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DESIGN AND EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF FLURBIPROFEN

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ABSTRACT

Controlled release matrix tablets of flurbiprofen were designed by employing chitosan and sodium alginate as release rate controlling polymers. A Combination of chitosan and sodium alginate in 1 : 1 ratio is employed for the preparation of the polymer matrix. As the release of the drug from the matrix tablets is very slow, various excipients such Microcrystalline cellulose, starch and lactose individually and in combination in different proportions are included in the matrix formulation to verify their influence on the drug release characteristics. The tablets were tested for drug content, weight variation, hardness, thickness, friability and swelling characteristic. The analysis of the release of the drug from different formulation prepared indicates that while there was only 57% drug release at the end of 12 hours from matrix tablets without the added excipients, the release of the drug is found to be increased but slow and sustained and complete when water soluble excipients starch and lactose are included in the matrix tablets. The inclusion of microcrystalline cellulose has further modified the release to achieve slow and controlled release of the over a period of 12 hours. The drug release is found to follow first order kinetics and is found to be diffusion controlled.

Key words: Chitosan, Flurbiprofen, Microcrystalline cellulose, Matrix tablets, Swelling ratio.

INTRODUCTION

Hydrophilic matrices containing swellable polymers are referred to as hydrogel matrices, swellable controlled release systems or hydrophilic matrix tablets. A number of polymers are investigated to develop in situ gel forming systems due to the ability of these hydrogels to control the release of drug in aqueous media and to regulate the release of such drug by the control of swelling and cross linking[1-3]. Water penetration, polymer swelling, drug dissolution and diffusion and matrix erosion of these dosage forms are controlled by hydration of the polymer which forms a gel barrier through which the drug diffuses. The adjustment of polymer concentration, viscosity grade and addition of different types and levels of excipients to the matrix can modify the drug release rate.

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There are reports of the potential use of chitosan as new matrix forming material in the design of sustained release dosage forms[4,5]. Chitosan is obtained by alkaline deacytalation of chitin and is one of the most abundant polysaccharides in nature. Because of its non toxicity, biocompatibility, chitosan has received considerable attention as novel excipient in drug delivery systems and is included in European Pharmacopeia since 2002. Chitosan is also utilized in various other fields of pharmaceutical technology including formulation of controlled release systems, mucoadhesive devices and in buccal drug delivery systems[6-8]. Sodium alginate is also widely used as matrix forming material in the design of prolonged drug delivery systems.

In the present study a 1 : 1 physical mixture of the two polymers chitosan and sodium alginate is employed to prepare the matrix tablets. The objective of this study is to develop a controlled release matrix tablet employing a combination of chitosan and sodium alginate and to evaluate the influence of different excipients added. Microcrystalline cellulose, starch and lactose are employed as release modifiers. Flurbiprofen a non steroidal anti-inflammatory agent is used as a model drug.

EXPERIMENTAL

Materials and methods

Chitosan was procured from, Central Fisheries Institute, Cochin; Sodium alginate was supplied by Qualigens, Microcrystalline Cellulose (Avicel PH105), starch (s.d. Fine Chemicals) and lactose (Loba Chem). All other chemicals and reagents are of analytical grade. Flurbiprofen is a gift sample from Knoll Pharma.

Preparation of matrix tablets

1 : 1 mixture of polymer blend (PB) chitosan and sodium alginate is employed in the preparation of matrix tablets. The details of compositions of matrix tablets are given in Table 1.

Table 1: Composition of matrix tablets prepared (in mg)

Formulation	Flurbiprofen (mg)	Polymer Blend (mg)	MCC (mg)	Starch (mg)	Lactose (mg)
MT1	200	160	--	40	--
MT2	200	150	10	40	--

Cont…

Formulation	Flurbiprofen (mg)	Polymer Blend (mg)	MCC (mg)	Starch (mg)	Lactose (mg)
MT3	200	140	20	40	--
MT4	200	160	--	--	40
MT5	200	150	10	--	40
MT6	200	140	20	--	40
MT7	200	160	--	20	20
MT8	200	150	10	20	20
MT9	200	140	20	20	20

The PB is mixed with the drug, microcrystalline cellulose, starch and/or lactose in a laboratory blend for 30 minutes. Thereafter the powders are granulated with 0.1 N acetic acid and sieved using standard sieve No. 16 and the granules obtained are dried in a hot air oven at 40^{o}C for 3 hours. Tablets of about 400 mg weight, each containing 200 mg of Flurbiprofen are prepared from these granules. The flow properties of the granules are determined by measuring the angle of repose and compressibility index. And the tablets are compressed using a single punch Cadmach tabletting machine with 5 mm flat round punches.

Weight, hardness and thickness

A total of 20 tablets of each formulation were evaluated for weight uniformity. From each formulation the hardness of 10 tablets was examined using Monsanto Hardness Tester.

The thickness was determined using a micrometer. Ten individual tablets of each formulation were used.

Friability

Twenty tablets were weighed and placed into a friabilator. The samples underwent 25 rotations per minute for 4 minutes and were then re-weighed. This process was repeated for all formulations and the percentage friability was calculated using the equation.

$$F = \frac{W_1 - W_2}{W_1} \text{ x } 100$$

Swelling

Swelling studies were carried out for all formulations. Metallic baskets containing the matrix tablets of each formulation were weighed and placed in 1000 mL of distilled

water. At the end of 3 hours the previously weighed basket with the tablet was removed, gently wiped with a soft tissue paper to remove surface water and weighed. The degree of swelling was calculated using the formula.

$$S = \frac{W_s - W_d}{W_d} \times 100$$

Where W_s and W_d are the swollen and dry matrix weights, respectively. The swelling degree is the mean of 3 determinations.

Drug release studies

The *in vitro* drug release studies from the matrix tablets of flurbiprofen were studied employing USP XXIV Type 1 Dissolution Rate Test Apparatus with a basket stirrer. 900 mL of 0.1 N Hydrochloric acid is employed as the dissolution medium for the first 2 hours and 900 mL of Phosphate Buffer of pH 7.4 is employed for the remaining 10 hours. A temperature of 37^{o}C and a speed of 50 rpm were employed. 5 mL samples were withdrawn at suitable intervals of time and analyzed for drug content by measuring the absorbance at 247 nm.

RESULTS AND DISCUSSION

Physical characterization of matrix tablets

The various physical characteristics are summarized in Table 2. These indicate good weight uniformity, as indicated by the very low relative standard deviation obtained (RSD < 1% in all formulations). The hardness of matrix tablets with different proportions of excipients is found to be between 5-6 Kg/cm^2. Tablets containing MCC exhibited marginally higher hardness values. This is probably because of improved compression characteristics of the granules in the presence of MCC. The tablets also passed the friability test (F < 1%) showing that all formulations are within USP 25[9] limits.

Swelling studies

Swelling studies were carried out in order to investigate whether the extent of swelling varied for the different formulations. When a matrix comes into contact with an aqueous solution, wetting occurs first at the surface and then progressing into the matrix through microscopic pores. The nature of the polymer plays an important role in this swelling process of the matrix tablets. The presence of water in the polymer causes a certain amount of stress, resulting in hydration of the polymer which starts to swell yielding a gelatinous viscous layer[10,11].

Table 2: Physical characteristics of matrix tablets prepared

Formulation	Weight (RSD) %	Hardness Kg/cm^2	Thickness (mm)	Friability (%) n = 20	Swelling index (%)
MX	0.43	5.50	4.95	0.64	4.98
MT1	0.56	5.19	4.92	0.71	5.67
MT2	0.42	5.37	4.79	0.87	6.23
MT3	0.62	6.13	4.78	0.57	7.01
MT4	0.17	5.32	4.99	0.39	5.97
MT5	0.37	5.76	5.12	0.53	6.95
MT6	0.28	6.27	5.15	0.75	7.85
MT7	0.54	5.56	4.98	0.69	5.34
MT8	0.28	5.89	4.76	0.26	6.87
MT9	0.35	6.12	4.98	0.31	7.65

It was observed that the swelling index value is higher for the formulation containing microcrystalline cellulose than for the other tablets containing only starch or lactose (Table 2). This is probably because of the swelling nature associated with the microcrystalline cellulose. The presence of starch or lactose, the 2 water soluble excipients did not greatly influence the swelling of the matrix tablets whereas the presence of MCC probably resulted in more water being taken into the swollen matrix. As the amount of MCC increased (In MT3, MT6, MT9) the swelling index also increased.

Drug release studies

Excipients play a unique functional role in the design of a CR tablet. The excipients used in the design of hydrophilic matrix tablet include fillers, binders, lubricants, glidants etc. These substances are often necessary to improve the tablets characteristics or modify the drug release. The effect of the excipient depends on the nature and also the level of the substance employed. In the present investigation the influence of 2 water soluble excipients-starch and lactose and one insoluble but swellable substance MCC are employed in an attempt to obtain modified release from the chitosan-alginate matrix tablets.

The release of the drug flurbiprofen Fig. 1 from the matrix tablets designed without the added excipients MX is found to be slow and sustained. But at the end of 12 hours only 57% of drug could be released. So to increase the amount of drug released the influence of starch, lactose and MCC is studied in different combinations.

Influence of starch and MCC

Soluble starch is employed in the studies. When starch alone is employed (MT1) at 10% the release of the drug ifs found to be increased Fig. 1. This is probably because of the soluble nature of the starch created a more porous matrix leading to increased release of the drug. At the end of 10 hours there is 100% release of flurbiprofen. The presence of Starch and MCC together can modify the release of the drug from the matrix tablets. In the presence of MCC the release is found to be slower and is extended upto 12 hours. As the proportion of MCC is increased in the matrix tablet the release is also lowered. This lowered release is probably due to the increased swelling of the matrix due to the presence of MCC which results in the formation of more gelatinous viscous layer. This observation is consistent with the results seen in the swelling studies where the matrix tablets containing MCC showed higher swelling index values. However the total percent released is found to be higher than the MX tablets without the excipients indicating that the combined presence of starch and MCC appeared to control the release of the drug from the matrices.

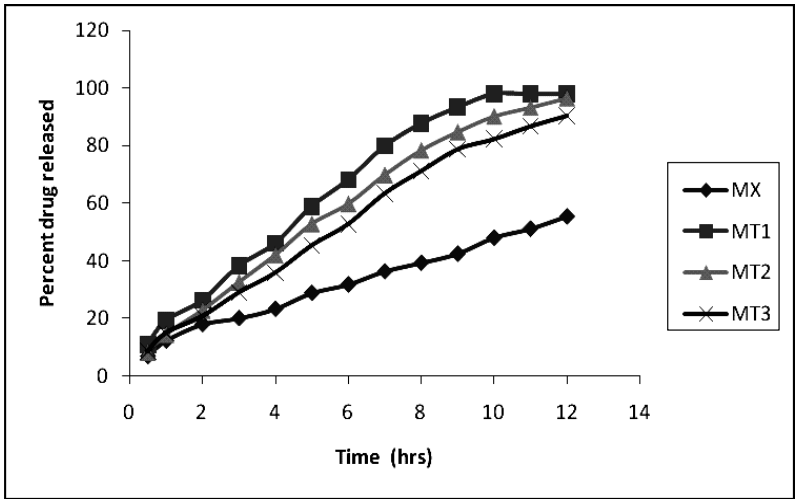

Fig. 1: Drug release studies from various matrix tablets

Influence of lactose and MCC

Lactose is the most useful excipient used in tablet formulations. It is water soluble and would modify the drug release for undergoing dissolution. Drug release profiles from matrix tablets containing lactose and MCC are shown in Fig. 2.

While the tablet MT4 (0% MCC and 10% lactose) showed faster drug release (98% after 10 hours), when MCC is incorporated in the formulations MT5 (2.5% MCC-10%

lactose), or MT6 (5% MCC-10% lactose) the release of the drug could be extended up to 12 hours. The higher dissolution with lactose containing matrix tablets is due to the increased channels created for the diffusion of the drug as a consequence of lactose dissolution in the penetrating dissolution fluid and also the tortousity of the diffusional path is probably reduced.

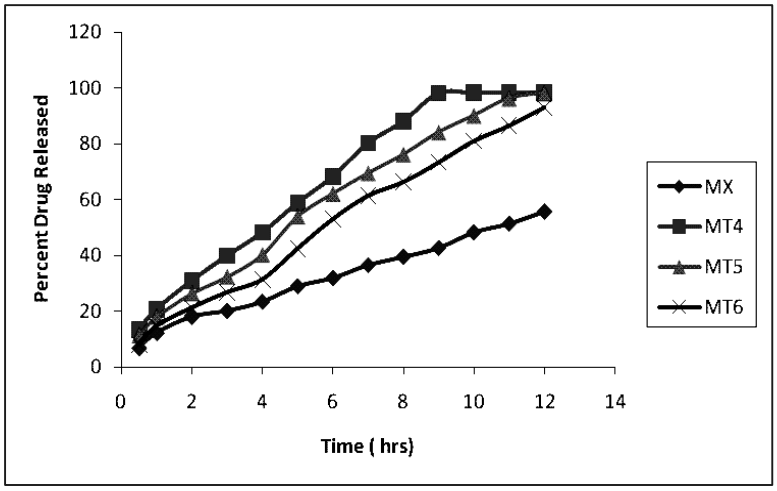

Fig. 2: Drug Release studies from various matrix tablets

It is observed that there is no significant difference in the release profiles obtained between the tablets prepared either with starch or lactose and the influence of MCC on the release is found to be similar on both the types of tablets.

Influence of Starch : Lactose mixture

Since starch and lactose have individually modified the drug release, in order to verify their combined effect on the drug release, the last 3 formulations are prepared by mixing starch and lactose in 1 : 1 ratio and by varying the MCC content as in the previous products Fig. 3. Represents the release profiles of drug from the matrix tablets MT7 (0 % MCC-5% starch-5% Lactose), and MT8 (2.5% MCC-5% Starch-5% Lactose) and MT9 (2.5% MCC-5% Starch-5% Lactose). The results obtained are in agreement with the release obtained with the earlier 2 products. Even with tablets containing 50% less of starch and 50% lactose, the release profiles are found to be similar to the tablets containing starch and lactose individually. This is in agreement with the earlier observation that the both starch and lactose had similar effect on drug release. Thus it may be concluded that the release is mainly controlled by the microcrystalline cellulose.

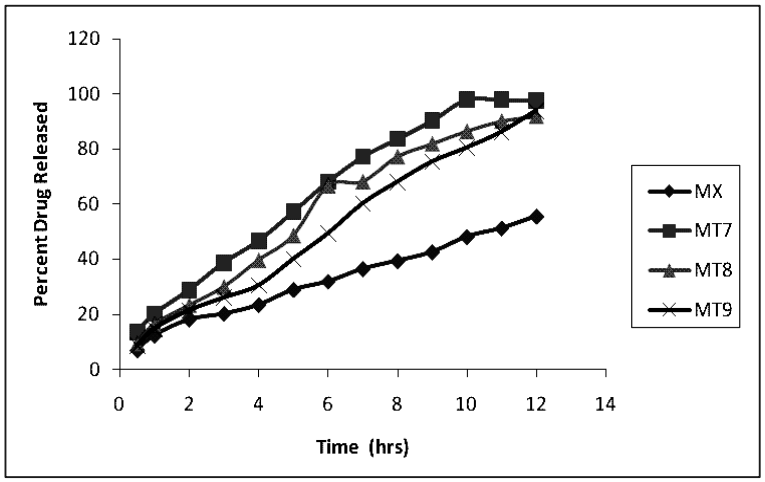

Fig. 3: Drug release studies from various matrix tablets

Drug release mechanism

To know the drug release mechanism from the formulations designed, the dissolution data are treated according to first order (log percent drug unreleased vs time) and Higuchi‘s (percent drug released vs square root of time) pattern. When plotted according to first order equation the release from all the formulations is fairly linear (not shown).

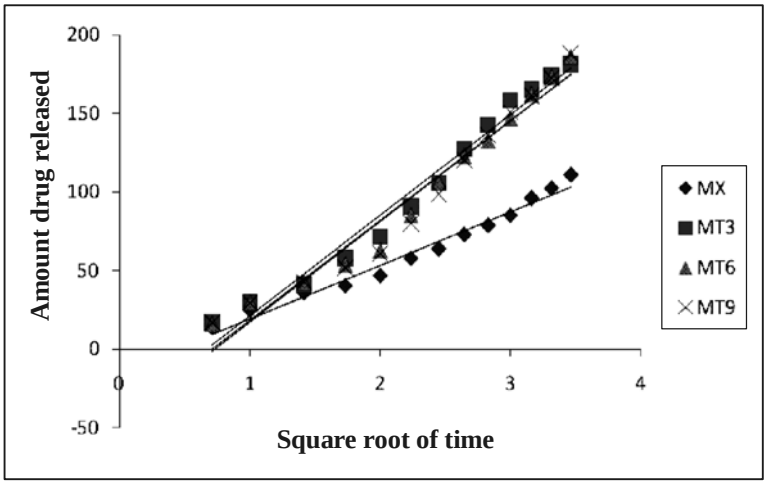

Fig. 4: Higuchi plot

Release of drugs from hydrophilic matrices is generally by diffusion and involves transport of the drug from the matrix into the dissolution medium depending on

concentration gradient. As the gradient varies, the drug is released and the distance for diffusion increases. In the experiments carried out in the present study, the release profiles from all the formulations can be explained by the Higuchi's equation as the plots showed high linearity (Fig. 4).

CONCLUSION

Controlled release matrix tablets of flurbiprofen could be designed by employing a polymer blend of chitosan and sodium alginate. Matrix tablets could be prepared by employing wet granulation method. The physical characteristics of the tablets prepared are found to be satisfactory. The drug release from the matrices of the polymer blend without the excipients is found to be very slow. When starch and lactose are included the release is found to be increased and complete by 10 hours. There is no significant difference in the release pattern between the matrix tablets prepared by either starch or lactose. The inclusion of microcrystalline cellulose has further modified the release by extending the drug release up to 12 hours. As the proportion of MCC increased the release also is found to be reduced. Thus in the matrix tablets designed the release of the drug is found to be principally controlled by the water soluble excipients starch and lactose and by the varying concentration of microcrystalline cellulose.

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