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ORIGINAL ARTICLE

Preparation of Alginate Microspheres for the Delivery of Risperidone

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Abstract:

Aim: The aim of this research is to prepare and evaluate alginate microspheres of prolonged delivery of a model drug, Risperidone.

Methods: Alginate microspheres containing Risperidone were prepared employing cross-linking method by calcium chloride. The formed microspheres were evaluated for percentage yield, drug content, drug loading, and encapsulation efficiency. In vitro release studies were carried out in phosphate buffer (pH 7.4).

Results: The formed microspheres exhibited good drug loading and encapsulation efficiency. The drug release was sustained over a period of 8 hours.

Conclusions: The fabricated Risperidone microspheres showed extended drug release, which could improve the therapeutic agent bioavailability and increase patient compliance. The delivery system developed can potentially serve for the delivery of many therapeutic agents.

Key words: Alginate, Microspheres, Sustained release, Risperidone

1. Introduction

Conventional therapeutic systems, though cheap and easy to manufacture, show many therapeutic problems including fluctuating plasma levels, inadequate activity, and poor compliance by patients due to the repeated dosing. Furthermore, conventional dosage forms are unpredictable and erratic; in many cases, a high amount of drug is required to guarantee that the effective concentration of drug is eventually achieved at the site of action. The pharmacokinetic parameters of the therapeutic agent are governed solely by drug's physicochemical properties, which are not always optimal (1).

Sustained drug delivery systems release encapsulated drugs in a prolonged fashion to maintain an effective therapeutic concentration for an extended period of time (2). Sustained drug delivery formulations often improves drugs' efficacy. In addition, drug reservoirs in sustained drug delivery systems protect the encapsulated therapeutic agents from possibly harsh physiological conditions and thus improve drug's stability and duration of action.

Microspheres are multiparticulate drug delivery systems that can be prepared by various methods and are used for the sustained delivery of drugs (3). They could be injected into the body due to their small size. This eliminates the need to surgically implant long-acting drug delivery reservoirs. Biocompatibility of the polymer and its degradation products is crucial for biomedical use (4). Moreover, the ability of the body to degrade/eliminate polymeric systems is favoured for drug delivery, since this opts out the need for surgical removal of the delivery system once the drug is depleted (5).

Many natural and synthetic polymers were investigated for their use in drug delivery. Alginates, natural polymers found in brown algae, have been investigated for the controlled drug delivery (6-9). Alginates consist of chains of mannuronic acid, guluronic acid, and mannuronic-guluronic. Alginate's safety is well-established and offers a further protective effect on the viability of mucous membranes of the gastrointestinal tract (6).

Risperidone is an antipsychotic agent, which belongs to the benzisoxazole family. It has a high affinity for serotoninergic 5-HT2 and dopaminergic D2 receptors. The active forms of the drug are both Risperidone and its active metabolite 9-hydroxy Risperidone. Risperidone is used for the treatment of schizophrenia and is widely accepted because Risperidone causes less motor activity depression than classical neuroleptics (10). Yet, as with most of antipsychotic therapeutic agents, patient incompliance is still one of the major reasons for therapy failure.

The aim of this work is to formulate alginate microspheres for the sustained delivery of a model drug, Risperidone.

2. Methods

Materials

Risperidone was procured as a gift from the Jordanian Pharmaceutical Manufacturing company JPM (Amman, Jordan).Sodium alginate was purchased from B.M.S (Italy).All chemicals used were of analytical grade and were used as received.

Preparation of microspheres

Risperidone containing microspheres were prepared by cross-linking technique with minor modifications (11, 12). Different concentrations of sodium alginate were dissolved gradually in distilled water (3% and 1.5%) and homogenized for one hour. Drug polymer solution was prepared by dissolving 200mg of drug slowly into formerly prepared alginate solution with constant mixing for 30 minutes. Five grams of calcium chloride were dissolved in 100 ml of distilled water to prepare the gelation medium. The drug-polymer solution was then extruded through glass syringe into the gelation medium. The agitation was carried out by propeller at 200 rpm.

After one hour, 2 millilitres of isopropyl alcohol were added drop wise to harden the formed microspheres (13, 14). After 10 minutes, the microspheres were collected by filtration and washed with deionized water. The microspheres were dried at 45ºC until they attained constant weight.

Characterization of microspheres

- Percentage yield

The Risperidone-containing microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula (15):

Percentage yield = {microspheres mass/ mass of polymer + drug}*100

- Drug content

The different prepared formulations were assayed for drug content. Microspheres samples were weighed and powdered. Then they were dissolved in of phosphate buffer. The drug content was determined by measuring the UV absorbance at 280 nm (16).

- Encapsulation efficiency and drug loading:

Encapsulation efficiency and drug loading of formed microspheres were determined employing the following equations (15):

Encapsulation efficiency = (Experimental drug mass in sample/ Hypothetical drug mass) * 100

Drug loading = (Drug mass in microspheres / Microspheres sample mass) * 100

In vitro drug release

The release of the drug from the alginate microspheres was determined in phosphate buffered saline solution (PBS, pH 7.4). The alginate microspheres (15 mg) were suspended in 1 mL of PBS. The samples were incubated at 37±0.5°C with continuous shaking (50 rpm). At predetermined time intervals, the sample was withdrawn and centrifuged at 2000 rpm for 5 min. The supernatant was collected and assayed for drug release (17).

3. Results

Two different formulations were prepared varying in polymer concentration (Table 1). The percentage yield of both formulations was found out to be 78.6% and 59.9% respectively (Table 2). Higher drug content (and hence, percentage yield) was observed in formulations containing 1.5 % alginate polymer.

Table 1. Composition of alginate microspheres

Formulation	Alginate concentration	Drug content (mg)	Drug: Polymer ratio
F1	1.5%	200	1:7.5
F2	3.0%	200	1:15

Table 2. Drug content and percentage yield of different formulations

Formulation	Theoretical drug content (mg)	Actual drug content (mg)	Percentage yield (%)
F1	200	113	78.6
F2	200	87	59.9

Table 3 shows the results of drug loading and encapsulation efficiency. Increasing drug to alginate ratio increased percentage of loading. Formulations exhibited good encapsulation efficiencies of 71.97% and 72.63% for formulations containing 1.5% and 3% polymer concentration, respectively.

Table 3. Drug loading and encapsulation efficiency of microspheres

Formulation	Drug Loading (%)		Encapsulation efficiency (%)
	Theoretical	Actual	
F1	11.76	8.45	71.97
F2	6.25	4.54	72.63

Phosphate buffer (pH 7.4) was used for in vitro release studies. Figure 1 shows the cumulative release of Risperidone from alginate microspheres in phosphate buffer. The drug release was prolonged for up to 8 hours in formulations containing 1.5% and 3% polymer concentration.

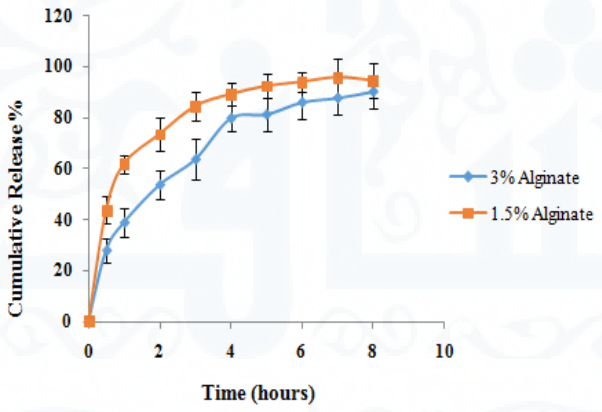

Figure 1. Effect of polymer concentration on the in vitro release of Risperidone

4. Discussion

The high percentage yields obtained in our study confirm that this delivery system was suitable for the formulation of Risperidone microspheres. Higher percentage yield was observed for formulations containing higher drug to polymer ratio. These findings comply well with results reported in other studies (15).Table 3 shows the effect of alteration of with polymer: Risperidone ratio on drug loading and encapsulation efficiency. Higher loading was achieved by increasing the percentage of Risperidone with respect to alginate.

Risperidone release from polymeric spheres can be explained by two mechanisms. The drug is released by diffusion from the encapsulating alginate microspheres. Secondly, the drug leaches out from the microspheres through the erosion and/or degradation of the matrix. The latter phenomenon could be attributed to the removal of the cross-linker, calcium, from the microspheres (18). The swelling of alginate molecules increases matrix porosity and thus increases both diffusion and erosion. These findings comply well with the higher drug to polymer ratio used in formulation F1 (19). Phosphate buffer has a chelating action due to the phosphate ions which helps further in the disruption of the matrix. Both of our formulations exhibited a sustained release of Risperidone over a period of 8 hours. A slower release pattern was observed for formulation containing higher amounts of the polymer. Similar results were obtained for verapamil loaded microspheres reported in a previous study (20). It was shown that drug release could be extended by increasing polymer proportion. Similarly, insulin and diaminopyridine microparticles were successfully prepared by solvent evaporation method and drug to polymer ratio was shown to affect microspheres characteristics and drug release profile (21, 22).

5. Conclusion

Alginate-based microspheres of Risperidone were successfully prepared and separated by cross-linking method. The formed microspheres showed good percentage yield and encapsulation efficiency. Drug release studies carried out in vitro showed prolonged release of Risperidone from both formulations employing phosphate buffer as a release media. Slower drug release was observed with increasing the polymer concentration. High burst release of Risperidone was observed in all formulations. It was feasible to prepare alginate-based microspheres capable of extending drug release over a period of time.

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