

SYNOPSIS

The controlled release technology evolved as an active discipline for the delivery of pesticides in earlier seventies. Since then the technology has found applications in diverse fields in the delivery of a wide range of bioactive molecules such as pharmaceuticals, pesticides, fertilizers, pheromones and plant growth regulators. A large number of products based on this technology have been commercialized. Over the recent years, there has been a distinct trend to elucidate the mechanism of release from various types of delivery systems. As a result, it is now possible to design controlled release delivery systems from the knowledge of the relevant physico-chemical data for the polymeric matrices chosen and the bioactive molecules being released. The types of controlled release delivery systems and their release patterns have been extensively reviewed in the literature (1). For the release of drugs which have short biological half life and low therapeutic index, the pharmacokinetic models have established the utility of delivery systems which are capable of releasing the drugs at a constant release rate. Amongst the various types of delivery systems developed only reservoir devices are known to provide zero order release of bioactive molecules .

The matrix systems are generally preferred because of the ease of fabrication, low cost and amenability to large scale manufacture. Unfortunately, the release rate from the matrix devices decreases with time. A number of approaches have been proposed in the past to achieve zero order release from the

matrix systems. These include, geometric modifications (2), establishment of nonuniform concentration profiles (3), use of polymer blends as matrices (4,5) and the swelling controlled delivery systems (6-7).

Swelling controlled delivery systems consist of glassy polymeric matrices. The penetration of the medium into the matrix follows case II transport kinetics. If the diffusivity of the bioactive molecule in the swollen matrix is sufficiently high, the kinetics of release is controlled by the case II transport of the penetrant. The criteria for the swelling controlled release of physically dispersed bioactive molecules from glassy hydrogels have been reviewed in the literature (6-7). However, no systems of pragmatic importance based on swelling controlled release have been developed as yet.

One of the limitations in this endeavour has been the limited swelling of the hydrogels. A number of copolymers have been tried as matrices for the zero order release of drugs such as theophylline. However, in most cases an increase in the equilibrium swelling is also accompanied by corresponding increase in the velocity of the penetrant medium. As a result, there is very little change in the release index.

This work was undertaken to elucidate the factors which govern the kinetics of release of active ingredients from the glassy and swollen hydrogels.

It was observed that the release index of theophylline as well as carbamazepine from the copolymers 2-hydroxyethyl methacrylate with 4-carboxy styrene, increases with the pH of the medium. A constant release rate was observed at a pH = 11.0

This was due to increase in the degree of swelling of the polymer matrices as a result of ionization of the carboxylic acid group. Surprisingly, the release of a low molecular weight moiety such as benzoic acid does not result in a constant release rate at pH 8.0. Even at a pH = 11.0, the release rate of benzoic acid was lower than that of theophylline. This was because of the lower degree of swelling of the polymer. It was therefore clear that bulkier molecules having acidic functional groups would not be released at constant release rate over extended time periods, when physically dispersed in such types of glassy hydrogels.

A series of substituted benzoic acids were therefore chemically linked to 2-hydroxyethyl methacrylate. These monomers were copolymerized with 2-hydroxyethyl methacrylate and the kinetics of release of the substituted benzoic acids from the glassy hydrogels in the alkaline and the acidic medium was investigated. It was observed that the kinetics of release of p-nitro benzoic acid was governed by the velocity of the penetrating medium whereas the release of 2,4-dinitrobenzoic acid was diffusion controlled. The kinetics of release of p-methoxy and p-amino benzoic acid was controlled by the hydrolysis step. This work thus clearly indicates that each of the steps involved in the release can become the rate controlling step depending upon the nature of the substituents on benzoic acid. It also provides the first experimental evidence of swelling controlled zero order release of an active ingredient from a pendant chain linked glassy hydrogel.

Further studies on the kinetics of release of p-nitrobenzoic

acid and 2,4-dinitrobenzoic acid from the respective glassy hydrogels for increasing the degree of hydrophobicity and hence the period of release, reveal intriguing features. Although the two moieties were released at constant release rate, the velocities of penetration experimentally measured were significantly higher than those estimated from the release rate. It, therefore, became apparent that the release at constant rate continued even when the hydrogels were in the rubbery state. This was experimentally verified independently indicating thereby that the release was no more swelling controlled. The results have been elucidated on the basis of increase in the diffusivity of the active ingredient as a result of hydrolysis and concomitant increase in the degree of swelling of the polymer matrix. This is the first reported finding of zero order release of an active ingredient from the swollen hydrogel matrices, as a result of bulk scale erosion of the polymer structure in contrast to zero order release reported in the past, by mass / phase erosion. The results also indicate that the concept of time dependent diffusivity debated in the literature for some time can be successfully exploited to achieve zero order release of the active ingredients from glassy/rubbery hydrogel matrices. (8-10)

Based on these mechanistic investigations matrix device based on glassy hydrogels which can release active ingredients at constant rate for periods upto five months have been synthesised and release kinetics investigated.

In summary, this work highlights newer concepts to achieve zero order release of active ingredients from matrix systems based on glassy as well as swollen hydrogels. These could be

successfully exploited to design matrix systems for the release of the bioactive molecules such as drugs of pragmatic importance over time periods of clinical significance.

REFERENCES

1. R.Langer and N.A.Peppas,Rev.Macromol.Chem.Phys.C 23 (1983) 61.
2. W.D. Rhine, V. Sukhatme , S. T. Hsieh and R. S. Langer , in: R.Baker (Ed.) Controlled Release of Bioactive Materials, Academic Press, New York (1980) 71.
3. P. I. Lee, Polymer, 25 (1984) 973.
4. S.K.Baveja and K.V.Ranga Rao, Int. J. Pharm., 31 (1985) 169.
5. S.K.Baveja, K.V.Ranga Rao and K.Padmalatha Devi, Int.J.Pharm., 39 (1987).
- 6 . H.B.Hopfenberg and H.S.Hsu, Polym. Engg.Sci.,18 (1978) 1186.
7. N. A. Peppas and N. M. Franson. J. Polym. Sci.,(Phys. Edn.) 21 (1983) 983.
8. R. K. Chang. J. Pharm. Sci., 75 (1986) 717
9. N. A. Peppas, J. Pharm. Sci.. 76 (1987) 267.
10. R. K. Chang, J. Pharm. Sci., 76 (1987) 267.