Effect of Electrolytes on Release of Diclofenac Sodium from Agarose Beads

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ABSTRACT: Diclofenac sodium loaded agarose beads were prepared and release profile of Diclofenac Sodium was investigated. Beads were prepared by dropping a hot aqueous agar solution into a beaker of chilled Paraffin oil and water. Water was made acidic to the pH of 1.65 using concentrated hydrochloric acid to reduce the prior diffusion of Diclofenac sodium into preparatory vehicle. Upon drying, the beads shrank and their dimensions were changed. *In-vitro* drug dissolution studies were carried out in distilled water. The release profile was found to be a function of polymer load and electrolytes incorporation into the beads. Increasing the polymer load decreased the rate and extent of drug release due to increased thickness and reduced the porosity of the system. Incorporation of mono & divalent metal salts by abating the amount of agarose in the formulations increased the release rate of the drug.

Key words: Diclofenac Na, Agarose bead, Electrolyte

INTRODUCTION

In the last several decades sustained-release dosage forms have made significant progress in terms of clinical efficacy and patient compliance.[1-4] The research of sustained-release dosage forms is an important field in pharmaceutics. Diclofenac sodium (DS) is one of a class of non steroidal drugs which has an anti-inflammatory, analgesic and antipyretic action as potent as indomethacin.[5] DS is a phenylacetic acid derivative with a pKa value of 4.0. The benefits of administering DS in a controlled release way has been demonstrated previously.[6,7] High viscosity grade hydroxy propyl methyl cellulose (HPMC 1000 & 1500 cps) were used to prepare controlled released DS dosage form,[8] although others employed low viscosity grade HPMC (15 cps) and cetostearyl alcohol as matrix material to produce tablets by direct compression.[9] Hydrogel beads of Diclofenac sodium have been studied in healthy humans.[10] Voltaren SR a commercial product of DS manufactured by Novartis is a hydrophobic matrix tablet consisting of a cetyl alcohol matrix.[11]

The first successful technique providing release at different times was the spansule, marketed by Smith Kline & French. Introduced in 1952, the product is still popular today. This dosage form contains beads or spheres of the drug that are coated with a material that differs in thickness from bead to bead, determining the times at which the drug will be released by diffusion through their pores. However, in this study, agar beads were prepared by a modified method[12]. Agar is prepared from various species of Gelidium and other red algae. It is an alternating copolymer of 3-linked β-D galactopyranose and 4-linked 3-6 anhydro-α-L-galactopyranose. It has a

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molecular weight of 120000. It is an unchanged polysaccharide having a low content of sulphate (<0.3% w/w) and carboxylate group. It is characterized by its gelling point (35 - 45° C for 1.5% gel). Agar is dissolved as a colloidal solution in water if heated to about 90° C and forms a solid gel upon cooling below its gelling point. Agar gelation is thermo-reversible that is the gel re-melts on heating to about 90° C. In the gel, the agar molecule form double helices which are linked together by hydrogen bonding in bundles to form network. In the bundles 10 to 50 double helical link in parallel aggregates, accounting for the large mesh size typical of agar gels.[13] In gels of low agar concentration (1% w/v), drug diffusivity can be the same as in water. Oral sustained release agar beads of sulphamethizole were prepared by adding drug to hot gel solution before the beads were formed.[14]

There are a number of techniques applied for the formulation as well as in the manufacturing of sustained release dosage form. But in the development studies of sustained release formulation, several new techniques and approaches are also proving their acceptability and feasibility. In recent years, controlled drug delivery formulations and the polymers used in these systems have become much more sophisticated with the ability to do more than simply extend the effective release period for a particular drug. Purpose of preparation of agarose beads is to control drug delivery system, increasing surface area and incorporating solubilizers (mono and divalent metal into agarose beads etc.).

MATERIALS AND METHODS

DS was kindly gifted by Square Pharmaceuticals limited, Bangladesh. Agarose, sodium chloride and calcium chloride were from Loba, Chemie, India. All the reagents used were of analytical grade.

Preparation of Agarose Beads. Agarose beads were prepared by dissolving DS in melted agarose according to the work of E. A. EI. Fattah.[15] At first agar was taken in water (4% w/v) and heated slowly. When it dissolved completely then DS was added and mixed properly by using a glass rod. When all the ingredients were mixed completely and gel was formed, then it was taken in a syringe and poured in a beaker filled with chilled acidified water (pH 1.65) and paraffin oil in a drop wise fashion by syringe. When gels were poured in paraffin oil from syringe as droplet, droplets become spherical due to the oily effect of paraffin & as soon as it reached to the acidified chilled water it became hard as the temperature was below the gelling point of agarose. Thus agarose beads were prepared. After completing the beads preparation, the beads were collected decanting the paraffin & acidified water. Then beads were washed by hexane to remove paraffin completely. Beads were then put in open space for air-dry. The composition of agarose beads of different formulations are given in Table 1. Finally 100 mg DS equivalent air-dried beads are taken for dissolution test.

Table 1. Formulation of Agarose Beads containing Diclofenac sodium

Code of formulation	Diclofenac Na (mg)	Agar (mg)	NaCl (mg)	$CaCl_2$ (mg)
F-1	2000	2000	-	-
F-2	2000	4000	-	-
F-3	2000	6000	-	-
F-4	2000	3200	800	-
F-5	2000	3200	-	800

***In vitro* Dissolution Study.** Dissolution studies were conducted according to the USP method (USP XXII) using apparatus II. The metallic driven shaft rotated at a speed of 50 rpm & temperature was maintained at 37 ± 0.5^0 C. The USP paddle system consists of six glass vessels, which contains dissolution medium. There were six baskets mounted in the shafts rotating at a predetermined rpm, 1000 ml of distilled water was placed in the vessel and the apparatus was assembled. Each formulation was placed in the basket. After each time interval, 10ml sample was withdrawn. For each sampling, the volume was adjusted with 10 ml fresh distilled water. This operation was continued for 8 hours. The released drug was assayed by using a UV spectrophotometer (Shimadzu, Japan) at λ_{max} 276 nm. The drug concentration was calculated with the help

of straight-line equation obtained from the standard curve.

RESULTS AND DISCUSSION

Effect of Polymer Loading on DS Release from Agar Beads. Figure 1A shows the effect of polymer (agar) loading on the release of DS from agar beads. The three formulations tested for polymer loading are F-1, F-2 and F-3 containing 50, 66.66 and 75% agar level in the beads. The rate and extent of drug release were found to vary inversely with polymer loading in agar beads. F-1 released 25% of DS while F-2 and F-3 released 13% and 11% of biologically active molecule after 8 hours. All the formulations did not release equally during the phase of dissolution and differences in release rate and extent through the period of dissolution was evident. While forming the gel an increase in the polymer load decreases the release of DS from the beads.

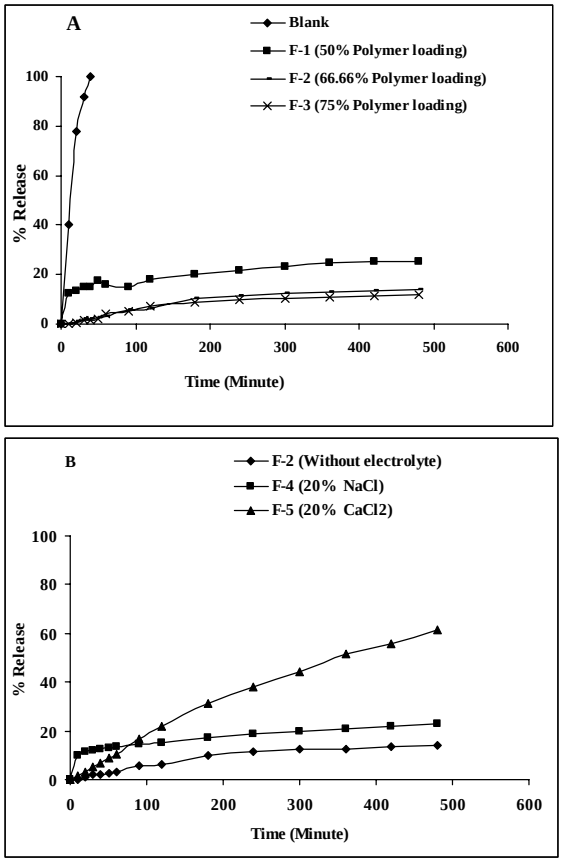

Figure 1. *In vitro* release profile of Diclofenac Sodium from Agarose Beads; A: Effect of polymer loading, B: Effect of electrolytes.

When the polymer level is increased in polymeric beads, the elevated agar level formed a thicker gel in contact with the dissolution fluid with reduced porosity and higher tortuosity. Increased gel thickness also increased the path-length of diffusion of DS from polymeric beads, which virtually elevated the time required for dissolution of DS from the dosage form. This factor can be attributed to the reduction of release rate with increment of polymer level in agar beads. Here again, a good linearity was found indicating that the drug molecules were homogeneously dispersed in the beads.

Effect of Different Electrolytes on Drug Release from Agar Beads. Two classes of release modulating agents were incorporated into the agar beads. These are NaCl and $CaCl_2$. It was observed that in formulation F-2 incorporation of 20% NaCl and $CaCl_2$ released 23% and 61% at 8 hours respectively which is shown in figure 1-B. All electrolytes were found to increase the rate and extent of drug release due to preferential salting out in water. When incorporated into a matrix system, it dissolves out rapidly from the system creating pores and channels through which dissolution medium can get into and leach the drug out of the dosage form. The release data show that the entire electrolyte incorporated elevated the rate and extent of drug release.

Table 2. *In vitro* release of Diclofenac Sodium from Agar Beads

Time (min)	F-0	F-1	F-2	F-3	F-4	F-5
0	0	0	0	0	0.0	0.0
10	40	12.5	0.04	0.04	9.8	1.7
20	78	13.5	0.8	0.4	11.4	3.0
30	92	14.7	2.0	1.5	12.2	5.1
40	100	14.9	2.3	1.6	12.7	6.9
50	-	17.3	2.5	2.0	13.1	8.8
60	-	16.2	3.0	4.3	13.4	10.6
90	-	15.1	5.5	5.0	14.3	16.6
120	-	18.0	6.0	7.1	15.2	22.1
180	-	20.2	10.1	9.0	17.0	31.4
240	-	21.9	11.5	9.8	18.6	37.9
300	-	23.4	12.4	10.3	19.6	44.4
360	-	24.7	12.7	10.7	21.0	51.8
420	-	25.3	13.6	11.1	22.0	56.0
480	-	25.5	13.9	11.7	23.1	61.3

CONCLUSION

DS loaded agarose beads were prepared and the release profile of DS was investigated. In wet condition the size of Agar beads were measured and found bigger than those in dry condition. The release profile was found to be a function of polymer loading and metal salt (mono and divalent) incorporation. Increasing the polymer load decreased the rate and extent of drug release due to decrease in drug availability on the bead surface. Incorporation of mono and divalent metal salt increased the release rate of drug. So it is possible to modify the release rate of drug from agarose beads by choosing suitable electrolytes according to the desired drug concentration at the target site.

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