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CHARACTERIZATION AND STABILITY ANALYSIS OF METFORMIN HCl MICROCAPSULES FORMULATED BY COMPLEX COACERVATION TECHNIQUE

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ABSTRACT

Objective: Metformin hydrochloride possesses a shorter sort of biological half-life of 1.5–1.6 h with having the absolute type of bioavailability that ranges between 50-60%, the moment it is administered orally. Reduced GIT disturbances and low bioavailability can be optimized by developing microencapsulation of metformin that could prove beneficial. **Method:** Paraffin oil had been used in obtaining specific types of primary emulsions, whereas the material that was used in the coating of microencapsulation had been identified as sodium alginate. In the process of complex coacervation, a substance known as Tween 20 was used as a surfactant in enhancing the stability of W/O/W double emulsion. Five different formulations with different concentrations of sodium alginate were tested. **Result:** Metformin's microencapsulation inside certain types of optimized atmosphere tends to ensure the specific size of 1 am of microcapsules in a combined form, and encapsulation efficiency reaches up to 84%. FTIR measurements have been used to determine the interaction between drug and polymer. The qualitative analysis result from FTIR ensures that the quality and effectiveness of the drug have been preserved. A calibration curve was used to estimate drug conc. from dissolution samples and kinetic analysis demonstrated anomalous release pattern. The test for drug content yielded >95% of concentration. **Conclusion:** Results extracted tend to tell us that specific complex coacervation that is using sodium alginate in wall material was a viable method that is used in the microencapsulation process of metformin hydrochloride.

Keywords: Metformin hydrochloride, Complex coacervation, Double emulsion, Sodium alginate.

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INTRODUCTION

Diabetes of type two is a chronic condition that hinders the body from full utilization of insulin. Insulin resistivity is a terminology that can be used in describing people who are having type 2 diabetes. The most susceptible age group for type two diabetes can be a middle age as well as older. Formerly it was known to be adult-onset diabetes. But due to childhood obesity, type two diabetes also has impacts on children as well as adolescents **[1]**.

The major symptoms of this disease are thirst, fatigue, frequent urination, and numbness in the hands and feet. Insulin is known to be a specific hormone that is produced in the pancreas of the body. It helps in converting glucose, a type of sugar extracted from food, into energy in the cells **[2]**. Insulin is produced by individuals who are having type 2 diabetes, but cells can't utilize it as effectively as they could. The pancreas of a patient initially produces more insulin to gain glucose into cells. But soon, it can't maintain its presence and the blood glucose levels increase instead **[3]**.

Metformin is used as an orally administered hypoglycemic agent for type 2 diabetes. Metformin is highly soluble in aqueous media because it is a small hydrophilic molecule, therefore, rendering having a small oral absorption Index **[4]**. The biological half-life of metformin is short which is 1.5–1.6 h, and it can be used daily (1.5–3 g/day) **[5]**.The most common adverse effect of this drug is stomach discomfort. The administration of metformin with a meal is a better option because it reduces the side effects of metformin like nausea, vomiting, and diarrhea are reduced **[6]**.

Microencapsulation is a resourceful pharmaceutical dosage form in which the small droplets are coated with continuous film **[7]**. Through the microencapsulation drug delivery system, we have a preprogrammed GIT transit time because of its

free-flowing properties of it. The microencapsulation system has advantageous protection and control of drug release. It protects the core compound and also reduces the loss of the drug due to vaporization **[8]**. The small size of the particle is very helpful in spreading over the small intestine to improve drug absorption and allows controlled GIT transit. Through this drug delivery system, the shelf life and colloidal properties of the drug can also be altered and improved **[9]**.

The study aims to microencapsulate the Metformin so that its dose frequency can be reduced which increases patient compliance **[10]**. Due to the shorter half-life, it is desired to make the effective extended-release formulation of metformin HCl.

MATERIALS AND METHODS

Chemicals

Metformin, Sodium Alginate (NaAlg), Calcium Carbonate ($CaCO_3$), Tween 20, Paraffin oil, Acetic Acid, Monobasic Potassium Phosphate, and Sodium Hydroxide (NaOH) were purchased from Sigma Aldrich Pakistan. Distilled water was also used throughout the study.

Pre-formulation Tests

Crystallinity

The degree of structural organization in a solid is known as crystallinity. A small quantity of metformin was taken onto the glass slide. Two drops of water were put on the drug which was covered with the slip onto it. The glass slide was placed onto the stage of a microscope. Crystals were observed by using a microscope under different objective lenses.

Hygroscopicity

A thin coating of powdered Metformin was placed inside the empty China dish after weighing it. After placing the drug on the china dish, it was weighed again. China dish was dehydrated for 10 minutes and set over the magnetic stirrer for the next 15 minutes. The china dish was weighed again and all the readings of weight were noted. The method given in the literature was used **[11]**. The difference in weight was measured by using the following formula:

$$\text{Moisture Content} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Final Weight}} \text{X}100$$

Melting Point Analysis

The Fisher-Johns Melting Point Apparatus was used for the melting point analysis. A few crystals were placed on the cover slip and the second cover slip was placed over it. On the rounded heating block, the sandwich of the compound and a cover slip were placed. The view was examined via the lens above the heating block. The increase in temperature rate around the melting point must be kept slow, at most 2°C per minute **[12]**.The heating block was quickly cooled with an aluminum cylinder. After finishing, the used coverslips were removed to the recycling jar behind the instrument.

Flow Properties

The angle of repose and Compressibility index (Carr's index) was used to determine the flow properties of the drug.

Carr's Index

The volume of the powder was measured by pouring it into a cylinder for measurement. The bulk density had been calculated through the division of the mass with density. The cylinder used to be tapped at a rate of 250 taps per minute. Carr's index was calculated by using the following formula:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{tapped density}} \text{ X } 100$$

The angle of Repose

The drug weight was evaluated precisely. The powder was poured into the funnel after positioning it upside down over a tripod platform. A heap was developed. The circle's diameter and the height of the heap were noted. The method was given in the literature **[13]**. The angle of repose had been calculated by implementing the following formula:

$$\text{The angle of Repose } = \tan^{-1} \frac{2 \text{ x height}}{\text{diameter}}$$

Size Distribution Analysis

The study of particle size distribution is termed micro metrics. For this purpose, the sieve method was used. and the % retained was calculated by using the formula:

$$\%\text{ retained } = \frac{\text{retained sample on the sieve}}{totalweightofsample} X100$$

Solubility Analysis

Standard buffer solutions of various ranges of pH between 1.2 and 8.0 were prepared according to USP and the solubility of metformin in these aqueous buffers was determined. To determine the solubility level of metformin in a certain organic solvent, the Partition Coefficient was determined by using the following formula:

$$\log \text{p} = log \frac{\text{solubility in organic solvent}}{\text{solubility in aqueous solvent}}$$

Microencapsulation of Metformin Hydrochloride

Sodium alginate (NaAlg) and metformin HCl were employed as the wall and core materials, respectively, in the microencapsulation of metformin HCl by complex coacervation technique. Metformin HCl and NaAlg were used in a ratio of 1:15. NaAlg (2%, w/w) were disseminated in distilled water for the tests using a disperser (T-25, IKA). Then, 5% (w/w) microcrystalline $CaCO_3$ was added. The NaAlg-$CaCO_3$ stock solution was

maintained at 4 °C to hydrate completely. The NaAlg-$CaCO_3$ stock solution was combined with the aqueous form of metformin HCl (1.5 mg/mL) while stirring with a magnetic stirrer. The aqueous mixture was then magnetically stirred into paraffin oil that included 1% (w/w) Tween 20 as the emulsifying agent. The aqueous to oil phases were split 30:70 (v/v). The wet microcapsules containing metformin HCl had been separated from the oil phase after 15 minutes of the gelling reaction by the addition of 200 mL of phosphate buffer (0.2 M, pH 7). The moist microcapsules began to settle after two hours. The oil supernatant was removed and thrown away. The filter paper was used to separate the wet microcapsules so they could be further dried and turned into powder.

Appearance

A small quantity of formulation was taken onto a glass slide. Two drops of Solvent were poured onto the formulation as provided in the literature **[14]**. Then placed the slide on the microscope stage. Then by using different objective lenses appearance of particles was observed.

Standard Calibration Curve

For the preparation of sample solutions of varying concentrations mcg/ml (2,4,6,8,10); a standard solution of concentration 1mg/ml got prepared by dissolving 50 mg Metformin HCl in 50 ml of distilled water. This standard solution was further diluted by taking a solution of 2 ml and then adding 98 ml of distilled water so that the concentration of the working solution is 200mcg/ml. After further dilution of this working solution, a solution of 20mcg/ml was prepared. The sample solutions of various concentrations were analyzed using a spectrophotometer at a wavelength of 234 nm. The calibration curve was obtained by plotting readings of samples against drug concentration.

Drug Uniformity Test

The drug of 10 mg was placed in a beaker and a buffer of 7.4 pH was added to it. It was shaken for 30 min and placed for 24 hours. After 24 hours, it was shaken again for 30 min. It was centrifuged for 15 min at 40000 rpm. When the clear solution is obtained, 1 ml of supernatant was diluted with 9 ml of buffer. This was observed in a UV spectrophotometer.

In-vitro Dissolution Test

The weighed metformin micro-capsules were placed in an empty teabag. It was tied with the paddle of the dissolution apparatus. The rotation was set at 50 rpm for 24 hours. The sample of 1 ml was taken after 30 min, 1 hour, 2-hour, 3-hour, 4-hour, 5-hour, 6 hours, 8 hours, 12 hours, 18 hours, and 24 hours. The samples were diluted ten times with phosphate buffer of pH 7.4 and were checked using a spectrophotometer. The absorbance was determined against 234 nm wavelength and a graph was plotted.

Differential Scanning Calorimetry (DSC)

By using an automatic thermal analyzer, differential scanning calorimetry analysis of Metformin, sodium alginate, and microspheres formulation was performed. The sample was accurately weighed (5 mg) and placed on a sealed aluminum pan. As a reference, an empty pan was also used. The nitrogen flow rate for the DCS runs was 60 mL/min, with a temperature range of 25 to 400°C. Using a Netzsch STA 449 PC Luxx® type DSC, DSC curves were recorded. Alumina pan was utilized as a reference during the calibration process along with various standards.

FTIR for Metformin Microcapsules

The sample was inserted into NicoletTM iS5 FTIR spectrometer having diamond attached to it at an angle of incidence of 42° and the spectra were recorded. The spectral range between 400 and 600 cm-1 was used to obtain ATR-FTIR spectra. Before use, the device was properly calibrated, cleaned, and corrected for air and carbon dioxide background levels. For each sample collected at a separate time interval, the IR spectrum was recorded. For interpretation, all spectra were recorded in absorption mode and overlapped.

Stability Analysis

Accelerated stability analysis was carried out using ten bottles of 60 ml suspension containing the Metformin Microspheres under a condition of (40°C ± 2°C, 75% ± 5% Relative humidity) for six months. The sample was withdrawn after one, two, three, and six months

Table 1: Ingredients used in the formulation.

Formulations	**F1**	**F2**	**F3**	**F4**	**F5**
Sodium Alginate	0.5g	0.7g	0.6g	0.5g	0.65g
Calcium Carbonate	1.25g	1.2g	1.3g	1.15g	1.20g
Tween 20	0.25g	0.3g	0.15g	0.2g	0.25g
Paraffin oil	25ml	25ml	25ml	25ml	25ml
Metformin HCl	7.5g	7.5g	7.5g	7.5g	7.5g
Acetic Acid	0.25ml	0.25ml	0.25ml	0.25ml	0.25ml
Monobasic Potassium Phosphate	200ml	200ml	200ml	200ml	200ml
Distilled Water	500ml	500ml	500ml	500ml	500ml

RESULT AND DISCUSSION

Pre-formulation Tests

The drug comprises needle-shaped crystals and it was slightly hygroscopic. The solubility of metformin was analyzed in the various aqueous buffers of pH 1.2 – 8.0 and organic solvents (**Table 2)**. Results of the analysis show that metformin was very slightly soluble at acidic pH and very soluble in organic solvents. Similarly, the Partition Coefficient (log P) value of metformin is -0.56 which marked it a hydrophilic drug.

Post-formulation Tests

This research work showed the preparation as well as evaluation of microcapsules of Metformin HCl. Complex coacervation got used for the preparation of microcapsules of metformin.

Physical characteristics were evaluated by various tests i.e., appearance and weight variation test. Various post formulation parameters were determined for five formulations (**Table 3)**.

In this study, metformin microcapsules were prepared using a complex coacervation method. SEM image shows that the microcapsules have a spherical shape. The mean particle size of metformin HCl-loaded microcapsules was 1 µm ($p>0.05$) **[15]**. The measurements were utilized to create a calibration curve, and an R-square value of 0.9958 was discovered. The test for drug content yielded an absorbance value of 0.105. Five different formulations were tested for the dissolution test. The absorbance was measured at 234 nm, and a graph of the five distinct formulations was created. The obtained R2 value was 0.9913. Formulation one follows zero-order kinetics which implies that it is concentration independent. The formulation follows the Korsmeyer-Peppas equation **[16]**and has a value of n 1.042 so, it shows zero order i.e. Metformin is being released at a constant rate.

Formulation two complied with the Higuchi model and first-order kinetics. It follows the 1st order means it is concentration dependent. Higuchi model is also followed by this means it is diffusion dependent. The formulation follows the Korsmeyer-Peppas equation and has a value of n 0.529 so, it shows pseudo first order release. It follows the non-Fickian transport as well as the first order. The value of n shows that the release is dependent mainly on the diffusion process. It is concentration dependent as well as diffusion dependent.

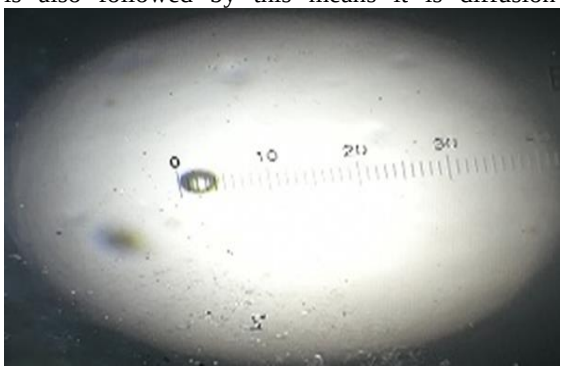

Figure 1: Microscopic image of metformin microcapsules.

Formulation three follows the 1st order kinetics means the release is concentration-dependent. The yield efficiency is 98.8% and the percentage release is 76% in 24 hrs. The release followed the biphasic pattern characterized by initially moderate drug release followed by a higher release phase. The formulation follows the Korsmeyer-Peppas equation and has a value of n 0.651 so, it expresses pseudo first order release. It follows the non-Fickian transport. The value of n shows that the release depends mainly on the diffusion process. It is diffusion dependent and also concentration dependent **[17]**.

Formulation four complied with the Korsmeyer-Peppas equation and first-order kinetics. It follows first-order mean it is concentration-dependent. As this formulation has a value of n 0.758 in Korsmeyer-Peppas which indicates that it follows non-Fickian transport and as well the first order. The value of n shows that the release is dependent on both the diffusion and dissolution processes. So, the drug release was anomalous. Formulation five follows zero-order kinetics which implies that it is concentration-independent. The formulation follows the Korsmeyer-Peppas equation and has a value of n 1.102 so, it shows zero order i.e., Metformin is being released at a constant rate.

DSC Thermogram

Pure metformin (C) exhibits an endothermic peak at 220°C on the thermogram. However, there is no such peak in the sodium alginate (B), indicating that the drug is molecularly disseminated in the polymer matrix, as shown in the figure 4. It was also evaluated from the literature **[18]**.

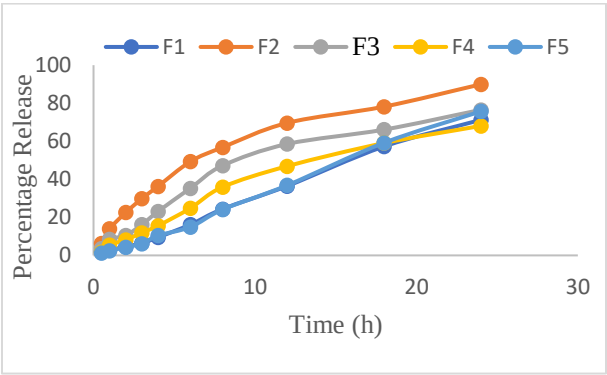

Figure 2: Drug release profile.

Table 2: Various pre-formulation studies.

Preformulation Studies	**Results**
Crystallinity Method	Needle shaped crystals
Hygroscopicity Test	Slightly hygroscopic
Size Distribution Analysis	90% passed from 60 mesh size
Melting point Analysis	223°C
Angle of Repose	30.6
Carr's Index	6.32
Hausner's Ratio	1.062

Table 3: Various post-formulation studies.

Post Formulation Analysis		**F1**	**F2**	**F3**	**F4**	**F5**
Appearance		Fine	Fine	Crystalline	Fine	Crystalline
Particle Size	μm	1.2 ± 0.1	1.1 ± 0.2	1.2 ± 0.2	1.0 ± 0.1	1.0 ± 0.2
Encapsulation Efficiency	%	82.2 ± 0.2	90.4 ± 0.3	98.8± 0.1	92.2 ± 0.1	86.3± 0.4
Drug Content	%	89.1 ± 0.1	93.5 ± 0.4	98.2 ± 0.1	94.2 ± 0.4	86.8 ± 0.1

Table 4: Kinetic model analysis.

Formulation	**Kinetic Model**				
	Zero order	**First order**	**Higuchi**	**Korsmeyer-peppas**	
	R^2	R^2	R^2	R^2	n
F1	0.9945	0.9592	0.7946	0.9945	1.042
F2	0.6668	0.9857	0.9793	0.9790	0.529
F3	0.8470	0.9858	0.9299	0.9631	0.651
F4	0.9384	0.9942	0.8997	0.9805	0.758
F5	0.9927	0.9440	0.7749	0.9964	1.102

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FTIR Analysis

The frequency range 4000-400 cm-1 was used to record the FTIR of the drug metformin. The qualitative analysis result from FTIR ensured that the quality and effectiveness of the Metformin HCl were preserved, as shown in figure 5.

In the range 3550-3250 cm-1, the N-H stretching vibrations can be found. The N-H stretching vibration in the IR spectrum appeared at 3372 cm-1. In the range of 1650 to 1581 cm-1, N-H deformation vibrations frequencies of 1626, 1583, 1455, and 1417 cm-1 appeared. Between 1170 and 1040 cm-1 C-N stretching vibrations typically occur and appeared. A band in the IR spectra at 800 cm-1 in metformin hydrochloride was attributed to NH2 vibrations. Compounds containing nitrogen produce particularly distinctive absorption bands in their infrared spectra bands of moderate to high intensity at 580 and 418 **[19]**. Infrared metformin hydrochloride had medium to moderate intensity bands at 580 and 418 cm-1 that were caused by C-N-C deformation. The qualitative analysis result from IR ensured that the quality and effectiveness of the Metformin HCl were preserved in the appropriate storage condition.

Stability Analysis

The results of the stability analysis are shown in the table 5.

The percentage of drug content was 99%, 98%, 96%, and 92% after one, two, three, and six months respectively. Hence the Suspension of Metformin Microspheres remained stable during the stability analysis.

This is consistent with the stability testing studies on microcapsules by storing in the oven which is thermostatically controlled at temperatures of − 15°C, 5°C, 25°C, as well as 40°C. All these temperatures should be with relative humidity set at 35%, for the time of 72 h and there must use the Angelantoni Environmental as well as Climatic Test Chamber, Italy. The microcapsules had been analyzed for drug contents **[20]**.

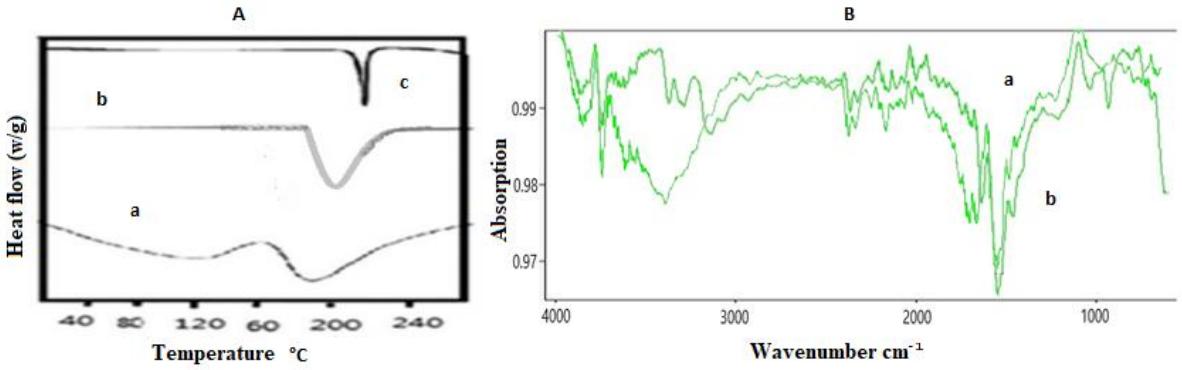

Figure 3: A: DSC Thermogram. a) sodium alginate b) Drug loaded Sodium Alginate c) Pure Metformin; **B:** FTIR graph for metformin.

Table 5: Stability Analysis at temperature 40 °C ± 2 °C and relative humidity 75% ± 5%

Time	Percentage drug content
1 month	99%
2 months	98%
3 months	96%
6 months	92%

CONCLUSION

In the above study, Metformin microcapsules which are having sodium alginate and are used in wall materials were successfully made through double emulsion that is followed by a complex sort of coacervation technique. All of our results tend to manage with certain types of objectives which were having high encapsulation yield. Some low particle sizes were offering metformin encapsulation yields ranging from 70% to the higher percentage like 85%. In the whole conclusion, Metformin hydrochloride's microencapsulation in certain optimized conditions tends to ensure the mean size (1 μm) of microcapsules as well as the highest yield reaching 84%. As a result, there is a newly proposed double emulsion which is seen to be followed by a certain type of complex coacervation technique in preparing polymeric microparticles of metformin had been found quite simple, controllable as well as economical through utilizing low cost excipient polymers (Sodium Alginate).

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