Research Article

Formulation and Comparison of Cobalt and Molybdenum Glucomannan Metallocomplexes

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ABSTRACT

Metallopharmaceutics is regarded as the subject in which drugs are complex with metals like platinum, zinc iron, etc. It is becoming the field of interest in medical sciences including oncology and diabetes. In this study, molybdenum and cobalt are used to prepare the metal complexes using glucomannan as the ligand. Pre-formulation studies performed for the drug proved to be of optimal results, which included angle of repose and swelling index. Stability studies were conducted for a time period of three months. The post-formulation studies including UV analysis and dissolution studies using egg membrane were performed. The drug had a distinct but weak peak at 267 nm. Formulation batch F5 had the best dissolution rate in terms of sustainability. Release kinetic studies showed that F5 (Glucomannan 500 mg + cobalt 1000 mg) had a linearity of 0.997 in the Higuchi diffusion plot. This infers that the plant-based extracts which possess low but significant therapeutic activity can be improved by using metals.

Keywords: Metallopharmaceutics, Glucomannan, Formulation, Metal complex, Molybdenum and cobalt.

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INTRODUCTION

A drug delivery system can be defined as the type of Pharmaceutical system of administration of a drug into the body.[1] A novel drug delivery system generally includes innovation to the product. This type of delivery system modifies the pharmacokinetics and pharmacodynamics of the drug within the body.[2] Metallopharmaceutics is regarded as the subject in which drugs are complex with metals like platinum, zinc iron, etc. Metals also possess therapeutic activities and when complexed with drugs, a drug complex of higher activity than both drug and metal can be obtained. It is becoming the field of interest in medical sciences.[3] The synthesis of metal complexes can be performed in either presence or absence of chemical solvents.[4-6] Although there are financial problems linked with this modern field, bio-compatibility can be easily achieved.[7-8] There are various applications emerging in fields:[9-12] Endocrinology, Oncology, Virology, Cardiology and Bio-chemistry. The toxicity of the metals which have therapeutic activity can be reduced by adding plant-based ligands having the same therapeutic activity.[7,13] Glucomannan is one such plant-based constituent, which is extracted from konjac tuber and roots. This hydrophilic polymer is made of glucose and mannose with β-(1→6)-glucosyl linkage. It has various therapeutic activities including anti-diabetic activities. But, the activity is very less compared to conventional treatment. So the therapeutic activity is enhanced by adding metals in a predetermined ratio. In this study, molybdenum and cobalt are used to prepare the metal complexes.[7,14-16]

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MATERIALS AND METHODS

Physical description / organoleptic properties[17-18]

The organoleptic quality of a medicinal item 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[17,19-21]

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

Preparation of Glucomannan-Cobalt Complex

Cobalt Chloride is dissolved by adding 250 mg (F2) in 10 ml of water to form a Cobalt Chloride solution. Follow the same step for other batches with the metal quantity mentioned (F3-F5 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 drop by drop; 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 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-molybdenum Complex

Molybdenum Chloride solution was synthesized by mixing 250mg (F6) in 10ml of solution (80% DMF). Follow the same step for other batches with the metal quantity mentioned (F7-F9). The solution of Glucomannan is prepared by dissolving 500mg in 20 ml of hot water. Metal salt solutions were prepared by mixing the metal solution with that of Ligand (Glucomannan) in ratios provided in the formulation table at room temperature. pH is maintained and adjusted between 6.5-8 by the addition of dilute NaOH solution. The mixture content is refluxed for 3hr at 800°C. It is followed by cooling of the resultant mixture leading to/ the formation of crystals. The complex was washed with 80% DMF and weighed. The preparation procedure is shown in the Table 1.

Post-formulation Studies

UV Spectral Analysis[22-23]

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

Calibration of Standard Graph

100mg of pure medication was dissolved in 15ml of 0.1N HCl, and the volume was increased to 100ml by adding more 0.1N HCl (stock solution-1). 10ml of the aforesaid solution was collected and 100ml of 0.1N HCl was added (stock solution-2, 100g/ml). To get 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 aforesaid dilutions was measured at 267 nm. Then, using Concentration on the X-Axis and Absorbance on the Y-Axis, a graph was created, yielding a straight line. The square of the correlation coefficient (R2), which was derived using least-square linear regression analysis, was used to examine the linearity of the standard curve. The results are shown in Table 2 and 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.

Table 1: Formulation of Glucomannan-metal complexes.

Sl.no	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Glucomannan (in mg)	500	500	500	500	500	500	500	500	500
2	Molybdenum (V) Chloride (in mg)	0	0	0	0	0	250	500	750	1000
3	Cobalt Chloride (in mg)	0	250	500	750	1000	0	0	0	0
4	DMF (as Solvent, in ml)	0	QS	QS	QS	QS	0	0	0	0
5	Ethanol	QS	0	0	0	0	QS	QS	QS	QS

Table 2: 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

By observing the UV spectral graph, it was noticed that the drug had a distinct but weak peak at 267 nm. The calibration graph of the drug is as follows:

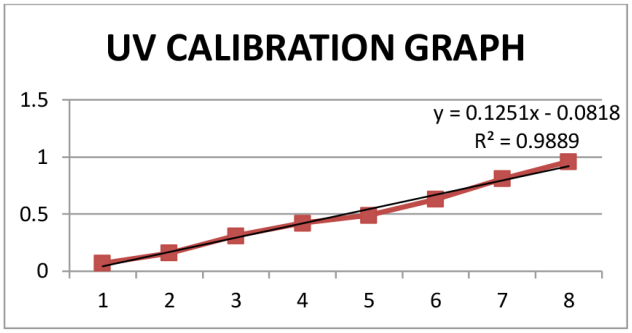

Figure 1: Calibration Graph of Glucomannan.

By the above calibration graph, the slope was determined to be 0.125. The regression coefficient shows that the graph is almost linear.

The dissolution studies were performed by applying the egg-membrane technique. The results are tabulated as follows:

Table 3: Cumulative % drug release of Formulation Batches (F1-F9).

Sl.No	Time	Cumulative% drug release ± SD*								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	15	9.562	14.431	11.65	11.342	8.778	11.535	16.214	24.234	27.732
3	30	32.279	32.664	28.765	20.185	16.402	38.813	45.321	44.516	43.567
4	60	41.973	39.195	41.332	30.735	27.307	47.927	51.312	51.238	58.999
5	120	57.333	53.021	49.008	44.257	38.656	67.118	58.521	58.476	61.122
6	180	68.357	63.412	59.997	58.436	51.532	71.156	65.432	62.214	63.786
7	240	75.211	70.832	66.143	62.851	54.454	78.324	69.115	66.778	65.632
8	300	86.684	76.667	73.211	69.994	61.286	80.653	75.868	69.567	68.555
9	360	98.638	80.643	77.432	73.187	67.338	84.349	79.321	73.962	70.121

*Mean±SD(n=3)

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 thin protein aceous 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. The membrane-bounded test tube is immersed in the beaker containing 900 ml of dissolution medium. The temperature was maintained at 37°C and speed was maintained at a constant rate using a magnetic stirrer. After each interval, 5 ml of the dissolution medium was pipetted out and replaced immediately. The drug concentration was analyzed by checking the absorbance at 267 nm up to 6 hr of study. The qualitative % of drugs released from the solid dispersion was calculated and reported. The results are shown in Table 3 and Figure 2.

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.

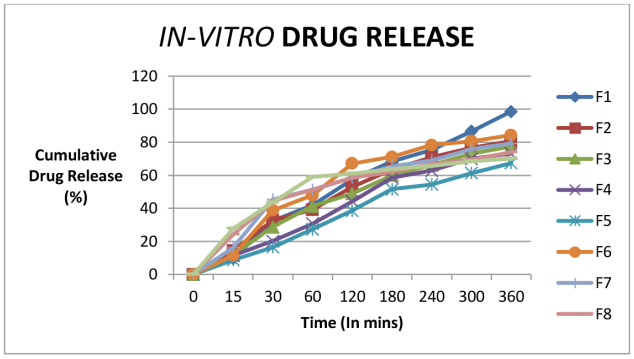

Figure 2: Cumulative % drug release of Formulation Batches (F1-F9).

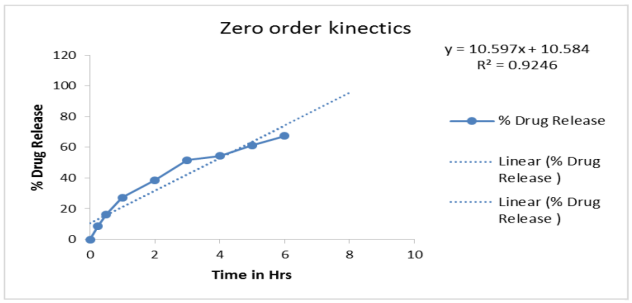

Figure 3: Zero Order Kinetics of Optimized Formulation F5.

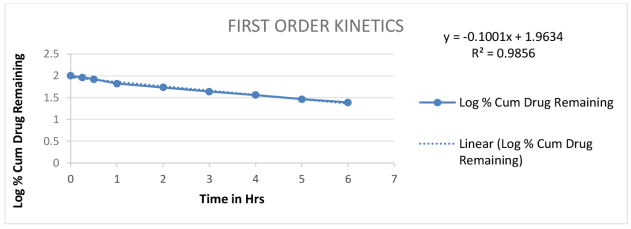

Figure 4: First Order Kinetics of Optimized Formulation F5.

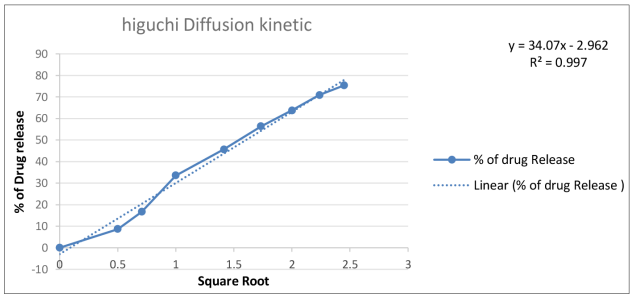

Figure 5: Higuchi Diffusion Kinetics of Optimized Formulation F5.

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

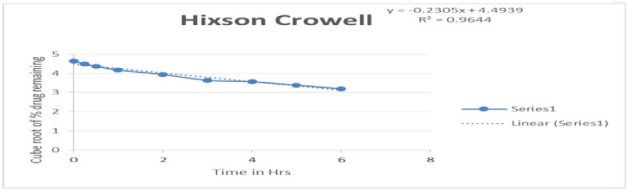

Figure 6: Hixson-Crowell Kinetics of Optimized Formulation F5.

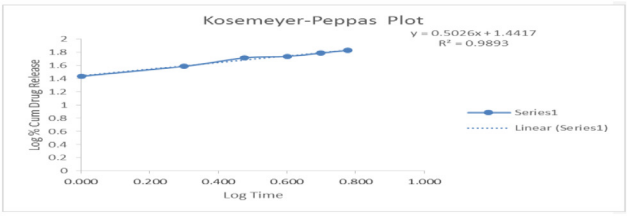

Figure 7: Korsemeyer-Peppas Plot of Optimized Formulation F5.

for three months in accordance with ICH norms. The temperature and humidity for each type of stability study were maintained at 40°C±2°C/75%RH±5%RH. The results are shown in the Table 4.

RESULTS AND DISCUSSION

Pre-formulation Characteristics

Physical Description / Organoleptic Properties

The organoleptic quality of a medicinal item 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. The smell, taste, and presentation were all excellent.

Properties of Drug

The average angle of repose for the drug done in triplicate was calculated to be 28.78^0. The angle of repose lies within the normal range for good flow. The Average bulk density calculated in triplicate was found to be around 0.620. On taking an average of the 3 attempts in each weight category the compressibility index as per the batches, based upon the compressibility index data, the flow property varied from excellent to fair. In Swelling index By employing the above formula for the test, the average swelling index of glucomannan was determined to be approximately 81.8%.

The Angle of repose shows, that the powder of the pure drug Glucomannan has good flow and is not highly cohesive in nature. The bulk density taking this

Table 4: Stability parameters of optimized formulation F5.

Sl.No	Tests performed	Optimized formulation f5			
		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±0.07	81±0.18	80±0.15	76±0.4
3	LOD	1.6±0.07	1.8±0.03	1.4±0.08	0.9±0.06

into account along with the angle of repose, the drug seems to be bulky but possesses good flow properties. Compressibility index determined that the drug powder possesses fair (or) passable flow properties. The average of Carr's index is calculated to be 20.23, which deduces the powder possesses fair flow. Swelling index proves the super-absorbing property of the drug to convert into mucilage. This property also means that the drug cannot be effectively compressed into tablet dosage form, since even minute traces of moisture can contaminate the physical appearance of the tablets. But, the super moisture absorbing capacity can be applied in a positive manner by converting it into a thin film (or) encapsulation.

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.

The above statistical graph infers that molybdenum complexes (F6-F9) show an immediate release of the drug when compared to that cobalt complexes (F2-F5). However, the drug release became more sustained in due course of time in the case of molybdenum complexes (F6-F9). Although molybdenum complexes showed sustained drug release after sharp immediate release at first, there is a toxicity risk when compared to cobalt. The chance of molybdenum toxicity is high during the first 2-3 hr, while there is no toxicity risk for cobalt throughout the dissolution period. So, formulation batch F5 had the best dissolution rate in terms of sustainability.

Kinetic Release Studies

Kinetic release studies were performed for all the formulations (F1-F9) and were found that F5 had the best drug release kinetics following the Higuchi Diffusion model with the linearity of 0.997. The release kinetic models for formulation batch F5 are illustrated as below:

In the dissolution studies, it was calculated that the Formulation batch F5 (Glucomannan 500 mg + Cobalt 1000 mg) was the best batch. It was also observed that F5 was the formulation batch showing sustained release, but the linearity of Korsemeyer-Peppa's plot was lesser than that of the pure drug.

Stability Studies

Since F5 proved to be the best batch in *in-vitro* dissolution studies; it was optimized to undergo Stability studies for a time span of 3 months. The data collected in the stability study are tabulated as follows:

SUMMARY AND CONCLUSION

The therapeutic effect of the drug has been widely enhanced in the modern field of Metallopharmaceutics. In this process, two subsequent processes happen in a communal manner. The drug efficacy is augmented 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 (F5) 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

DMF: Dimethyl Formamide; **F1:** Formulation 1; **M:** Molarity; **Nm:** Nanometer; **Q.S:** Quantity Sufficient; **U.V:** Ultra Violet.

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