Development and Characterization of Sodium Alginate Beads for Metformin

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1. Introduction

1.1. Hydro Gel

The materials of interest are primarily hydrogels, which are polymer networks extensively swollen with water. Hydrophilic gels that are usually referred to as hydrogels are networks of polymer chains that are sometimes found as colloidal gels in which water is the dispersion medium

Researchers, over the years, have defined hydrogels in many different ways. The most common of these is that hydrogel is a water-swollen, and cross-linked polymeric network produced by the simple reaction of one or more monomers. Another definition is that it is a polymeric material that exhibits the ability to swell and retain a significant fraction of water within its structure, but will not dissolve in water. Hydrogels have received considerable attention in the past 50 years, due to their exceptional promise in wide range of applications. They possess also a degree of flexibility very similar to natural tissue due to their large water content.

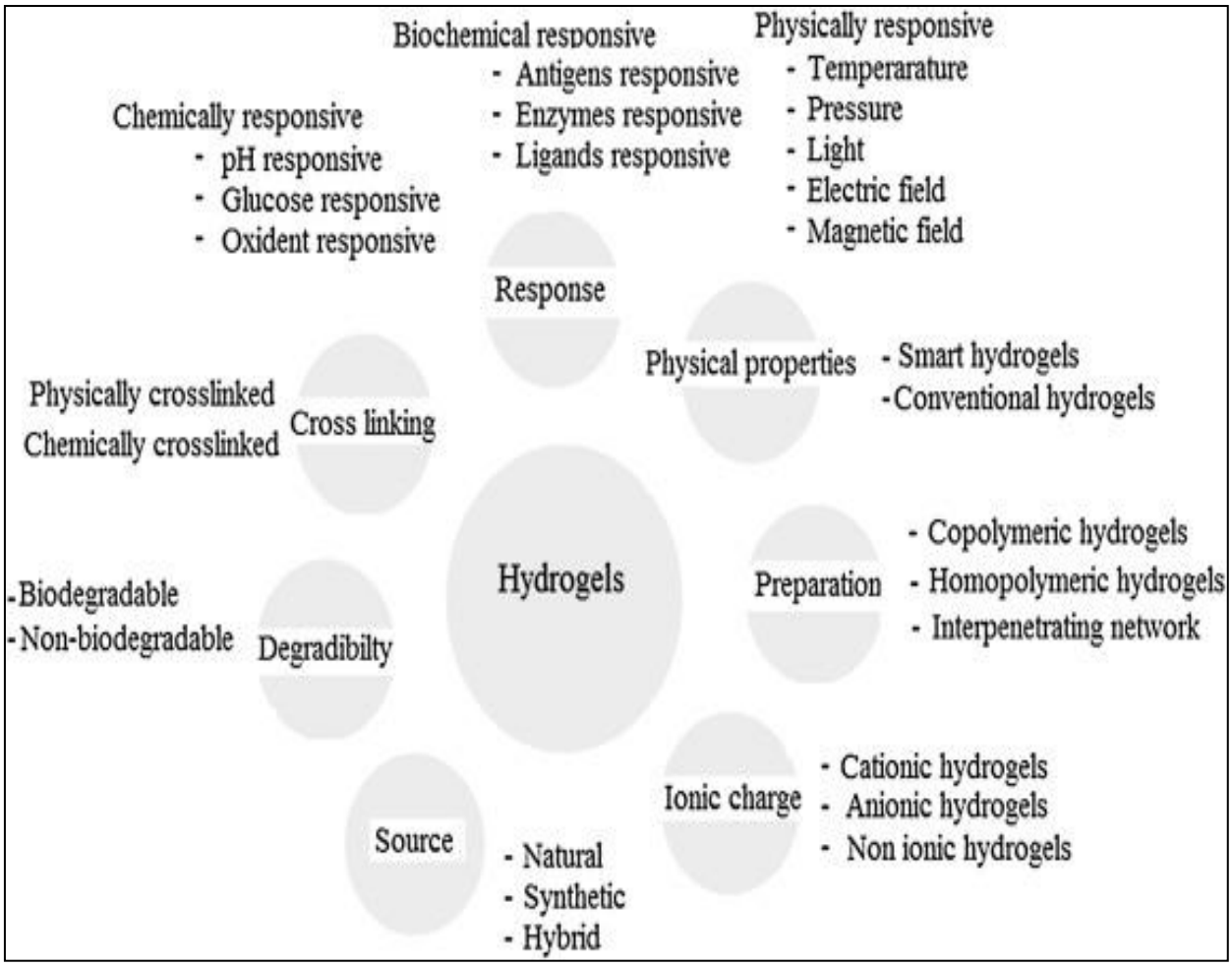
The ability of hydrogels to absorb water arises from hydrophilic functional groups attached to the polymeric backbone, while their resistance to dissolution arises from cross-links between network chains. Many materials, both naturally occurring and synthetic, fit the definition of hydrogels.

During last two decades, natural Hydrogels were gradually replaced by synthetic hydrogels which had long service life, high capacity of water absorption, and high gel strength. Fortunately, synthetic polymers usually have well-defined structures that can be modified to yield tailor able degradability and functionality. Hydrogels can be synthesized from purely synthetic components. Also, it is stable in the conditions of sharp and strong fluctuations of temperatures.

Recently, hydrogels have been defined as two- or multi-component systems consisting of a three-dimensional network of polymer chains and water that fills the space between macromolecules. Depending on the properties of the polymer (polymers) used, as well as on the nature and density of the network joints, such structures in an equilibrium can contain various amounts of water; typically, in the swollen state, the mass fraction of water in a hydrogel is much higher than the mass fraction of polymer. In practice, to achieve high degrees of swelling, it is common to use synthetic polymers that are water-soluble when in non-cross-linked form.

Hydrogels may be synthesized in a number of "classical" chemical ways. These include one-step procedures like polymerization and parallel cross-linking of multifunctional monomers, as well as multiple step procedures involving synthesis of polymer molecules having reactive groups and their subsequent cross-linking, possibly also by reacting polymers with suitable cross-linking agents. The polymer engineer can design and synthesize polymer networks with molecular-scale control over structure such as cross-linking density and with tailored properties, such as biodegradation, mechanical strength, and chemical and biological response to stimuli [1, 2].

1.2. Classification of Hydrogel

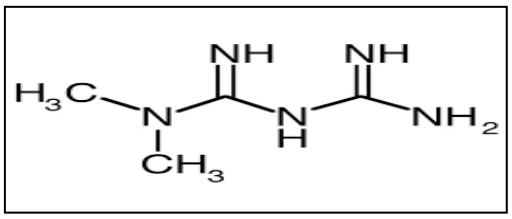


1.3. Metformin

Metformin is a biguanide antihyperglycemic agent used for treating non-insulin-dependent diabetes mellitus (NIDDM). It improves glycemic control by decreasing hepatic glucose production, as well as decreasing glucose absorption and increasing insulin-mediated glucose uptake.

Another well-known benefit of this drug is modest weight loss. Metformin is the drug of choice for obese NIDDM (non-insulin dependent diabetes mellitus) patients. Metformin was approved in Canada initially in 1972, the 1970s in Europe, and in 1995 in the USA [3].

a. Structure



b. Pharmacology

Indication: for use as an adjunct to diet and exercise in adult patients with non-insulin dependent diabetes mellitus. Metformin may also be used for the management of metabolic and reproductive abnormalities associated with polycystic ovary syndrome (PCOS). Metformin may be used concomitantly with a suifonylurea or insulin to improve glycemic control in adults.

c. Pharmacodynamics

Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

d. Mechanism of Action

Metformin's mechanism of action is unique from other classes of oral antihyperglycemic drugs. Metformin decreases blood glucose levels by decreasing hepatic glucose production (gluconeogenesis), decreasing the intestinal absorption of glucose, and increasing insulin sensitivity by increasing peripheral glucose uptake and utilization. It is well established that metformin inhibits mitochondrial complex I activity, and it has since been generally postulated that its potent antidiabetic effects occur through this mechanism.

Findings of recent studies however, show that metformin, at clinically relevant plasma concentrations, inhibits hepatic gluconeogenesis in a redox-dependent manner independently of reduction in citrate synthase flux, liver nucleotide concentrations, acetyl-CoA carboxylase enzyme activity, or gluconeogenic enzyme protein expression. Studies show that clinically relevant concentrations of plasma metformin attained by acute intravenous, acute intraportal or chronic oral administration in awake healthy and diabetic rats inhibit gluconeogenesis from lactate and glycerol, but not from pyruvate and alanine, implying an increased cytosolic redox state in mediating metformin's glucose-lowering effects. These effects have occurred independently of complex I inhibition demonstrated by unaltered hepatic energy charge and citrate synthase flux. Normalizing the cytosolic redox state by infusion of methylene blue or substrates contributing to gluconeogenesis independently of the cytosolic redox state stopped metformin-mediated inhibition of gluconeogenesis in vivo. In mice expressing constitutively active acetyl-CoA carboxylase, metformin acutely reduced hepatic glucose production and increased the hepatic cytosolic redox state without altering hepatic triglyceride content or gluconeogenic enzyme expression.

Previous studies indicate that the glucose-lowering effects of metformin are mediated by the activation by metformin of AMP-activated protein kinase (AMPK), a liver enzyme which plays an important role in insulin signalling, energy balance, and the metabolism of both glucose and lipids. The activation of AMPK is thought to be necessary for metformin's inhibitory effect on the production of glucose by liver cells. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors. Metformin administration also increases AMPK activity in skeletal muscle. AMPK is known to trigger GLUT4 transporter deployment to the plasma membrane, resulting in insulin-independent glucose uptake [4].

e. Absorption

The absolute bioavailability of a metformin 500 mg tablet administered under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin 500 to 1500 mg, and 850 to 2550 mg, show that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma

concentration (T_{max}) after administration of a single 850 mg tablet of metformin with food, compared to the same dose administered fasting. The clinical relevance of these decreases is unknown [5].

f. Volume of Distribution

654 L for metformin 850 mg administered as a single dose. The volume of distribution following IV administration is 63-276 L, likely due to less binding in the GI tract and/or different methods used to determine volume of distribution.

g. Protein Binding

Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound.

h. Metabolism

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Half Life

Approximately 6.2 hours in the plasma and in blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Clearance

Renal clearance is about 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours [6].

i. Toxicity

Acute oral toxicity (LD50): 350 mg/kg in the rabbit.

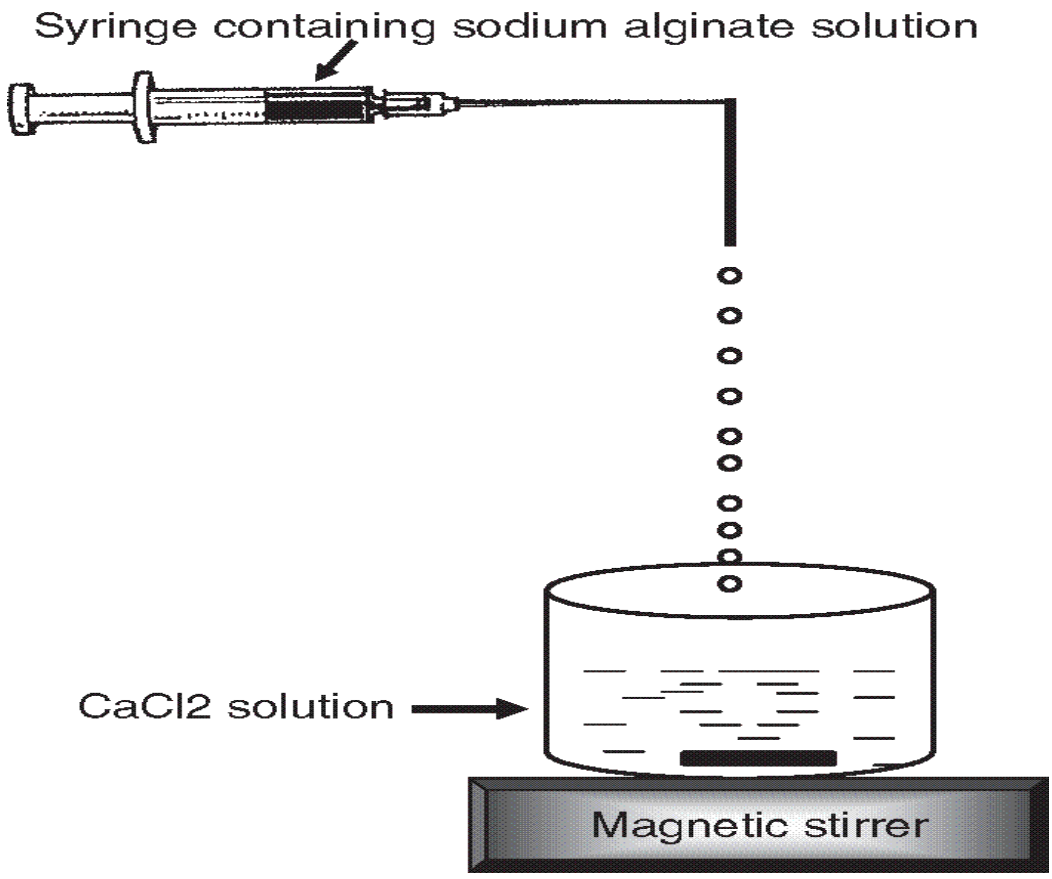
j. Common Adverse Effects

The most common adverse effects of metformin include: epigastric discomfort, nausea, flatulence, and vomiting. Diarrhoea, drowsiness, weakness, dizziness, malaise, and headache may also occur [7].

2. Experimental Work

The beads containing Metformin hydrochloride were prepared by using emulsion-gelation method. Required amount of sodium alginate was dissolved in 20 ml distilled water with constant stirring. Add different variety of oil then add accurately weighed quantity of Metformin HCl to sodium alginate solution. The final mixture containing sodium alginate was stirred at 400 rpm continuously for 15 min until the homogenous and stable suspension remained formed. Then the suspension is drop by drop 22 G needle into 5% (w/v) calcium chloride solution (100ml) [8,9].

Formulation	Metformin(mg)	Sodium Alginate (mg)	Calcium Chloride (5%w/v) (ml)	RPM	Oil(2.5ml)
F1	500	1000	100	400	Castor oil
F2	500	1000	100	400	No oil
F3	500	1000	100	400	Liquid paraffin



Diagramatic representation for preparation of sodium alginate beads

3. Evaluation Parameters

Percentage yield: The percentage of production yield was calculated from the weight of dried microspheres recovered from each batch and the sum of initial weight of starting materials. The percentage yield was calculated using the following formula [10]

Percentage yield = (practical yield/theoretical yield) *100

Drug entrapment efficiency: Accurately weighed 50mg of prepared beads from each batch were taken separately and were crushed using pestle mortar. The crushed powder was placed in 50ml of phosphate buffer7.4 and kept for 24h with occasionally shaking. After the stipulated time, the mixture was stirred at 200rpm for 30min on a magnetic stirrer. The polymer debris formed after disintegration of beads was removed by filtering through Whatman filter paper. After that drug content in the filtrate samples were determined using a UV spectrophotometer by measuring absorbance at ʎ max at 262nm [11].

The EE of beads was calculated using this following formula.

EE = (Actual drug content in beads/Theoretical drug content in beads) x 100

Determination of buoyancy: 50g of microbeads were placed in 100ml stimulated gastric fluid (SGF, pH 7.4) the mixture was stirred at 100rpm on a magnetic stirrer. After 2h, the floating and settled microbeads were collected separately, dried at 400°C and weighed [12]

Buoyancy = (Weight of floating Microbeads / weight of floating Microbeads+ weight of settled Microbeads) x 100

Swelling study: Swelling ratio of different dried microbeads were determined gravimetrically in simulated gastric fluid pH 7.4. The microbeads were removed periodically from the solution, blotted to remove excess surface liquid and weighed on balance. Swelling ratio (%w/v) was determined [13].

4. Result & Discussion

Percentage yield:

Formulation	%yield
F1	96.5±1.2%
F2	95.3±2.3%
F3	97.1±0.5%

The percentage yield of formulation F1-F3 ranges from 95.3 to 97.1%.

Drug entrapment efficiency

Formulation	Entrapment efficiency
F1	92.3±1.2%
F2	94.1±1.9%
F3	93.2±0.8%

The entrapment efficiency of the formulation F1-F3 ranges from 92.3 to 94.1%.

Determination of buoyancy

Formulation	Buoyancy
F1	90.3±0.8%
F2	89.6±0.6%
F3	84.1±0.9%

The buoyancy of the formulation F1-F3 ranges from 90.3 to 84.1%.

Swelling study:

Formulation	Swelling ratio
F1	212.1±0.8%
F2	189.1±2%
F3	302.1±0.3%

The swelling study of the formulation F1-F3 ranges from 189.1 to 302.1%.

The results are up to the mark as compared to the standard values.

5. Conclusion

A new sustained release system of oil entrapped sodium alginate beads was formulated by an emulsion gelation method. Its morphology and release characteristics were studied. The beads were easy to prepare. The pore-size of oil-entrapped beads was affected by the concentration of the oil. The beads showed excellent sustaining properties as compared to the conventional beads. Thus, oil entrapped technique appears to be a useful tool for the development of multi-particulate system even for water -soluble drug. The F3 shows the best result among all formulations.

Beads of Metformin HCl are prepared using polymer. Sodium alginate beads has attained highest yield (%) and showed maximum drug loading capacity and drug encapsulation efficiency. Swelling index studies shows that the beads swelled more in intestinal region. Process parameters such as the polymer concentration, polymer/drug ratio, and the amount of hardening agent were analyzed for their influences on the bead properties.

6. References

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