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Research Article

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Effect of Polymer Concentration and Crosslinking Time On Drug Release from Microspheres of Mucuna Gum

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Abstract

The study investigated the feasibility of delivering diclofenac sodium in microspheres of mucuna gum and whether polymer concentration and crosslinking time would affect drug release. Diclofenac sodium microspheres were successfully prepared using the chemical and thermal crosslinking method. Gluteraldehyde was used as the crosslinking agent. Thereafter, invitro release of diclofenac sodium from the microspheres was evaluated using simulated intestinal fluid as the medium. Increase in mucuna gum concentration did not delay rate of drug release but increased total cumulative drug released. Increase in crosslinking time slowed down release of the drug from the microspheres, an indication that modification of crosslinking time is important for sustained release. This could contribute towards producing sustained release diclofenac sodium which will improve patient compliance as a result of subsequent reduction in dosing frequency. None of the batches gave 100% drug release. This being the case, drug loading can be modified for optimum therapeutic effect.

Keywords: Microsphere; Polymer; Crosslinking; Drug Release, Drug Delivery

Introduction

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm (1 mm) [1]. They are sometimes referred to as spherical microparticles. The microspheres have the drug located centrally within the particle where it is encased within the unique polymeric membrane [2]. Developments of novel drug delivery systems have been on the increase in recent times in a bid to navigate challenges faced with conventional drug delivery systems like stability and bioavailability among others [3, 4].

Microspheres in drug delivery are used for targeted as well as prolonged drug release in the diseased area. It also protects the unstable or pH-sensitive drugs before and after the administration, and therefore enhances uptake by intestinal cells [5-7]. Microspheres have been the focus of several research not only for the prolonged release of drugs, but also for targeting of anticancer drugs [8, 2]. At the target tissue, optimal quantity of the active ingredient should be delivered at the right time with the minimum side effect and maximum therapeutic effect. It is therefore very essential that microspheres be made to optimum standard as much as possible.

Polymers act as carriers for drugs. They are either hydrophilic or hydrophobic in nature. This in the long run affects release behaviour in different media and plays an important role in selection of polymers for controlled, sustained or immediate release formulations [9]. Mucuna gum is got from the seed of Mucuna flagillepes. It is used as polymers for microparticles, stabilizers in suspension and emulsion, and as binders in tablet dosage form and so forth [7]. Controlled release of drugs and long acting effect has been achieved with gluteraldehyde as crosslinking agent [10, 11]. Gluteraldehyde has been widely used as crosslinking agent in producing microparticles of drugs such as diclofenac sodium, glibenclamide, ibuprofen, etc. Because of its unique characteristics, namely, the ability to exist in many forms depending on prevailing conditions [7, 12]. Its availability and cost effectiveness distinguish it as well. It effectively stabilizes polymers even collagen sponges [13]; in fact, collagen-based biomaterials such that it has become the traditional crosslinking agent for bioartificial devices [14, 12].

Materials and Methods

The materials include Diclofenac Sodium, mucuna seed, acetone, distilled water, olive oil, gluteraldehyde, sodium hydroxide pellets, monobasic potassium phosphate, and diclofenac sodium.

Extraction of mucuna gum: Mucuna seeds were dehusked. The cotyledons were air dried, pulverized in a hammer mill and the powder was obtained. The powder was soaked in distilled water and allowed to hydrate for 24 hours. The solution was passed through a muslin cloth. The resultant filtrate was desolvated with several fresh volumes of acetone. The acetone trapped by the precipitate was pressed out through the muslin cloth again. The cake was broken up and stored in a vacuum desiccator containing CaCl2 as desiccant and later on placed in hot air oven to dry. After drying, the cake was pulverized into fine powder, sieved with sieve no 0.52 and stored in an amber-coloured bottle to prevent darkening of the preparation by oxidation [7].

Preparation of microspheres: Chemical and thermal crosslinking method was used. Mucuna gum was used as a polymer. A 50ml volume of a 2.5% m/v dispersion of the mucuna gum in distilled water was prepared and added drop wise to a beaker containing 50ml of olive oil on a magnetic stirrer at the speed of 5000 rpm. Diclofenac sodium was incorporated into the mucuna gum solution at concentration of 10 µg of drug per mg of the polymer. It was stirred for 30mins at a temperature of 40°C. A 15ml volume of acetone was then added and the mixture was further stirred for 30mins. The microspheres formed were then crosslinked with 1 ml solution of gluteraldehyde and stirred at 40°C for a pre-determined time. The mixture was then centrifuged at a speed of 5000 rpm for 5mins and the microspheres recovered. The resulting microspheres were thereafter washed with acetone and dried at a temperature of 28°C. Other batches were similarly prepared with some formulation variables, namely, mucuna gum concentration and crosslinking time [7].

Preparation of simulated intestinal fluid (SIF): SIF was prepared by weighing out 2g of monobasic potassium phosphate using the electronic balance. This was dissolved in small volume of distilled water, and mixed with 190ml of 0.2N sodium hydroxide solution. The pH was adjusted to 7.4 with 0.2 N of NaOH and was made up to 1000ml using distilled water. The SIF was prepared without pancreatin.

Determination of loading efficiency: 50mg of the drug loaded microspheres was put in a 25 ml volumetric flask, 0.1 mol/l sodium hydroxide solution was added to the mark and the content was allowed to hydrate for 24 hours at 28°C. The solution was filtered, appropriately diluted and then analyzed for diclofenac sodium content spectrophotometrically at 250nm, which was repeated three times for each batch. This was used to calculate the absolute drug content of the various microspheres. Beer's plot for diclofenac sodium was made at a wavelength of 250nm and subsequently used for drug release studies.

Determination of invitro release of diclofenac sodium: A magnetic stirrer hot plate assembly was used. A 250 ml volume of SIF (pH 7.4) consisting of the release medium was placed in a 500ml beaker containing a magnetic stirring rod. The temperature was maintained at 37 ± 1°C with the aid of a thermo regulated hot plate. In each case 50mg of drug loaded microspheres was placed in a small beaker with open bottom to which a mesh of aperture size of not greater than 1µm was attached. This was immersed in the dissolution medium under agitation of 100 rpm provided by the magnetic stirrer. Ten milliliters of sample were withdrawn and filtered at pre-determined time intervals from the dissolution medium outside the smaller beaker containing the microspheres. For each sample withdrawn, an equivalent volume (10ml) of SIF maintained at the same temperature was added to the contents of the dissolution medium to maintain sink conditions throughout the release period. The samples were thereafter analyzed spectrophotometrically at 250nm.

Results and Discussion

Total drug released at 20 minutes crosslinking time is bigger (17.543%) than that with crosslinking time of 30 minutes (8.403%) with mucuna concentration of 1g but the reverse was the case with mucuna gum concentration of 1.5g and 2g as seen in Tables 1, 2 and 3.

Table 1: Invitro Release (%) Of Diclofenac Sodium from Microspheres of Mucuna Gum (1g)

$T^{1/2}$	MC 1g CR 20 mins	MC 1g CR 30 mins
0.000	0.000	0.000
3.162	10.981	2.072
5.477	11.797	5.112
7.671	13.029	8.294
8.367	17.543	8.403
9.487	17.543	8.403
10.488	17.543	8.403

Table 2: Invitro Release (%) Of Diclofenac Sodium from Microspheres of Mucuna Gum (1.5 G)

$T^{1/2}$	MC 1.5g CR 20 mins	MC 1.5g CR 30 mins
0.000	0.000	0.000
3.162	16.147	5.549
5.477	17.748	14.429
7.671	18.299	18.163
8.367	21.529	23.709
9.487	26.181	27.848
10.488	26.181	27.848

Table 3: Invitro Release (%) Of Diclofenac Sodium from Microspheres of Mucuna Gum (2g)

$T^{1/2}$	MC 2g CR 20 mins	MC 2g CR 30 mins
0.000	0.000	0.000
3.162	18.333	7.172
5.477	20.326	7.885
7.671	23.845	8.534
8.367	44.491	9.684
9.487	44.491	51.288
10.488	44.491	51.288

Figures 1 and 2 show that maximum release time was the same for batches of mucuna gum concentration of both 1g and 1.5g irrespective of crosslinking time. For mucuna gum concentration of 2g, maximum drug release was attained earlier with crosslinking time of 20 minutes than with 30 minutes crosslinking time as seen in Figure 3. In all batches, delayed drug release is seen with 30 minutes crosslinking time compared to 20 minutes crosslinking time (see Table 4). Efficiency of drug release is improved with increase in polymer concentration.

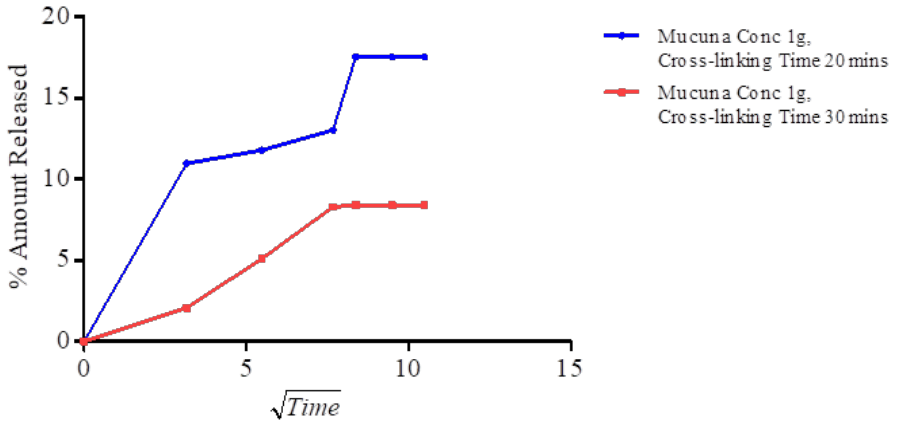

Figure 1: Invitro Release (%) Of Diclofenac Sodium from Microspheres of Mucuna Gum (1g)

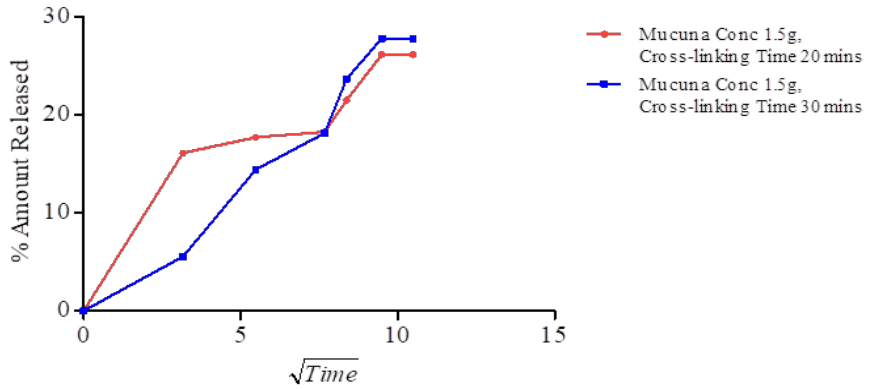

Figure 2: Invitro Release (%) Of Diclofenac Sodium from Microspheres of Mucuna Gum (1.5g)

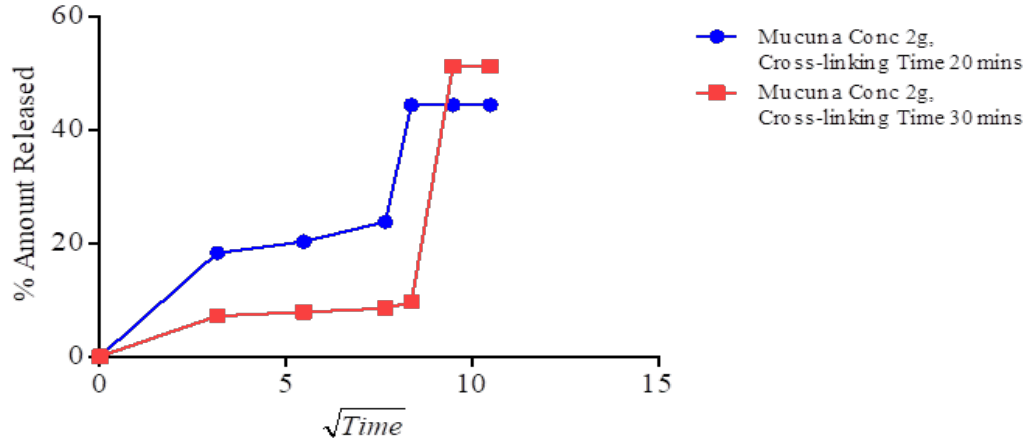

Figure 3: Invitro Release (%) Of Diclofenac Sodium from Microspheres of Mucuna Gum (2g)

Table 4: Invtro Release (%) Of Diclofenac Sodium from Microspheres of Mucuna Gum (1g, 1.5 G and 2g)

$T^{1/2}$	MC 1g CR 20 mins	MC 1g CR 30 mins	MC 1.5g CR 20 mins	MC 1.5g CR 30 mins	MC 2g CR 20 mins	MC 2g CR 30 mins
0.000	0.000	0.000	0.000	0.000	0.000	0.000
3.162	10.981	2.072	16.147	5.549	18.333	7.172
5.477	11.797	5.112	17.748	14.429	20.326	7.885
7.671	13.029	8.294	18.299	18.163	23.845	8.534
8.367	17.543	8.403	21.529	23.709	44.491	9.684
9.487	17.543	8.403	26.181	27.848	44.491	51.288
10.488	17.543	8.403	26.181	27.848	44.491	51.288

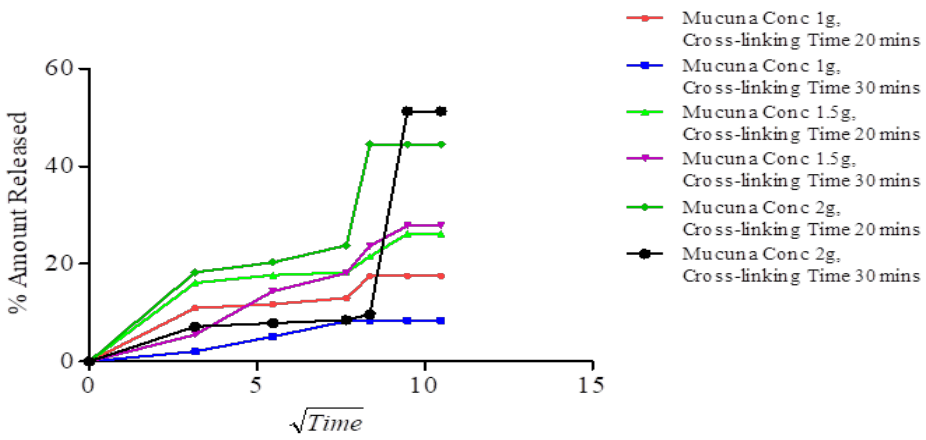

Figure 4: Invitro Release (%) Of Diclofenac Sodium from Microspheres of Mucuna Gum (1g, 1.5g and 2g)

The rate of release for batches with crosslinking time of 20 minutes was faster compared with their counterparts of crosslinking time, 30 minutes. In fact, increase in crosslinking time delayed drug release. A study had shown that microspheres that were not crosslinked had fastest release while crosslinking delayed drug release [7]. Another study found that crosslinking significantly reduced immunomodulatory capacity of injectable muscle tissue scaffold [15]. Sustained release delivers the required dose at a programmed rate for a period of time [16]. Constant plasma drug concentration is maintained. Poor patient compliance and multiple dosing which is one of the major challenges faced by healthcare givers and subsequently patients, is navigated. Moreover, the nature of pain makes it debilitating. There is need therefore for constant controlled sustained release of drug into the system such that the goal of appropriately managing patients' pain can be achieved.

Many people are affected by chronic pain coupled with additional burden of watching round the clock to administer drugs to ease pain. Quality of life is impacted negatively; therefore, the need for sustained analgesia cannot be overemphasized [17]. Gastro intestinal adverse effects are also minimized [18, 19].

Increase in mucuna gum concentration did not delay rate of drug release but increased total drug released. This corroborates prior works done to evaluate impact of polymer concentration on rate of drug release [20-22]. Our present result deviates from what was reported where increase in polymer concentration led to decrease in overall drug release [23].

None of the batches gave 100% drug release. Prior studies have found similar results [7, 23-24]. The implication is that the quantity of drug loaded into the microspheres should be bigger than the actual dose needed to exert the desired therapeutic effect. For example, since mucuna concentration of 2g with crosslinking time of 30 minutes had an ultimate yield of 51.288%, if 100% yield is required for the optimum analgesic effect, then drug loading should be increased by 1.95% with same mucuna concentration and crosslinking time.

Conclusion

Increase in crosslinking time delayed release. Increase in mucuna gum concentration did not delay rate of drug release but increased total drug released. Hence, diclofenac sodium microspheres can be produced using mucuna gum as polymer by chemical and thermal crosslinking method to provide an extended duration of drug action. Crosslinking affected drug release rate. Therefore, modification of crosslinking time is important for sustained release. Since drug yield was lower than 100% in all batches, drug loading can be modified for optimum therapeutic effect.

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