Research Article

Formulation and Comparison of Glucomannan Metallocomplexes Made of Cobalt and Copper

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ABSTRACT

The broad category of pharmaceutical science in which drugs are complex with metals like platinum, zinc iron, etc is defined as Metallopharmaceutics. The earliest work on Metallopharmaceutics is around 700 BC. In this work, Glucomannan, which is a plant-based drug, is used as a ligand to prepare anti-diabetic metal complexes of Cobalt and copper. Glucomannan is basically a polymer thought up of -(14)-linked D-mannose and D-glucose in a straight chain in a ratio of 8:5. Various pre-formulation studies were performed including swelling index and angle of repose for the pure drug only. The pre-formulation parameters inferred that the pure drug has fair flow properties with a swelling index of 81.8%. Formulations were analyzed spectrophotometrically using ATR-IR and UV-spectroscopy. In UV spectroscopy, it was analyzed that Glucomannan showed a distinct peak at 267 nm. Formulation of metal complexes was performed using the solvent-assisted method. The dissolution studies and release kinetics were performed for prepared Formulations (F1-F9). The Formulation F9 proved to be the best formulation following the Higuchi Diffusion plot with maximum linearity of 0.997. Thus, 500 mg Glucomannan + 1000 mg Cobalt (F9) had the sustained drug release throughout the dissolution period.

Keywords: Metallocomplex, Metallopharmaceutics, Glucomannan, Release kinetics, Formulation.

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INTRODUCTION

A drug delivery system is a type of pharmaceutical system that is primarily consisting of drugs and excipients and is used to efficiently provide drugs to the body.[1] The basic goal of an excellent medication delivery system is to hide the medicine's toxicity while increasing its effectiveness.[2] The broad category of pharmaceutical science in which drugs are complex with metals like platinum, zinc iron, etc is defined as Metallopharmaceutics.[3] This subsection of coordination chemistry produces a promising drug delivery system, which possesses more than one therapeutic activity.[4-6] There are 5 types of synthesis for metal complexes, which are as follows:[7-10]

i. Mechanochemical synthesis
ii. Gas-phase synthesis
iii. Direct Electrochemical synthesis
iv. Liquid phase synthesis
v. Miscellaneous

It is mentioned that a variety of metal ions has a very long history in pharmacology, toxicological studies and medicine in various research and review articles. The earliest work on Metallopharmaceutics is around 700 BC. It was around the 13th century when metals were first proposed to have medicinal effects in the treatment of various ailments like diabetes, hypertension and many more. This proposal was made by Paracelsus.[5] There are various applications for metallopharmaceuticals in the world of science during this modern era. Alfred Werner made a breakthrough in 1893 with his intense research in metal complexes using Chlorine, Cobalt and

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Ammonia.[11] In the late 20th century, a huge number of drug-metal complexes have been synthesized, which process crucial applications in the biomedical field of study.[12] There is a new strategy in metallopharmaceutics called Metallotherapy. This was initiated around 1980 by Coulson and Dandona to enhance lipogenesis in rats which is similar to the action of insulin.[13-14] This work deals with the synthesis of cobalt and copper metal complexes using Glucomannan which possess anti-diabetic activity. Glucomannan is basically a straight-chain polymer with just an 8:5 ratio of -(14)-linked D-mannose and D-glucose.[15-16]

MATERIALS AND METHODS

Physical description / organoleptic properties[17-18]

The organoleptic characteristic of a pharmaceutical material relates to its appearance, odour, colour, and taste. The study's first stage is to characterise these features, which aids in the primary identification of the drug ingredient as well as estimating the possibility of patient acceptance of the raw material's odour, taste, and colour, as well as its probable inclusion in the final dose form. Changes in the colour and odour of the raw material in the formulation might sometimes indicate changes in the formulation's stability (under identical circumstances).

Properties of drug[19-22]

The flow properties of the drug were observed by measuring the angle of repose, bulk density, Hausner ratio, and swelling index.

Preparation of Glucomannan-Cobalt Complex

Cobalt Chloride is dissolved by adding 250 mg (F6) in 10 ml of water to form a Cobalt Chloride solution. Follow the same step for other batches with the metal quantity mentioned (F7-F9 in both tables). The solution of Glucomannan is prepared by dissolving 500mg in 20 ml of hot water. Cobalt Chloride solution was added to a solution of glucomannan in the ratio given in the formulation table in 30 ml ethanol. To adjust the pH to 8.5, aqueous NaOH (5%) was added dropwise; the solution coloured a deeper crimson, and a precipitate developed. The reaction mixture was refluxed for 90 min, after which the precipitate was recovered by vacuum filtering of the filtrate while it was still warm. The solid was rinsed in cold water (2-5 mL) before being vacuum-dried overnight.

Preparation of Glucomannan-Copper Complex

Copper chloride salt is dissolved by adding 250 mg (F2) in 10 ml of water to form a Copper Chloride solution. Follow the same step for other batches with the metal quantity mentioned (F3-F5). The solution of Glucomannan is prepared by dissolving 500mg in 20 ml of hot water. Copper Chloride solution is added to the solution of Glucomannan and mixed well in the ratios provided in the formulation table in 30 ml ethanol. A precipitate is created when aqueous NaOH (10%) is introduced dropwise to adjust the pH to 8.5. After 30 min of refluxing, the reaction mixture is cooled to room temperature. To make the final product, the solid was vacuum filtered, rinsed with cold water (2-5 ml), and dried overnight under a vacuum.

POST-FORMULATION STUDIES

UV SPECTRAL ANALYSIS[22-23]

In a volumetric flask, the drug (5 mg) was dissolved in 500 mL 0.1N HCl, and the solution was scanned for the measurement of λmax (Absorption Maxima) in the ultraviolet-visible area between 100 and 400 nm.

Calibration of Standard Graph

100mg of pure drug was dissolved in 15ml of 0.1N HCl, as well as the volume was increased to 100ml by adding more 0.1N HCl (stock solution-1). 10ml of the above solution was collected and 100ml of 0.1N HCl was added (stock solution-2, 100g/ml). To obtain 200, 400, 600, and 800 g/ml of pure drug solution dilute 0.2, 0.4, 0.6, 0.8, and 1 ml of solution with 7.4 phosphate buffer to create up to 10 ml. Using a UV-Spectrophotometer and a pH 7.4 phosphate buffer as a blank, the absorbance of the above dilutions was measured at 267 nm. Then, using Concentration on the X-Axis and Absorbance on the Y-Axis, a graph was plotted, yielding a straight line. The square of the correlation coefficient (R2), which was determined via least-square linear regression analysis, was used to evaluate the linearity of the standard curve. The results are shown in the Table 1, Figure 1.

Dissolution Studies[24]

Preparation of pH 7.4 phosphate buffer: In the 1000mL volumetric flask, 250 mL of 0.2M potassium dihydrogen orthophosphate and 195.5 mL of 0.2M NaOH were accurately measured. With distilled water, a volume of 1000mL was created.

Procedure for Dissolution

The outer eggshell was separated from the egg yolk by extracting the egg yolk and other inner contents by making a small hole on the top of the egg. The egg shell is immersed in Concentrated Hydrochloric acid for nearly 30-45 min. This helps in the digestion of the outer hard membrane made of calcium.

The calibration graph of the drug is as follows:

Table 1: Calibration graph of Glucomannan.

Sl. No	Concentration (ug/ml)	Absorbance
1	100	0.07
2	200	0.16
3	300	0.31
4	400	0.42
5	500	0.49
6	600	0.63
7	700	0.81
8	800	0.96

The calibration graph of the drug is as follows:

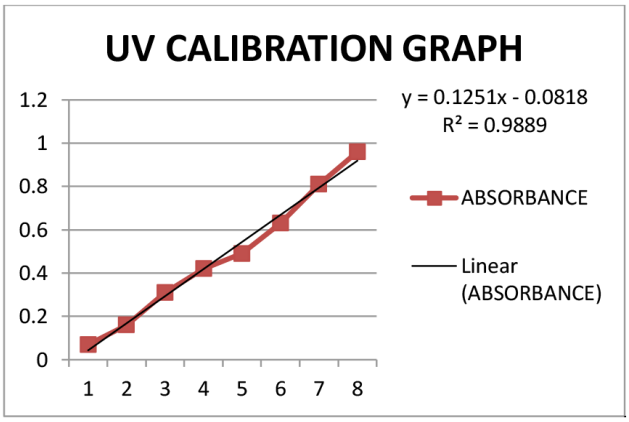

Figure 1: Calibration Graph of Glucomannan.

Table 2: Cumulative drug release of the Formulations (F1-F9).

Sl. No	Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	15	9.562	8.878	10.743	10.743	8.614	14.431	11.65	11.342	8.778
3	30	32.279	27.325	23.412	23.412	16.654	32.664	28.765	20.185	16.402
4	60	41.973	44.381	44.345	42.433	33.516	39.195	41.332	30.735	27.307
5	120	57.333	51.617	53.276	50.555	45.674	53.021	49.008	44.257	38.656
6	180	68.357	58.335	61.716	54.322	56.332	63.412	59.997	58.436	51.532
7	240	75.211	66.664	68.984	60.214	63.743	70.832	66.143	62.851	54.454
8	300	86.684	72.912	75.673	69.543	70.899	76.667	73.211	69.994	61.286
9	360	98.638	87.245	83.513	77.056	75.375	80.643	77.432	73.187	67.338

**Inclusive of ±SD*

The thin proteinaceous membrane remains is rinsed well with sufficient distilled water carefully. The egg membrane was tied to the one-end open-ended test tube. The drug formulation was loaded onto the tube from the other end. Membrane bounded test tube is immersed in the beaker containing 900 ml of dissolution medium.

A magnetic stirrer has been used to keep the temperature at 37°C and the speed at a constant rate. 5 ml of the dissolution medium was pipetted out and replenished at each interval. The drug concentration was determined by measuring the absorbance at 267 nm during the first 6 hr of the investigation.

The qualitative % of drugs released from the solid dispersion was calculated and reported. The results are shown in Table 2, Figure 2.

The cumulative drug release of the drug formulation batches is as follows:

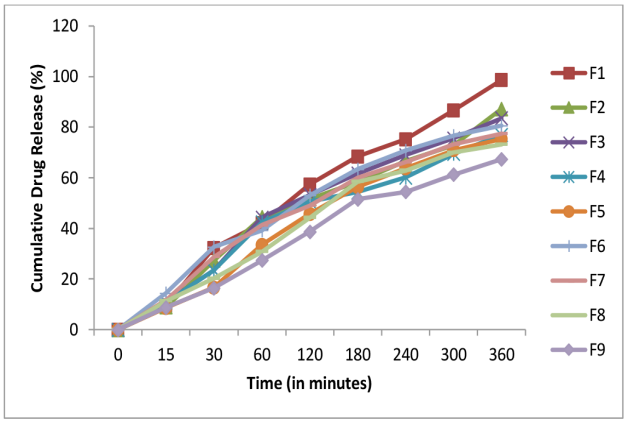

Figure 2: % Cumulative drug release of Formulation batches (F2-F9) along with drug (F1).

Kinetic Release Studies

These studies are used to calculate medication release consistency in extended-release products. This sort of research is very valuable in the development of controlled-release dosage formulations. Higuchi diffusion model, Hixson-Crowell model, and other kinetic models. The results are shown in the Figure 3-7.

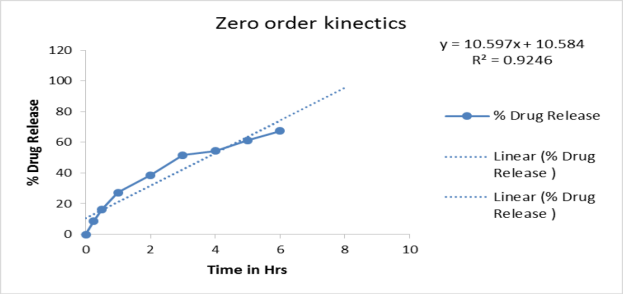

Figure 3: Zero Order Kinetics of Optimized Formulation F9.

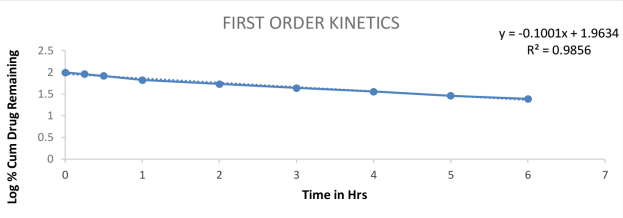

Figure 4: First Order Kinetics of Optimized Formulation F9.

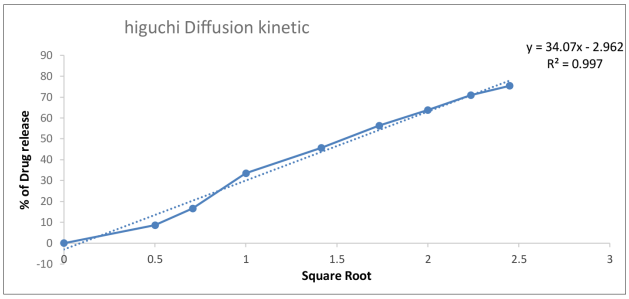

Figure 5: Higuchi Diffusion Kinetics of Optimized Formulation F9.

Stability Studies[25-26]

The stability of the active component must be a significant consideration in selecting whether or not to accept or reject dosage forms for medications in any design or assessment. Stability testing was carried out for three months by ICH norms. For each kind of stability investigation, the temperature and humidity were kept at 40°C±2°C /75 % RH±5 % RH. The results are shown in the Table 3.

RESULTS

Pre-formulation Characteristics

Organoleptic Properties

The organoleptic property of a pharmaceutical material relates to its appearance, odour, colour, and taste. The study's first stage is to characterise these properties, which aids in the primary identification of the drug ingredient as well as estimating the possibility of patient acceptance of the raw material's odour, taste, and colour, as well as its probable inclusion in the final dose form. The smell, taste, and presentation were all excellent.

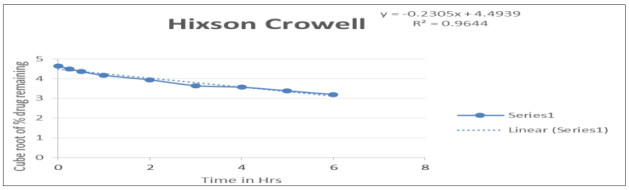

Figure 6: Hixson-Crowell Kinetics of Optimized Formulation F9.

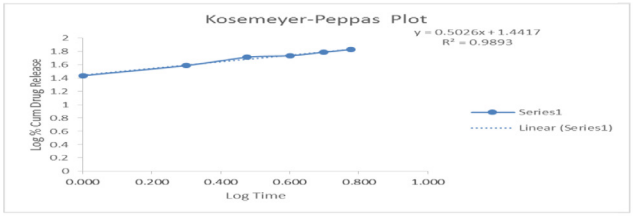

Figure 7: Korsmeyer-Peppas Plot of Optimized Formulation F9.

Properties of Drug

The angle of repose for the drug done in triplicate was calculated to be 28.78^0, and the bulk density calculated in triplicate was found to be around 0.620. Hausner's ratio of pure drug infers that it has excellent flow properties, the average swelling index of glucomannan was determined to be approximately 81.8%.

POST-FORMULATION STUDIES

UV Spectral Analysis

Since the drug (Glucomannan) had a gelling property with water, it was not used. In the variety of solvents used, it was found it had significant solubility against 0.1N HCl.

Stability Studies

Since F9 proved to be the best batch in *in-vitro* dissolution studies; it was optimized to undergo Stability studies for a period of 3 months. The data collected in the stability study is tabulated as follows:

DISCUSSION[27-28]

Pre-formulation Characteristics

Organoleptic Properties

The pharmacopeial acceptability of the odour, taste and colour of the raw material and its possible inclusion in the final dosage form. The odour, taste and physical appearance were perfect.

Table 3: Stability studies of Optimized Formulation F9.

Si.no	Tests performed	Optimized formulation f9			
		Initial	After 1 month	After 2 months	After 3 months
1	Appearance	According to specification	According to specification	According to specification	According to specification
2	Dissolution	67±0.05	81±0.16	80±0.15	76±0.3
3	LOD	1.6±0.06	1.8±0.05	1.4±0.05	0.9±0.04

Properties of Drug

The angle of repose lies within the normal range for good flow. The bulk density of the drug seems to be bulky but possess good flow property. Hausner's ratio of the flow property varied from excellent to fair. The swelling index proves the super-absorbing property of the drug to convert into mucilage.

Post-formulation Characteristics

UV Spectral Analysis

It was noticed that the drug had a distinct but weak peak at 267 nm. By the above calibration graph, the slope was determined to be 0.125. The regression coefficient shows that the graph is almost linear and it obeys the beer lambert's law.

Dissolution Studies

In the above statistical graph, it is clear that the glucomannan-copper complexes (F1-F5) release most of the drug content within the 6 hr time. But, Glucomannan-Cobalt complexes (F5-F9) help in the immediate release of drug in the dissolution medium of phosphate buffer pH 7.4 but release steadily and slower with due course of time. Drug-metal complex formulations (F2-F9) have better drug release in the duration of 6 hr when compared to normal drugs. All the formulation batches (F2-F9) have better drug release when compared to that of the drug alone.

Kinetic Release Studies

Kinetic release studies were performed for the all the formulations (F1-F9) and were found that F9 had the best drug release kinetics following the Higuchi Diffusion model with a linearity of 0.997. In the dissolution studies, it was calculated that the Formulation batch F9 (Glucomannan 500 mg + Cobalt 1000 mg) was the best batch.

It was also observed that F9 was the formulation batch showing sustained release, but the linearity of Korsemeyer-Peppa's plot was lesser than that of the pure drug. However, the linearity in zero-order, First Order, Higuchi and Hixson-Crowell plot proved to be superior to all other formulation batches from F1-F8.

Stability Studies

The stability studies were carried out for the optimized formulation (F9) for 3 months with several parameters like appearance, Dissolution and LOD were shown to be significantly different and more stable.

SUMMARY AND CONCLUSION

Metallopharmaceutics have a promising therapeutic effect on the drug. In this process, two processes happen mutually. The drug efficacy is increased and secondly, the toxicity of the metal is reduced which already has high medicinal properties as well. However, this study focuses on the above statement along with drug release kinetics in which the formulation (F9) composed of 500 mg Glucomannan + 1000 mg Cobalt had sustained drug release throughout the dissolution period. This infers that the plant-based extracts which possess low but significant therapeutic activity can be improved by using metals. Metal toxicity can also reduce during the process and simultaneously the therapeutic activity of the metal resides in the required amount.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ATR-IR: Attenated Total Reflectance- Infrared; **F:** Formulation; **LOD:** Loss Of Drying; **NaOH:** Sodium Hydroxide; **UV:** Ultra Violet.

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