacement of a semi-polar solvent, miscible with water, from a lipophilic solution. The rapid diffusion of the solvent into non-solvent phase results in the decrease of interfacial tension between the two phases, which increases the surface area and leads to the formation of small droplets of organic solvent. Polymers and drugs are dissolved in a polar, water-miscible solvent such as acetone, acetonitrile, ethanol, or methanol. The solution is then poured in a controlled manner into an aqueous solution with surfactant. Nanoparticles are formed instantaneously by rapid solvent diffusion. Finally, the solvent is removed under reduced pressure and evaporation [25].

Solvent Evaporation Method: In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform, or ethyl acetate. The drug (hydrophobic drug) is dissolved or dispersed into the preformed polymer solution. The mixture of polymer and drug solution is then emulsified in an aqueous solution containing an emulsifying agent to form oil in water (o/w) emulsion. The most commonly used surfactant/emulsifying agents for this purpose are gelatin and polyvinyl alcohol. After the formation of a stable emulsion, the organic solvent is evaporated by increasing the temperature or reducing pressure along with continuous stirring of the solution. Process parameters such as stabilizer and polymer concentration and stirring speed have a great influence on the particle size of the nanoparticles formed [26].

Salting Out / Emulsification–Diffusion Method: In this method, the polymer is dissolved in the organic phase, which should be water-miscible, like acetone or tetrahydrofuran **Fig. 10**. The organic phase is emulsified in an aqueous phase, under strong mechanical shear stress. The aqueous phase contains the emulsifier and a high concentration of salts that are not soluble in the organic phase. Typically, the salts used are 60% w/w of magnesium chloride hexahydrate or magnesium acetate tetrahydrate in 1:3 polymer to salt ratio. Contrary to the emulsion diffusion method, there is no diffusion of the solvent due to the presence of salts. The fast addition of pure water to the o/w emulsion under mild stirring reduces the ionic strength and leads to the migration of the water-soluble organic solvent to the aqueous phase inducing nanospheres formation. The final step is a purification of nanoparticles by cross flow filtration or centrifugation to remove the salting-out agent [27].

Super Critical Fluid Technology: A supercritical fluid can be generally defined as a solvent at a temperature above its critical temperature, at which the fluid remains a single phase regardless of pressure. Supercritical CO_2 is the most widely used supercritical fluid because of its mild critical conditions (Tc = 31.1 °C, Pc = 73.8 bars), nontoxicity, non-flammability, and low price. The most common processing techniques involving supercritical fluids are supercritical anti-solvent and rapid expansion of the critical solution. The supercritical anti-solvent method employs a liquid solvent (methanol), which is completely miscible with the supercritical fluid, to dissolve the solute to be micronized. The solution is charged with the supercritical fluid in the precipitation vessel containing a solute of interest in an organic solvent (*e.g.*, methanol) [28].

METHODOLOGY:

Materials:

Glimepiride: IPCA Laboratories Ltd., Mumbai.

Salicylic Acid: E.MERCK (INDIA) LIMITED.

Anthranilic Acid: LOBA CHEMIE.

Succinic Acid: E.MERCK (INDIA) LIMITED.

Benzoic Acid: QUALIGENS FINE CHEMICALS.

Gallic Acid: LOBA CHEMIE.

Xanthan Gum

Sodium per Iodate: MERCK

Chitosan: EVEREST BIOTECH, Bangalore

Instruments:

UV-VIS Spectrophotometer: Thermo Scientific Evolution-201, Great Britain.

Balance: Dhona 160 D, Dhona Instrument Pvt. Ltd. Kolkata- 700020, India.

pH Meter: Digital pH meter 335, Systronics, Ahmedabad, India.

Magnetic Stirrer: 1 ML DX, Remi Equipment's Pvt. Ltd.

Digital Balance: Metler Toledo, AB 204-S, Switzerland.

FTIR: Id5 ATR, model- Nicolet iS5, Thermo Fisher Scientific, USA.

Centrifuge Machine: Remi Equipment Pvt. Ltd.

Shaker Bath: Lunar, Amalgamated Suppliers, Kolkata-73.

Hot Air Oven: Lunar, Amalgamated Suppliers, Kolkata-73

Lyophiliser: EYELA, FDU-1200.

Water Bath: Lunar, Amalgamated Supplier, Kolkata-73.

Magnetic Stirrer: 1 MLH magnetic stirrer, Remi Equipment's Pvt. Ltd.

Methods:

Selection of Drug: To improve water solubility by a co-crystallization technique, we have to require water-insoluble or poorly water-soluble drugs for that reason we used a water insoluble drug that was Glimepiride which comes under BCS class II category. The water solubility of the drug was 0.0347 mg/ml.

Selection of Co-formers: We used five different co formers like anthranilic acid, gallic acid, benzoic acid, salicylic acid, and succinic acid because of its easy availability and use by several researchers.

Analytical Monitoring:

Preparation of Phosphate Buffer pH 6.8 (1000 ml): At first, two beakers were taken, in one beaker 6.8 gm. potassium dihydrogen orthophosphate was taken and dissolve by some double distilled water, and in another beaker 1.8 gm. of sodium hydroxide was taken and dissolved by the addition of double-distilled water. After that, two solutions were mixed, and volume was made up to 1000 ml by double-distilled water; and after that, pH was checked in the pH meter, and pH was adjusted by the addition of 0.6 ml of concentrated HCl.

Preparation of Standard Curve of Glimepiride: At first, Glimepiride was heated at 105 °C for 3 h in a hot air oven for dry. 10 mg drug was weighed in and transferred in a 100 ml volumetric flask and to it firstly 20 ml phosphate buffer pHs 6.8 was added and dissolved and then the volume was made up to 100 ml with phosphate buffer pH 6.8 and concentration of the stock solution was 100 µg/ml. The solution was scanned, and ƛmax was found to be 230 nm. Then, ten pieces of 10 ml of the volumetric flask were taken, and from the stock solution subsequently, 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1 ml, 1.2 ml, 1.4 ml, 1.6 ml, 1.8 ml, and 2 ml was transferred into the 10 ml volumetric flask and volume were made up to 10 ml with phosphate buffer pH 6.8 and absorbance was measure at 230 nm. The absorbance standard was prepared by plotting concentration (µg/ml) in X-axis and absorbance in Y-axis. From the curve, the equation and R2 value were calculated.

Methodology used in the Preparation of Co-crystals: Glimepiride (Drug) mixed with different co formers like Salicylic acid, Anthranilic acid, Succinic acid, Benzoic acid, and Gallic acid in the different ratio (1:1, 1:2, 1:3) mixed properly. 15 ml Ethanol was added to it, and slight heat was given to dissolve the mixture into the solvent. The solution at room temperature to evaporate the solvent, and then the samples were collected (cocrystals).

After the preparation of co-crystals, the samples were analyzed and Glimepiride :succinic acid and salicylic acid 1:2 ratio show better profile than others and these two samples were selected for further study [29].

Preparation of Crosslinker by Xanthan Gum and Sodium per Iodate:

Preparation of Xanthan Gum Solution 1 gm: Xanthan Gum was weighed in electric balance properly and 25 ml DDW was taken in a 50 ml beaker. The beaker was placed in a magnetic stirrer and to it Xanthan gum was added, and Xanthan Gum solution was prepared (Solution A).

Preparation of Sodium-per-Iodate Solution: Different concentrations of sodium periodate (0.1, 0.2, 0.4 gm) were dissolved in 10 ml of DDW. The beakers were wrapped by using aluminium foil and kept in the dark for 24 h. Hence solution B was prepared. Solution A and solution B were mixed and kept for 4-6 hours in dark and washed with ethanol by using muslin cloth and after that transferred into Petri plates and dry at room temperature (Petri plates were greased previously) and we get modified xanthan gum [30].

Preparation of 0.25% Chitosan Solution: 250 mg Chitosan was weighed properly and transferred into a 100 ml beaker. 4 ml acetic acid solution was added to dissolve the Chitosan, and after that, the volume was made upto 100 ml with DDW by adjusting the pH up to 4.

Preparation of Modified Xanthan Gum Solution (1%): 0.1 gm. modified Xanthan gum was taken in a 10 ml borate buffer (pH-8.4) with continuous stirring.

Preparation of Borate Buffer:

For 100 ml- Boric Acid: 0.62 gm.
NaCl: 0.44 gm.
Sodium Tetra borate (Borax): 0.95 gm.

Preparation of Salicylic Acid Co-crystal Nano Particle: At first 60 ml /70.4 ml Chitosan solution was taken in a 250 ml beaker, and the beaker was kept in the magnetic stirrer. Drug loading was done by adding the drug into the solution (10 mg). Then 20 ml gelatin solution was added to the Chitosan solution when the drug was dissolved. To it 1.4 ml of modified Xanthan gum solution was added dropwise by the help of a pipette and turbidity occurs. From it 5 ml solution was kept for particle size analysis and rest of the solution was centrifuged at 2000 rpm for 10 min. After that the supernatant was collected and transferred into a B426 RBF for freeze (24 h). After 24 h the RBF was transferred to Lyophilizer for lyophilisation. After that the sample was collected for further study. Blank was prepared just omitting the drug into the solution.

TABLE 1: FORMULATION TABLE

S. no.	Formulation name	Chitosan used (mg)	Gelatin used (mg)	Amount of cross linker (Xanthan dialdehyde) added (ml)
1	Formulation A	150	200	1.4
2	Formulation B	176	200	1.4
3	Formulation C	200	200	1.4

Characterization of Prepared Co-crystal:

Melting Point Determination: At first thrills capillary tube was taken, and to the tubes, a pinch of different drug co former mixture was filled and it tied with a thermometer and hanged from a stand and dipped into the liquid paraffin. It was constantly heated by Bunsen burner and the melting point of the sample was noted.

Fourier Transformed Infrared Spectroscopy (FTIR) Study: FTIR spectral analysis was performed to evaluate the chemical stability of the drug as well as to confirm if there any interaction in the drug and co former by using FTIR spectrometer (iD5 ATR, Nicolet iS5, Thermo Fisher Scientific, USA). 4.3.6.3 Powder X-Ray Diffraction (PXRD).

PXRD analysis of pure drug (Glimepiride), drug and two different co formers salicylic acid, succinic acid in 1:2 ratio was performed to identify the crystalline phase.

Evaluation of Nano Co-crystal Formulation:

Size Distribution: Particle sizes, size distribution of prepared nanoparticles were determined by particle size analyser that was Malvern Zeta Seizer

as follows- 5 mg drug was loaded into 0.25% of Chitosan and 1% gelatin solution mixture with continuous stirring. When the drug was dissolved in the solution, then 0.25% of 1.4 ml of the cross linker that was modified Xanthan gum solution was added dropwise with the help of a syringe (10 ml) with continuous stirring. The formation of nanoparticles was indicated by the appearance of the turbidity. From that 5 ml of sample was taken and analyzed in Malvern zeta sizer.

Drug Entrapment Study: The yield of nanoparticles were obtained by dividing the theoretical weight of the drug and polymers used by the weight of the nanoparticles obtained. The encapsulation efficiency was determined as follows; 5 mg drug was loaded into 0.25% of Chitosan and 1% gelatin solution mixture with continuous stirring. When the drug was dissolved in the solution, then 0.25% of 1.4 ml of crosslinker that was modified Xanthan gum solution was added dropwise with the help of a syringe (10 ml) with continuous stirring. The formation of nanoparticles was indicated by the appearance of the turbidity. After that, the solution was centrifuged at 2000 rpm for 10 min and the supernatant was collected from the supernatant 5 ml was withdrawn, and absorbance was measured at 230 nm. From that, Drug Entrapment Efficiency was calculated.

***In-vitro* Drug Release Study:** At first, 5 mg of each formulation was weighed and transferred into a dialysis membrane, which was previously washed and soaked in water for 6 h. To that 1 ml of phosphate buffer pH, 6.8 was added for soaking and tied properly with a magnetic bead with the help of thread. Two 250 ml of beakers were taken, and to that, 200 ml of phosphate buffer pH 6.8 was added subsequently. Drug-loaded dialysis membranes were put into two beakers, and the beakers were shifted into the magnetic stirrer, and the rpm maintained at 50. Firstly, 5 ml sample was withdrawn, and 5 ml fresh buffer pH 6.8 was added. The timing of sample withdrawn that is 15 min interval for one hour then 30 min interval till 3.5 h and lastly after 1 h till 29 h. Lastly, the absorbance of the solution was measured at 230 nm. From it, drug release profile was calculated.

RESULTS AND DISCUSSION:

Preparation of Standard Curve and Calculation of r^2 Value and Slope:

TABLE 2: CONCENTRATION AND ABSORBANCE TABLE

Concentrate (µg)	Absorbance
0	0
2	0.099
4	0.181
6	0.276
8	0.377
10	0.479
12	0.62
14	0.731
16	0.788
18	0.925
20	0.988

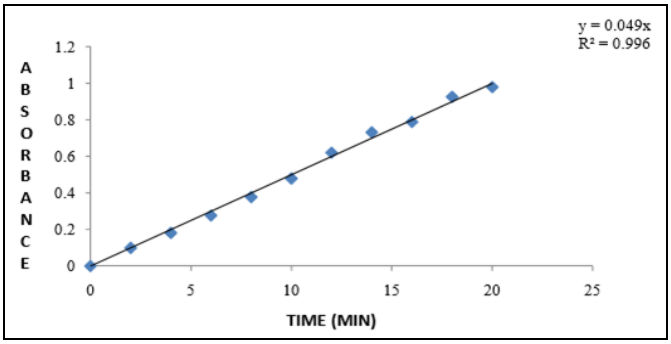

FIG. 4: STANDARD CURVE OF GLIMEPRIDE

So from the standard curve of Glimepiride, we get $R^2 = 0.996$ and slope = 0.049.

TABLE 3: TABLE OF MELTING POINT OF DRUG, CO FORMER AND DRUG AND CO FORMER IN DIFFERENT RATIO

Sample	Ratio	Solvent used	Melting point
Glimepiride (Dug)	-	-	207 °C
Salicyclic acid	-	-	(156-158) °C
Anthranilin acid	-	-	(146-148) °C
Gallic acid	-	-	(244-246) °C
Succinic acid	-	-	(188-189) °C
Benzoic acid	-	-	(121-122) °C
Drug: Salicyclic acid	1:2	Ethanol (C_2H_5OH)	(160-162) °C
Drug: Salicyclic acid	1:3	Ethanol (C_2H_5OH)	(144-146) °C
Drug: Anthranilin acid	1:2	Ethanol (C_2H_5OH)	(132-134) °C
Drug: Anthranilin acid	1:3	Ethanol (C_2H_5OH)	(122-124) °C

Drug: Benzoic acid	1:2	Ethanol (C_2H_5OH)	(178-180) °C
Drug: Benzoic acid	1:3	Ethanol (C_2H_5OH)	(98-101) °C
Drug: Succinic acid	1:2	Ethanol (C_2H_5OH)	(140-142) °C
Drug: Succinic acid	1:3	Ethanol (C_2H_5OH)	(138-140) °C
Drug: Gallic acid	1:2	Ethanol (C_2H_5OH)	(188-191) °C
Drug: Gallic acid	1:3	Ethanol (C_2H_5OH)	(188-189) °C

The melting point determination of the prepared drug and co formers like salicylic acid, benzoic acid, succinic acid, anthranilic acid, and gallic acid in two different ratios 1:2 and 1:3 gave us some idea. All the melting points of drug and co formers in 1:2 ratio having a melting point in between the melting point drug and different co formers. But in the case of drug and co formers in 1:3 ratio, there is a haphazard change or rather decrease in the melting point. So, we select the drug and co formers in 1:2 ratios for our study purpose**.**

Fourier Transformed Infrared Spectroscopy (FTIR):

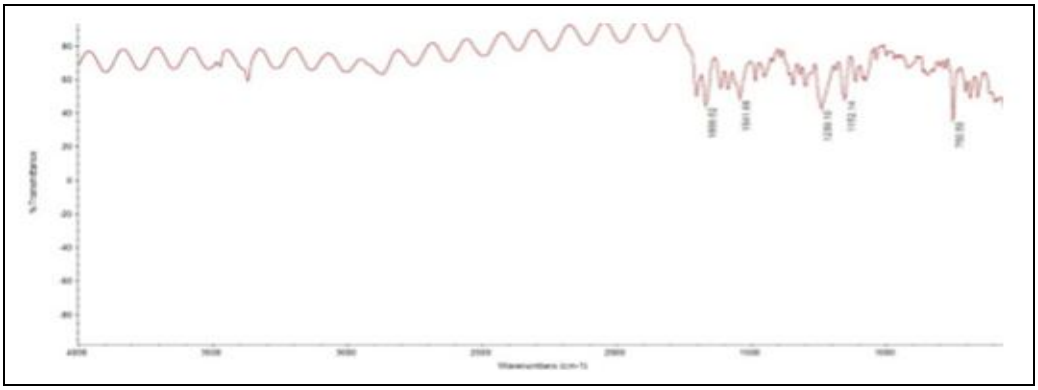

FIG. 5: DRUG: ANTHRANILIC ACID IN 1:2 RATIO

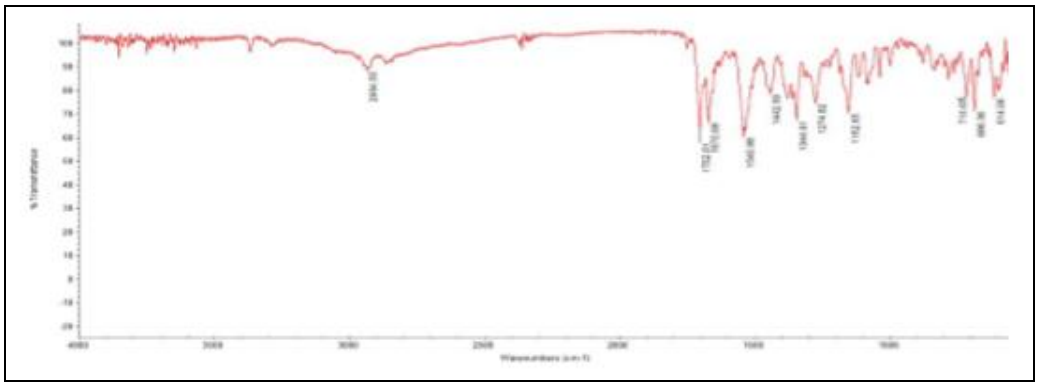

FIG. 6: DRUG: BENZOIC ACID IN 1:2 RATIO

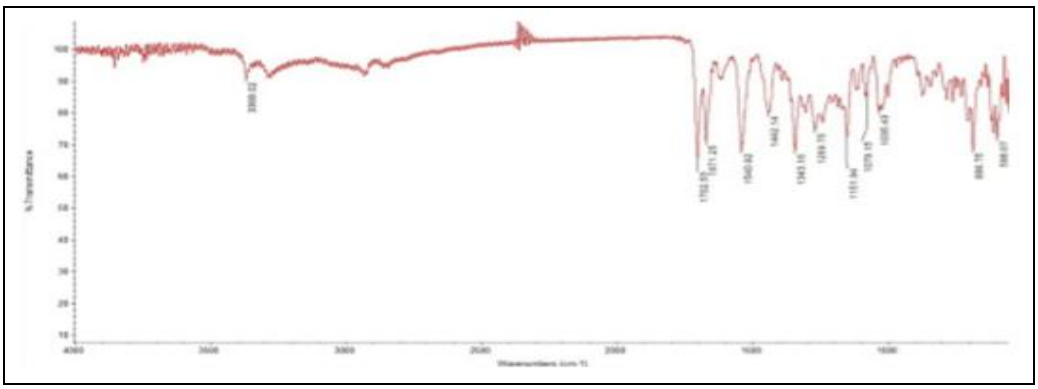

FIG. 7: DRUG: GALLIC ACID IN 1:2 RATIO

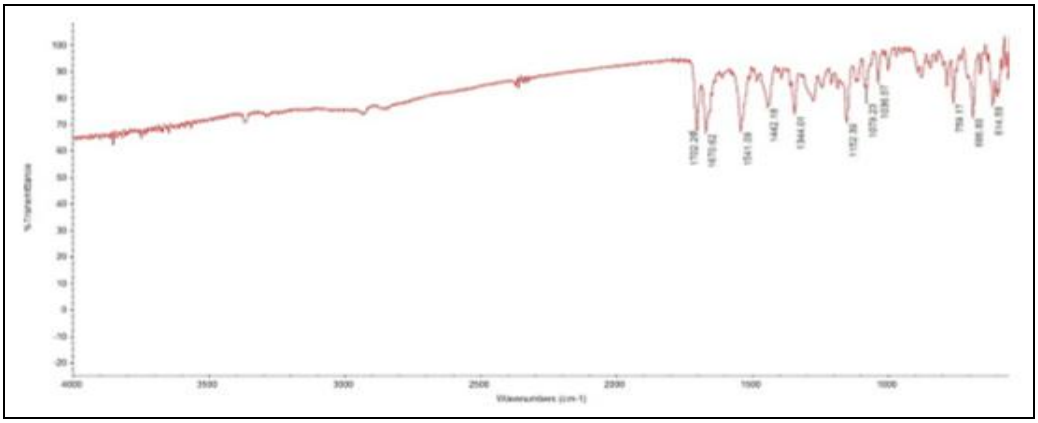

FIG. 8: DRUG: SALICYLIC ACID IN 1:2 RATIO

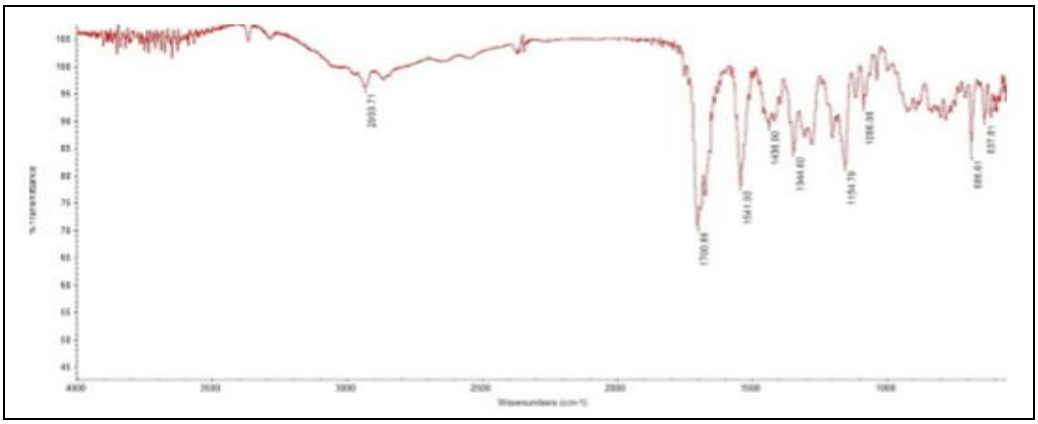

FIG. 9: DRUG: SUCCINIC ACID IN 1:2 RATIO

After comparing the FTIR spectra of Glimepiride with different co formers like salicylic acid, succinic acid, gallic acid, benzoic acid and anthranilic acid in 1:2 ratio with pure glimepiride spectra all the peaks which we get 1700 cm^{-1} and 1670 cm^{-1} for carbonyl group, 1152 cm^{-1} and 1344 cm^{-1} for sulphonyl group, Three bands due to ring stretching vibrations in the region of 1550 to 1300 cm^{-1} in case of pyrrole. We also get a peak 1435 cm^{-1} to 1445 cm^{-1} for cyclohexane. But in the case of pure Glimepiride, the peak was present at 3288 cm^{-1} and 3369 cm^{-1} for the amidic nitrogen group, but in the case of the drug: salicylic acid, the peak is absent, and for a drug: succinic acid, the peak was shifted to 2933 cm^{-1} and occurrence of a small peak near 3400 cm^{-1} which indicates the formation of hydrogen bond (-O-H).

Powder X-Ray Diffraction (PXRD):

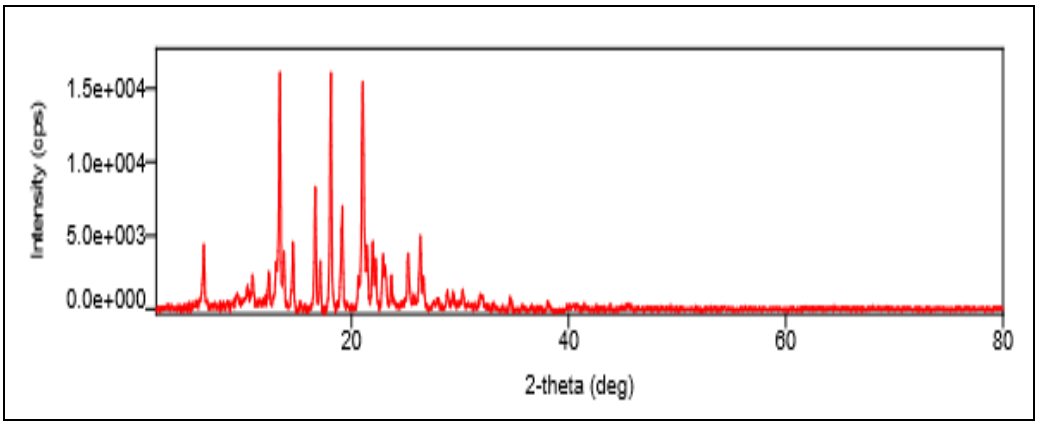

FIG. 10: POWDER X-RAY DIFFRACTION OF GLIMEPIRIDE

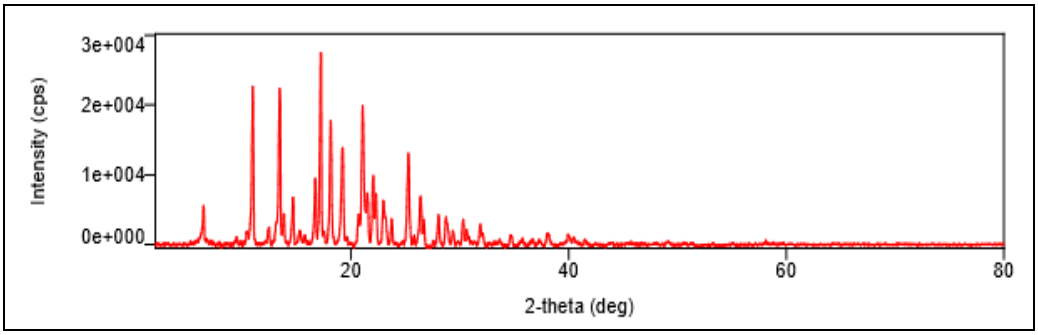

FIG. 11: POWDER X-RAY DIFFRACTION OF GLIMEPIRIDE: SALICYLIC ACID IN 1:2 RATIO

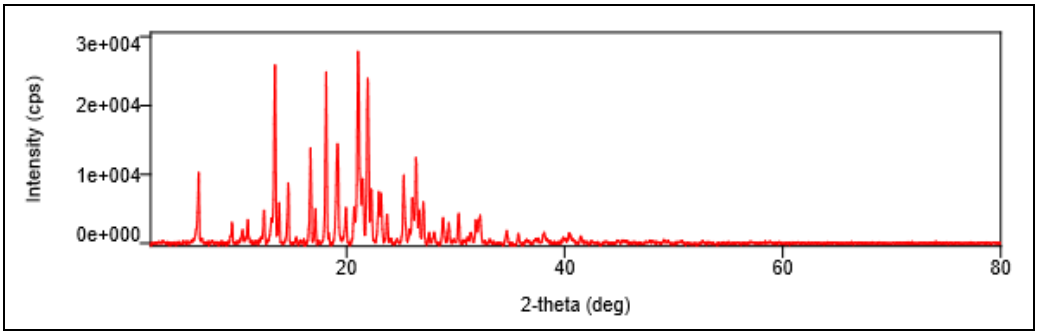

FIG. 12: POWDER X-RAY DIFFRACTION OF GLIMEPIRIDE: SUCCINIC ACID IN 1:2 RATIO

PXRD is a reliable technique to characterize the nature of new solid forms in crystallization experiments. Differences in the peaks of the new solid dosage forms compared to the peaks of the drug indicate the formation of a new phase. When the PXRD of the drug overlay to the two different mixtures, it proves the pure and homogeneous crystals were obtained. After comparing figures 12 and 13 that is Glimepiride, Glimepiride: salicylic acid, and Glimepiride: succinic acids, are evidently different from **Fig. 11** that is Glimepiride. Changes of the position, the intensity of the peaks which indicates these were not just a physical mixture and exist in the different crystalline state by the formation of the hydrogen bond.

In the case of the drug: salicylic acid ratio 1:2, there is an appearance of a sharp, high intense peak. This indicates that the drug: salicylic acid in 1:2 ratio exists in more than one crystalline form.

Size Determination of the Formulation:

TABLE 4: SIZE DETERMINATION OF FORMULATIONS

S. no.	Formulation	Z average (d. nm)	PdI
1	Formulation A	101.6	0.387
2	Formulation A	428.2	0.453
3	Formulation A	631.9	0.347

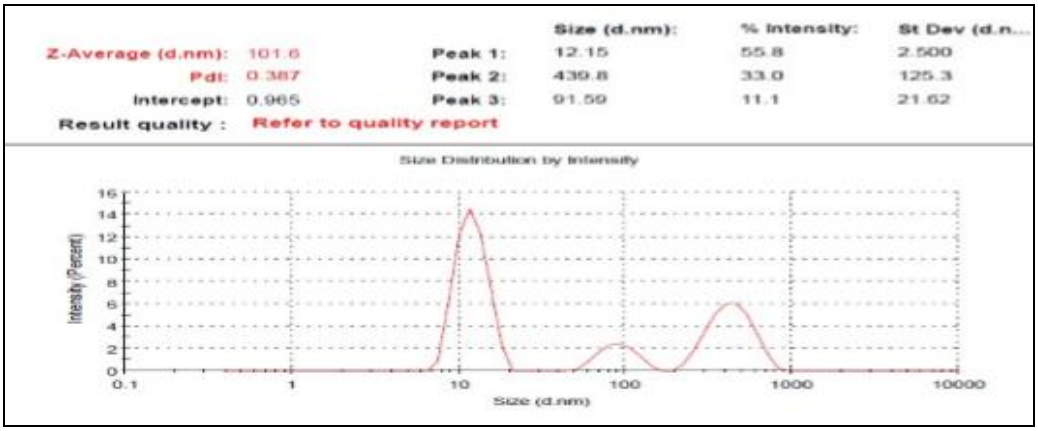

FIG. 13: SIZE DETERMINATION OF FORMULATION A BY MELVERN ZETA SIZE

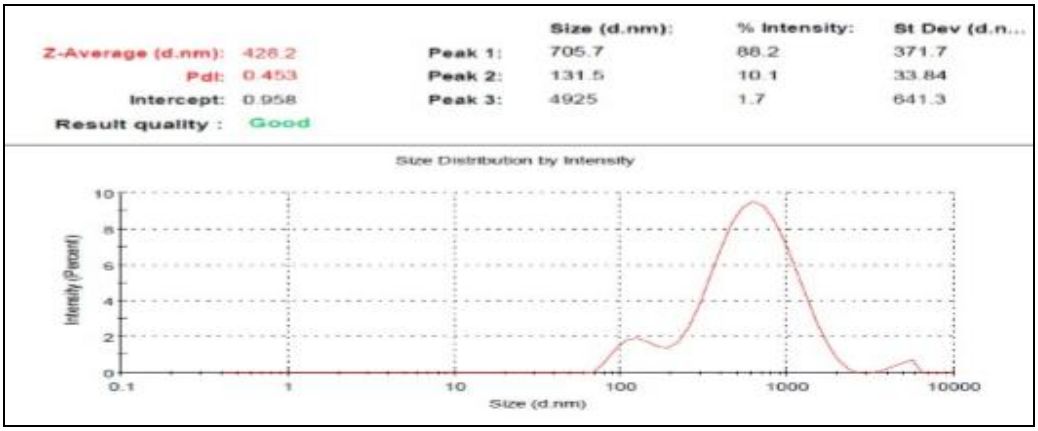

FIG. 14: SIZE DETERMINATION OF FORMULATION B BY MELVERN ZETA SIZER

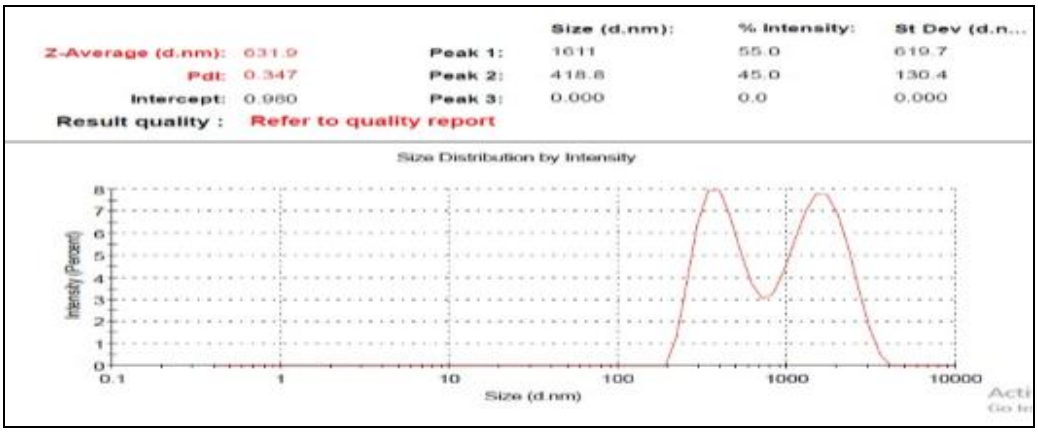

FIG. 15: SIZE DETERMINATION OF FORMULATION C BY MELVERN ZETA SIZER

By size measurement method by Malvern zeta sizer, we saw that all the formulations were in the nano range of 10-1000 nm. From the value, we can see that the particle size is reduced with a low concentration of the cross linking agent. But the polydispersity index (PdI) showed that the agglomeration of a particle in the formulation. In the case of formulation A and formulation C, there was a small amount of agglomeration, so PdI value increased rather than decreased. In case of formulation B, the agglomeration was not happened that much.

TABLE 5: FORMULATION TABLE AND DRUG ENTRAPMENT EFFICIENCY (DEE)

S. no.	Formulation name	Chitosan used (mg)	Gelatin used (mg)	Amount of cross linker (xanthan di aldehyde) added (ml)	Drug co., former (mg)	Absorbance	%DDE
1	Formulation A	150	200	1.4	80	0.840	97.26%
2	Formulation B	176	200	1.4	80	0.989	96.765
3	Formulation C	200	200	1.4	80	0.728	97.62%

After performing the drug entrapment efficiency, we saw that %DEE of formulation A was 97.26%, formulation B was 96.76%, and formulation C was 97.62%. The highest entrapment efficiency occurs with a high concentration of polymer and the addition of a cross linking agent.

In-vitro Release Study:

TABLE 6: *IN-VITRO* RELEASE STUDY OF FORMULATION A

Time	Absorbance	Concentration (µg/ml)	Amt in 5ml (in µg)	Amt in 200ml (in µg)	CAR (in µg)	CPR (in µg)	CPR (in mg)
0	0	0	0	0	0	0	0
15	0.007	0.14	0.71	28.57	28.57	589.09	0.59
30	0.008	0.16	0.82	32.65	33.37	687.99	0.69

60	0.012	0.24	1.22	48.98	48.98	1041.45	1.04
90	0.015	0.31	1.53	61.22	61.22	1319.17	0.32
120	0.018	0..37	1.84	73.47	77.76	1603.20	1.60
150	0.026	0.53	2.65	106.12	112.24	2314.33	2.31
180	0.032	0.65	3.27	130.61	139.39	2873.97	2.87
210	0.123	2.51	12.55	502.04	514.08	10599.62	10.60
270	0.274	5.59	27.96	1118.37	1142.96	23566.17	23.57
330	0.308	6.29	31.43	1257.14	1309.69	27004.00	27.00
390	0.358	731	36.53	1461.22	1545.20	31859.88	31.86
1380	0.5	10.20	51.02	2040.82	2161.33	44563.43	44.56
1440	0.531	10.84	54.18	2167.35	2338.88	48224.28	48.22
1500	0.601	12.27	61.33	2453.06	2678.78	55232.48	55.23
1560	0.583	11.90	59.49	2379.59	2666.63	54982.12	54.98
1620	0.617	12.59	62.96	2518.37	2864.90	59070.06	59.07
1680	0.689	13.65	68.27	2730.61	3140.10	64744.37	64.74
1740	0.689	14.06	70.13	2812.24	3290.00	67835.05	67.84
1800	0.704	14.37	71.84	2873.47	3421.53	70547.02	70.55
1860	0.715	14.59	72.96	2918.37	3538.27	72953.92	72.95

TABLE 7: *IN-VITRO* RELEASE STUDY OF FORMULATION B

Time	Absorbance	Concentration (µg/ml)	Amt in 5ml (in µg)	Amt in 200ml (in µg)	CAR (in µg)	CPR (in µg)	CPR (in mg)
0	0	0	0	0	0	0	0
15	0.01	0.20	1.02	40.82	28.57	590.55	0.59
30	0.01	0.20	1.02	40.82	41.84	864.75	0.86
60	0.012	0.24	1.22	48.98	51.02	1054.58	1.05
90	0.018	0.37	1.84	73.47	76.73	1586.08	1.29
120	0.021	0..43	2.14	85.71	90.82	1877.15	1.88
150	0.033	0.67	3.37	134.69	141.94	2933.83	2.93
180	0.08	1.63	8.16	326.53	337.14	6968.64	6.97
210	0.102	2.08	10.41	416.33	435.10	8993.43	8.99
270	0.131	2.67	13.37	534.69	563.88	11655.18	11.66
330	0.289	5.90	29.49	1179.59	1222.14	25261.32	25.26
390	0.34	6.94	34.69	1387.76	1459.80	30173.54	30.17
1380	0.603	12.31	61.53	2461.22	2567.96	53078.94	53.08
1440	0.6	12.24	61.22	2448.98	2617.24	54097.66	54.10
1500	0.648	13.22	66.12	2644.90	2874.39	59412.73	59.41
1560	0.681	13.90	69.49	2779.59	3075.20	63563.54	63.56
1620	0.681	13.90	69.49	2779.59	3144.69	64999.87	65.00
1680	0.699	14.27	71.33	2853.06	3287.65	67954.80	67.95
1740	0.711	14.51	72.55	2902.04	3407.96	70441.49	70.44
1800	0.724	14.78	73.88	2955.10	3533.57	73037.86	73.04
1860	0.766	15.63	78.16	3126.53	3778.88	78108.26	78.11

TABLE 8: *IN-VITRO* RELEASE STUDY OF FORMULATION C

Time	Absorbance	Concentration (µg/ml)	Amt in 5ml (in µg)	Amt in 200ml (in µg)	CAR (in µg)	CPR (in µg)	CPR (in mg)
0	0	0	0	0	0	0	0
15	0.01	0.18	0.92	36.73	28.57	585.35	0.59
30	0.01	0.27	1.33	53.06	53.98	1105.91	1.11
60	0.02	0.37	1.84	73.47	75.71	1551.20	1.55
90	0.01	0.29	1.43	57.14	61.22	1254.34	1.25
120	0.03	0.55	2.76	110.20	115.71	2370.71	2.37
150	0.07	1.41	7.04	281.63	289.90	5939.31	5.94
180	0.11	2.20	11.02	440.82	456.12	9344.86	9.34
210	0.13	2.73	13.67	546.94	573.27	11744.83	11.74
270	0.13	2.63	13.16	526.53	566.53	11606.86	11.61
330	0.16	3.16	15.82	632.65	685.82	14050.73	14.05
390	0.24	4.88	24.39	975.51	1044.49	21399.09	21.40
1380	0.62	12.61	63.06	2522.45	2615.82	53591.81	53.59

1440	0.67	13.69	68.47	2738.78	2895.20	59315.80	59.32
1500	0.70	14.27	71.33	2853.06	3077.96	63060.01	63.06
1560	0.73	14.88	74.39	2975.51	3271.73	67030.01	67.03
1620	0.72	14.59	72.96	2918.37	3288.98	67383.31	67.38
1680	0.74	15.00	75.00	3000.00	3443.57	70550.53	70.55
1740	0.74	15.00	75.00	3000.00	3518.57	72087.10	72.09
1800	0.74	15.14	75.71	3028.57	3622.14	74209.03	74.21
1860	0.74	15.10	75.51	3020.41	3689.69	75592.99	75.59

TABLE 9: TIME AND CPR OF THREE DIFFERENT FORMULATIONS TABLE

Time (min)	Formulation A (3:4)	Formulation B (1:1)	Formulation C (4:3)
0	0.000	0.000	0.000
15	0.589	0.591	0.585
30	0.688	0.865	1.106
60	1.041	1.055	1.551
90	1.319	1.586	1.254
120	1.603	1.877	2.371
150	2.314	2.934	5.939
180	2.874	6.969	9.345
210	10.600	8.993	11.745
270	23.566	11.655	11.607
330	27.004	25.261	14.051
390	31.860	30.174	21.399
1380	44.563	53.079	53.592
1440	48.224	54.098	59.316
1500	55.232	59.413	63.060
1560	54.982	63.564	67.030
1620	59.070	65.000	67.383
1680	64.744	67.955	70.551
1740	67.835	70.441	72.087
1800	70.547	73.038	74.209
1860	72.954	78.108	75.593

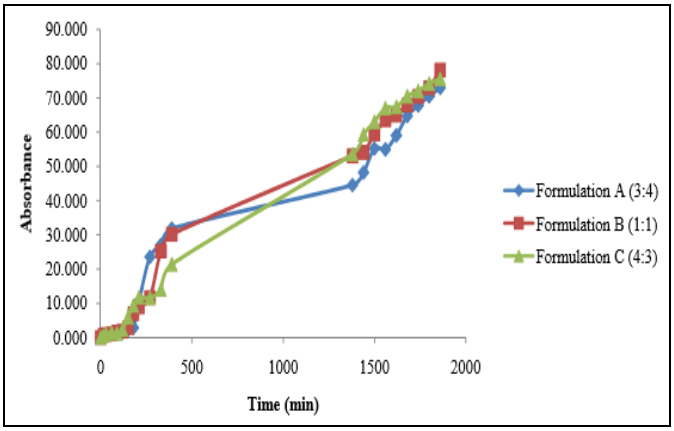

FIG. 16: COMPARISON OF DRUG RELEASE PROFILE OF FORMULATION A, B AND C

From the *in-vitro* release study, it is seen that CPR is decrease with an increase in the concentration of Chitosan. Maximum efficiency occurs in the case of Formulation B. The release involves two different mechanisms of drug molecule diffusion and polymer degradation. The burst release of the drug is associated with those drug molecules dispersing close to the nanoparticle surface, which easily diffuse in the initial point. Since the molecule is smaller than formulation, Glimepiride diffuses easily through the surface or the pore. That indicates that the release medium penetrates into the particle due to hydrophilic nature of Chitosan.

Study of Release Mechanism by Fitting into Different Model:

TABLE 10: VALUE OF r AND n BY FITTING INTO DIFFERENT KINETICS MODEL

Model	Fl	F2	F3
Zero order	r = 0.948	r = 0.978	r = 0.996
First order	r = 0.226	r = 0.227	r = 0.221
Koshmeyer	r = 0.988	r = 0.992	r = 0.995
Peppas model	n = 0.892	n = 0.897	n = 0.897
Hixson crowell	r = 0.818	r = 0.861	r = 0.888
Hill equation	r = 0.976	r = 0.979	r = 0.982

By fitting into different kinetics models we get the value of r and n from the CPR and time value. From this value, we get to understand that the release follows kinetics and the type of the flow. All the three formulations follow zero-order, koshmeyer-peppas, and hill equations, and these follow non-Frikian diffusion.

CONCLUSION: Our study demonstrates the successful application of slow evaporation to prepare the Glimepiride with different co formers like salicylic acid, succinic acid, benzoic acid, anthranilic acid and gallic acid co-crystals in 1:2 ratio among all of them drug: salicylic acid show better physicochemical properties and delivery of this co-crystals as nanoparticle by using Chitosan and gelatin polymeric matrix and modified aldehydic oxidized Xanthan gum with improved *in-vitro* activity.

Initial confirmation was made by determination of melting point followed by spectroscopic characterization. At first, by melting point determination, we select the drug with co formers in a specific ratio that is 1:2. After that, by FTIR spectra, we select the co former on the basis of formation of hydrogen bond formation, and that finalize the Glimepiride with salicylic acid and succinic acid co-crystals. Then we go for PXRD to determine the crystalline structure, and we get that in the case of the drug: salicylic acid in 1:2 ratio.

After that, we successfully prepare the formulation was prepared by preparing the nanoparticles of the drug: salicylic acid in 1:2 ratio, and by determining the entrapment efficiency and performing the in-vitro release study, we get a promising result and release for a prolong period of time. So in the future, we will study its *in-vivo* and other physicochemical property. Lastly, we can say that the co-crystal of Glimepiride by using salicylic acid and nanoparticle of was prepared successfully.

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CONFLICTS OF INTEREST: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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