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Design and Characterization of Metformin Hydrochloride Microbeads using the Ionotropic Gelation Technique

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Abstract: Microbeads containing Metformin Hydrochloride were effectively developed using the ionotropic gelation technique, employing sodium alginate as the polymer matrix and calcium chloride ($CaCl_2$) as the cross-linking agent. This study aimed to develop Metformin HCl microbeads for controlled drug release, improved therapeutic efficacy, and enhanced bioavailability. Microbeads encapsulating Metformin Hydrochloride were formulated through extruding a blend of sodium alginate and Metformin HCl through a 22-gauge needle was used to introduce the solution into a calcium chloride bath, initiating ionotropic gelation. The resulting microbeads were characterized for various physicochemical properties, including Product yield, active pharmaceutical ingredient (API) content, and drug release behavior under in vitro conditions. Preformulation studies characterized the drug, evaluating Sensory characteristics, melting point determination, solubility profile, bulk and tapped density measurements, flow property assessment via angle of repose, and structural analysis using FTIR spectroscopy. An analytical method using UV-visible spectroscopy at 234nm was developed for Metformin HCl quantification. The prepared microbeads exhibited [Insert key findings here, e.g., a spherical shape and a yield of X%]. Drug content analysis revealed [Insert drug content percentage here, e.g., a drug loading of Y%]. "In vitro drug release studies revealed a sustained release pattern of Metformin HCl, extending over a period of 12 hours, indicating the formulation's potential for prolonged therapeutic action. These results suggest that the ionotropic gelation method is a suitable technique for preparing Metformin HCl microbeads with controlled release characteristics; this could potentially enhance its therapeutic effectiveness and bioavailability. Additional research is needed to [Mention future research directions, e.g., investigate the in vivo performance of the microbeads].

Keywords: *Metformin HCl, Microbeads, Ionotropic Gelation, Controlled Release*.

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I. INTRODUCTION

Effective drug delivery systems ensure accurate medication delivery to the correct body location, maintaining therapeutic levels over time. The oral route of drug administration is commonly preferred because it is user-friendly, offers greater patient convenience, and is cost-effective. However, traditional immediate-release formulations often lead to variable plasma drug concentrations and necessitate repeated dosing. In contrast, multiple-unit systems such as microspheres, pellets, microcapsules, and microbeads are designed to provide a more controlled and sustained release profile. Microbeads (0.5-1000µm) made from polymers like chitosan, sodium alginate, and gelatin, provide sustained or multiple release profiles. They enable targeted delivery, maximizing therapeutic effects while minimizing side effects [1].

Oral medicine delivery systems have evolved beyond immediate- release phrasings to include controlled- release, time- controlled, and point-specific delivery. Controlled-release medicine delivery systems (CRDDS) are finagled to deliver medicines at a steady and pre-defined rate, icing sustained remedial situations over an extended duration [2].

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Sustained-release systems, a category within controlled-release drug delivery, are designed to prolong drug release over an extended duration without relying on fixed dosing intervals. These innovations help maintain optimal drug concentrations, promote better patient adherence, and improve overall therapeutic efficacy [3].

II. MICROBEADS

Microbeads are Flowable, multiparticulate formulations composed of biodegradable Proteins or synthetic polymers, generally with a size of less than 200 µm [4]. These homogeneous globular systems are composed of medicine motes unevenly distributed within a nonstop polymeric matrix. They represent an advanced strategy for achieving controlled medicine delivery and help overcome several downsides associated with traditional phrasings. crucial benefits include dragged and harmonious remedial action, dropped dosing frequencies to ameliorate patient adherence, ease of administration, bettered bioavailability for acid-sensitive medicines, reduced threat of gastric vexation, and the capacity to control both the rate of medicine release and the declination geste of the polymer matrix [5]. Despite their advantages, controlled- release systems face certain challenges similar as oscillations in medicine release caused by food input and gastrointestinal conveyance time, implicit toxin from high medicine attention, and the need to maintain the stability of the lozenge form to help unbridled medicine release. Microbeads can be fabricated using a variety of natural and synthetic substances, including polymers, pottery, and glass. Their structure can be either solid or concave, with concave microbeads generally employed to drop the overall viscosity of a expression, while solid microbeads are employed across a range of operations depending on their composition and flyspeck size [5]. Natural polymers like alginate, agar, chitin, agarose, gellan, gums, and chitosan have been successfully used, proving their versatility in pharmaceutical applications. The selection of natural or synthetic polymers is influenced by several factors, including their biocompatibility, biodegradability, cost-effectiveness, and the targeted drug release characteristics.

III. METHODS FOR PREPARATION OF MICROBEADS

- Ion-induced gelation techniques
- Polymer-electrolyte interaction method
- Solvent removal by evaporation
- Dual emulsion method
- Spray evaporation and spray solidification
- Solvent extraction
- Phase separation coacervation.

IV. IONOTROPIC GELATION APPROACH

Ionotropic gelation is a widely adopted and gentle encapsulation technique ideal for sensitive therapeutic agents. This method utilizes the ability of negatively charged natural polymers to form hydrogels through ionic interactions with divalent or trivalent metal ions, polymers such as alginate, chitosan, gellan gum, and carboxymethyl cellulose have anionic sites that interact with multivalent cations such as calcium or zinc. When a polymer-drug mixture is introduced into a solution containing such ions, a network of ionic crosslinks forms, yielding a hydrogel matrix. The mildness of this process is particularly advantageous for preserving the structural integrity of delicate molecules.

V. EXPERIMENTAL PROCEDURES

A. Organoleptic Evaluation:

The physical characteristics of Metformin HCl, including its appearance, color, and odor, were assessed through visual inspection and olfactory evaluation.

B. Melting Point Determination:

The melting point of Metformin HCl was determined using the open capillary method, as outlined in the USP guidelines. A tiny portion of the material was sealed inside a capillary tube and subjected to slow heating.The temperature range, starting from the initial signs of melting to the point where the process was fully completed, was carefully documented.

C. Solubility Studies:

To determine the solubility of Metformin HCl, An excess volume of the substance was mixed with 10 mL each of distilled water, methanol, and diluted HCl. The solution was kept under constant stirring at ambient temperature for duration of two days. After the reaction was complete, the resulting mixture was filtered, adulterated meetly, and anatomized to estimate solubility parcels.

D. Bulk Density Measurement:

The weight of the sample was recorded, and its bulk viscosity (Db) was determined using the following equation:

$$Db = M / Vb$$

E. Tapped Density Measurement:

The tapped density of Metformin HCl powder was assessed using a bulk density apparatus. The powder underwent tapping repeatedly until the variation between consecutive volume readings fell below 2%. The number of tapping cycles was limited to a maximum of 1250.Tapped The density (Dt) was determined using the equation: $Dt = M / Vt$

F. Angle of Repose:

Free- fluid natures to the greasepaint was examined by allowing it to pass through a channel onto a flat face.

➢ *Formula:*

$$\theta = arctan\,(h/r)$$

G. API Identification:

Infrared spectroscopy was employed to confirm the identity of Metformin HCl by comparing its spectral data with reference standards.

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H. Fourier Transform Infrared Spectroscopy:

Fourier Transform Infrared Spectroscopy analyses were conducted for evaluate presence of Chemical groups and verify structural integrity.

I. UV-Visible Spectroscopic Analysis of Metformin:

To prepare the reference solution, 100 mg of Metformin HCl was precisely measured, dissolved in a buffer solution, and the final volume adjusted to 100 mL. A 10 mL sample was further diluted with a suitable solvent to obtain a secondary working solution. Subsequently, samples ranging from 1 to 5 mL were transferred into 10 mL volumetric flasks and diluted to the calibration mark with buffer. The absorbance of the prepared dilutions was recorded at 234 nm using a UV-Visible spectrophotometer.

VI. FABRICATION OF SODIUM ALGINATE BEADS

To prepare the microbeads, 2 grams of sodium alginate were gradually added to 100 mL of distilled water while stirring continuously to form a 2% solution. Next, 1 gram of Metformin HCl was added and thoroughly dispersed. The resulting solution was carefully dripped dropwise using a 22-gauge needle into 100 mL of a 2% CaCl2 solution, maintained at room temperature. The solution was carefully agitated for 10 minutes to promote ionic gelation. Following this, the beads were separated through filtration, thoroughly rinsed with distilled water to eliminate residual calcium ions, and subjected to drying in an oven at 50°C for a period of four hours.

VII. EVALUATION OF METFORMIN HCL-ENCAPSULATED SODIUM ALGINATE BEADS

A. Percentage Yield Determination:

The percentage yield, reflecting the efficiency of the bead preparation process, was determined using the equation below:

Percentage yield = (Weight of dried beads) / (Total weight of drug and polymer used) × 100

B. Drug Content Analysis:

To determine the drug content, 459 mg of the set Metformin HCl- loaded sodium alginate droplets were dissolved in 100 mL of buffer result. A 10 mL aliquot was farther thinned to 100 mL with buffer. Subsequently, 1 mL of the diluted sample was taken, transferred into a 10 mL volumetric flask, and adjusted to the calibration mark using buffer solution. A 1 mL aliquot of this diluted solution was then placed into a separate 10 mL volumetric flask and adjusted to the mark with buffer. The absorbance of the prepared solution was measured at a wavelength of 234 nm using a UV-visible spectrophotometer.

$$Drug\ content = \frac{\text{Concentration of sample}}{\text{Concentration of standard}} \times 100$$

C. In Vitro Drug Release Investigation:

The in vitro release of Metformin HCl from sodium alginate beads was evaluated using phosphate buffer at pH 7.4 over duration of 8 hours.

VIII. RESULTS AND DISCUSSIONS

➢ *Organoleptic Evaluation:*

Metformin HCl was appears as a white, crystalline, and odorless powder.

➢ *Fusion Point:*

The Fusion Point of Metformin HCl, determined by the capillary melting point system, was set up to be 222 °C.

➢ *Solubility:*

Metformin HCl exhibited the following solubility properties: highly soluble in water, soluble in methanol, and highly soluble in hydrochloric acid.

➢ *Bulk Density:*

Table 1: Apparent Density

S.No	WEIGHT OF POWDER	VOLUME OF THE POWDER SAMPLE	APPARENT DENSITY	MEAN BULK DENSITY
1.	5	11	0.4545	0.4094 g/cm^3
2.	5	12	0.4166	
3.	5	14	0.3571	

➢ *Tapped Density:*

Table 2: Tapped Density

S.No	WEIGHT OF POWDER	VOLUME OF THE POWDER SAMPLE	COMPACT DENSITY	MEAN TAPPED DENSITY
1.	5	8	0.625	0.6018 g/cm^3
2.	5	9	0.5555	
3.	5	8	0.625	

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➢ *Angle of Static Friction:*

Table 3: Angle of Static Friction

S.No	SOLVENT	DRUG SOLUBILITY
1.	<20	Excellent
2.	20-30	Good
3.	30-34	Passable
4.	>40	Very poor

➢ *Analytical Method for Metformin*

Table 4: Analytical Method for Metformin

CONCENTRATION (MICROGRAMS PER MILLILITER)	Optical Density
0	0
2	0.163
4	0.345
6	0.462
8	0.656
10	0.779

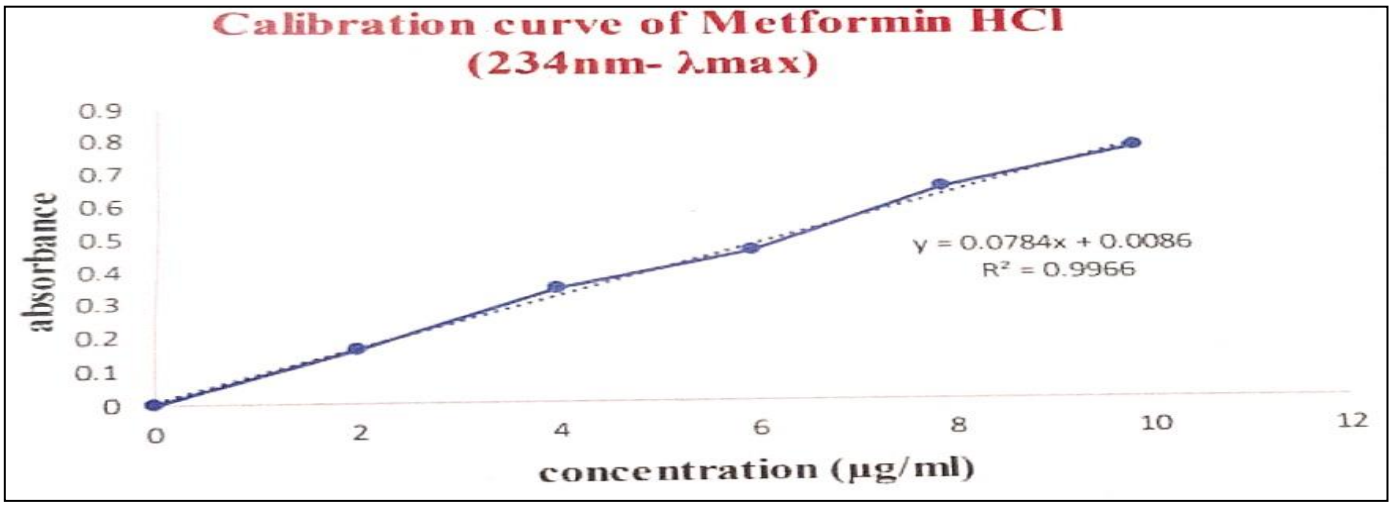

Fig 1: Calibration Curve of metformin HCL

IX. DRUG EXCIPIENT COMPATIBILITY STUDIES

A. *FTIR Spectroscopy*

FTIR spectra of the drug, chosen excipients, and their combination were examined to assess any interactions. The spectra along with the key peaks of the individual compounds and their mixtures are presented in the figures below:

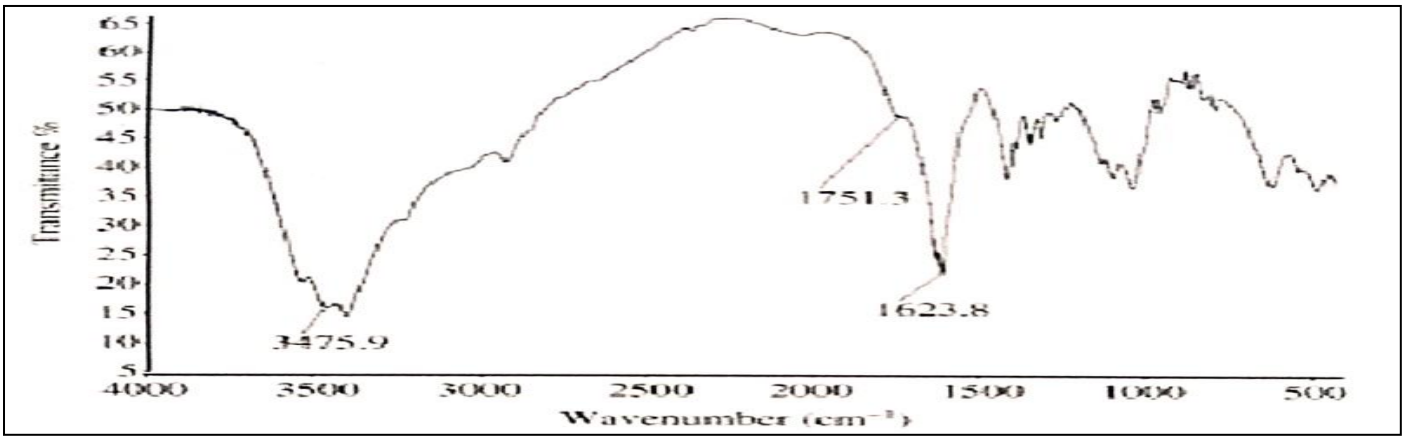

Fig 2: FTIR Spectrum of Sodium Alginate

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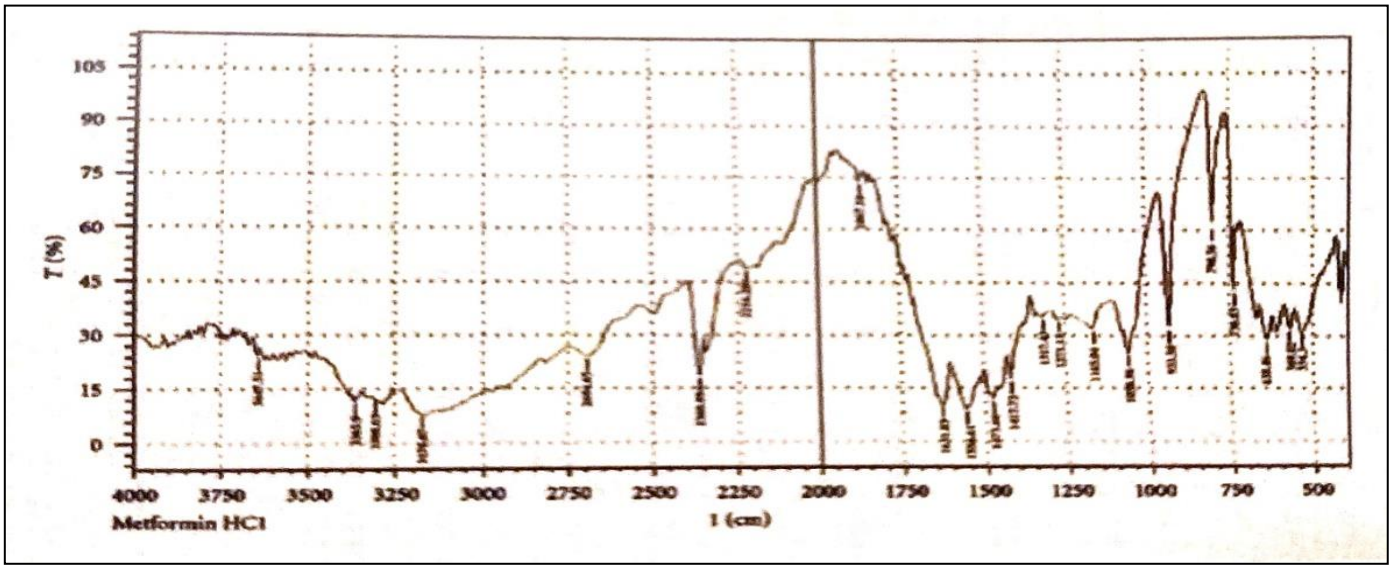

Fig 3: FTIR Spectrum of Metformin

B. Metformin Plus Sodium Alginate:

For the combined formulation, the FTIR report evaluates the compatibility between metformin and sodium alginate. It assesses any potential interactions or changes in the spectra when the drug is mixed with the excipients. This analysis is crucial to ensure that the combination remains stable, preserving the drug's efficacy and safety while not altering its chemical structure adversely.

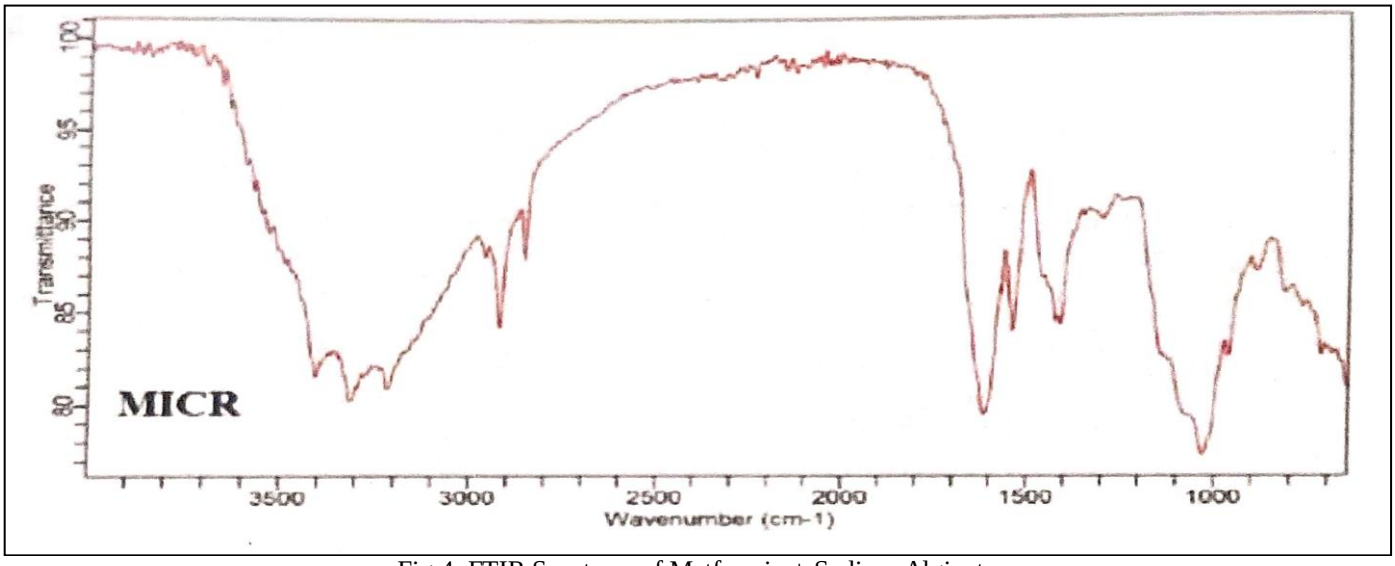

Fig 4: FTIR Spectrum of Metformin + Sodium Alginate

C. Evaluation of Sodium Alginate Beads

➢ *Ayield Percentage:*

- Actual Product Weight = 5.41g
- Total Mass of drug and polymer = 6g

$$\textbf{Chance Yield} = \frac{\textbf{factual weight of product}}{\textbf{Total weight of medicine and polymer}} \times \textbf{100}$$

=5.41/6×100

=90.16%

➢ *Drug Content (%):*

$$\textbf{Drug content} = \frac{\textbf{concentration of sample}}{\textbf{concentration of standard}} \times \textbf{100}$$

=5.9/10×100

= 59%

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➢ *In Vitro Drug Dissolution Studies:*

Table 5: In Vitro Drug Dissolution Studies

Time (Min)	Absorbance	Concentration (µ/ml)	Actual Concentration (mg/ml)	% Drug Release	% CDR
0	0	0	0	0	0
30	0.239	2.880615	0.259255	2.592553	2.592
60	0.288	3.512226	0.3161	3.161003	5.753003
90	0.38	4.698108	0.42283	4.228297	9.9813
120	0.401	4.968798	0.447192	4.471918	14.45322
240	0.455	5.664859	0.509837	5.098374	19.55159
480	0.576	7.224552	0.65021	6.502097	26.05369

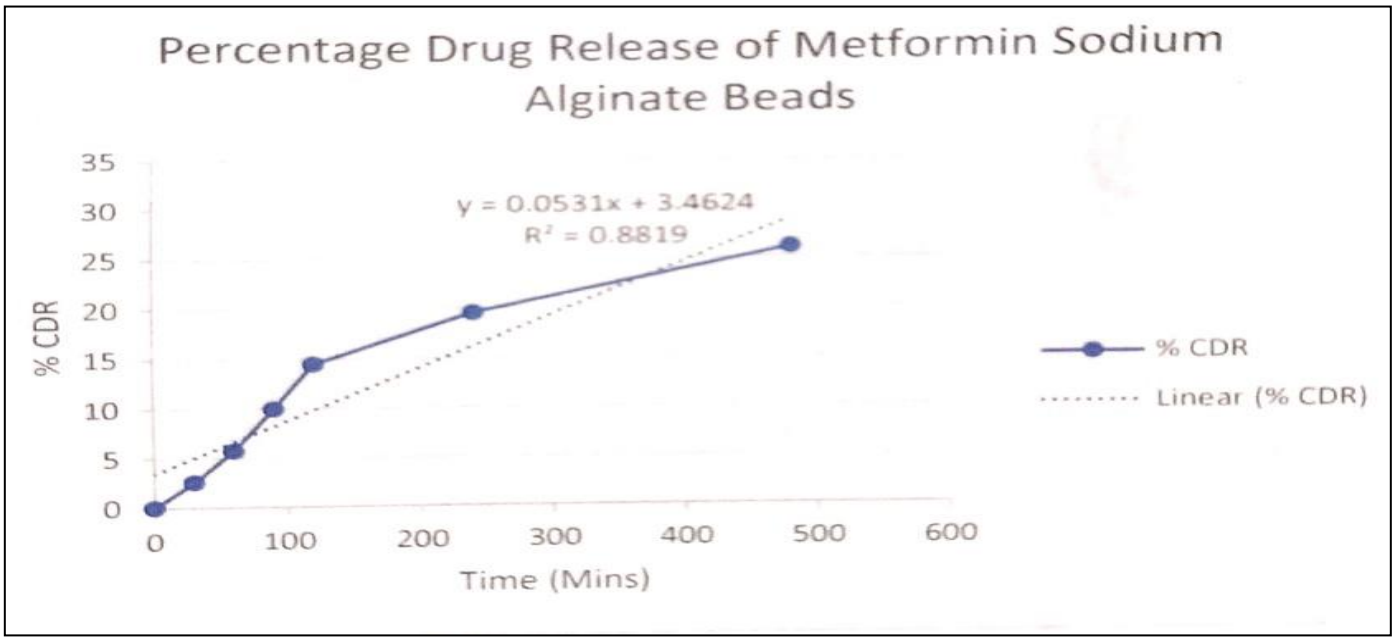

Fig 5: Percentage Drug Releases of Metformin Sodium Alginate Beads

X. CONCLUSION

Metformin Hydrochloride-loaded microbeads show great potential as drug delivery carriers owing to their numerous benefits. Sodium alginate, a biocompatible and biodegradable synthetic polymer, is an ideal choice due to its water solubility and mild, simple preparation methods. These properties make sodium alginate microbeads suitable for a wide range of drugs, including macromolecules and sensitive compounds. The Metformin Hydrochloride-loaded microbeads were successfully fabricated using the ionotropic gelation technique, yielding 90.16%, with 59% drug content and 26.05% drug release over 8 hours. The ionotropic gelation method is advantageous due to its mildness and effectiveness, avoiding harsh chemicals while achieving controlled drug delivery.

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