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Original Research Article

Matrix release from tablets prepared with aqueous dispersion of an acrylate methacrylate (a water – insoluble) copolymer as binder

Abstract

PURPOSE: To investigate the binder effect of aqueous dispersions of acrylate methacrylates (AMA) copolymer with a view to obtaining matrix (non-disintegrating) tablets with a retard release property.

METHODS: Aqueous dispersions of AMA (1-15% w/v) were formed by a coacervation procedure using ethanol (10 ml) as solvent and water (90 ml) as non-solvent for the copolymer. The aqueous dispersions were used to wet–mass the drug (paracetamol) powder. Resulting granules were compressed to 500 mg tablets using a single punch machine. The tablets were subjected to hardness, friability, disintegration and dissolution tests.

RESULTS: The granules formed hard tablets (tensile strength 1 - 2.0 MNm^{-2}) with low friability decreasing from 2 to 1 % as the AMA binder concentration increased from 0.75 to 11.25% w/w. The tablets failed to disintegrate in 3 hr. Drug release generally followed the Higuchi square root of time kinetic ($R^2 \geq 0.95$). The AMA binder markedly retarded drug release as reflected by the sharp decrease in the dissolution rate constant from 30 min^{-2} (AMA, 0.75% w/w) to 9 min^{-2} (AMA, 11.25% w/w).

CONCLUSION: The AMA dispersion is an effective binder, producing matrix tablets with a retard release property controlled by the binder content in the tablets.

Keywords: Acrylate methacrylate copolymer; Aqueous dispersions; Matrix tablets, Retard release; Friability index; Tensile strength.

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Introduction

The term matrix release refers to drug release from non-disintegrating systems in which the drug has been dispersed such that drug release is controlled by slow diffusion through the matrix to an external leaching fluid. Initial leaching from the surface layers will create a zone of depletion, which recedes inwards with time. In other words the diffusion path length increases with time, and hence drug release is progressively retarded. Higuchi showed that release from such matrix system is linearly related to the square root of time ($t^{1/2}$). Water – insoluble polymers [1-4] and lipids [5] are frequently used as matrix formers and serve mainly as drug release retardants

The acrylate methacrylates are water insoluble copolymers that have been used as release retardants by spray application of their organic solution on drug particles [6-7]. The use of organic solvent in the coating procedure is hazardous and expensive. Aqueous systems of the polymers can be used in spray application but the rapid drying essential to the success of the spray coating technique is not readily achievable with the aqueous systems. By considering these limitations, the objective of the present study is to carry out simple wet – granulation of the drug powder (paracetamol) with aqueous systems of the copolymer to see whether resulting granules can form tablets with a retard release property. Paracetamol was selected for the study because it is readily available and easily assayed by spectrophotometric methods.

Materials and Methods

Materials

An acrylate methacrylate (a water insoluble but water swellable) copolymer was received under the trade name Eudragit RS 100 as a gift from Rohm Pharma GMBH, Darmstadt, Germany. The test drug was paracetamol obtained from BDH Chemicals, Poole UK.

Preparation of aqueous dispersions of the AMA copolymer

The coacervation technique [8] was followed. Varying amounts of the polymer (1-15 g) were dissolved overnight in ethanol (10 ml). Excess water, 90 ml (as non-solvent for the polymer), was added gradually to the ethanolic solution with continuous stirring for 5 min to obtain a latex dispersion. Polymer particles in the dispersion were of colloidal (submicron) size and therefore not visible under a light microscope.

Granulation technique

The polymer dispersion (75 ml) was used to wet-mass a sample of the drug powder (100 g) in a Kenwood planetary mixer (Kenwood Electrus, UK). The wet mass was passed through a sieve of aperture size (1.7 mm) and dried at 60 ^{o}C for 1hr, passed through a sieve (aperture size 710 µm) and dried finally at 60 ^{o}C for 5hr to moisture content of 2.4$\pm$0.71% w/w. The granules were stored overnight in a desiccator before compression.

Tableting technique

The single punch-tableting machine (Kilian and Co, Frankfurt, Germany) was used for the production of the tablets. The die and punch surfaces were first lubricated with 1% dispersion of magnesium stearate in chloroform. A sample of the granules (500 mg) was filled into the die and compressed to tablets of thickness 3.87mm, diameter 12.36 mm. The compression load was held constant at 6.5 (arbitrary unit on the load scale). The resulting tablets were stored overnight in a desiccator to allow for complete equilibration before their evaluation.

Evaluation of the tablet tensile strength (T)

The load (P) required to cause a diametrial fracture of the tablet was determined using the Monsanto hardness tester [9]. The

determination was carried out using ten tablets from each batch and T was computed using the expression below [10]:

$$T = \frac{2P}{\pi Dt} \quad\quad (1)$$

where t and D represent the thickness and diameter of the tablet respectively. Triplicate determinations were carried out for the various concentrations of binder employed and mean values reported.

Determination of tablet friability

Ten tablets (randomly selected) were weighed and placed in the Ewerka friabulator (GMBh Heusenstamin, Germany) rotating at 20 rpm for 10 min. The tablets were reweighed after dusting off adherent particles. The % dust produced by the impact was determined and taken as index of friability. Triplicate determination were carried out for each batch of tablets made from the various concentrations of the binder and mean values reported.

Determination of tablet disintegration time

Tablet disintegration time was carried out using the British Pharmacopoiea [11] method. The tablets were observed for up to 3h (same period as for the dissolution test). Triplicate determinations were carried out and mean results reported.

Dissolution studies

The stirred beaker method described previously [5] was followed. A tablet was placed in a single cylindrical basket (mesh aperture size 425 µm, diameter 20 mm; and height 30 mm). The basket containing the tablet was stoppered and immersed in 1000 ml leaching fluid (water) maintained at $37 + 0.5\ ^{o}C$. The leaching fluid was stirred (100 rev.min^{-1}) using a Gallenkamp stirrer fitted with a single blade (model APP SS530). At predetermined intervals, samples of the leaching fluid (5 ml) were withdrawn

with a pipette plugged with cotton wool. 5ml of water maintained at the same temperature was used to replace the withdrawn samples, taken for up to 3 hr. The samples were analyzed spectrophotometrically at λ_{max} 257 nm. (Model: Unico UV- 2110 England). The determination was carried ort in triplicate and the mean results are reported.

Test for the drug release kinetics

The release data were subjected to the commonly reported kinetics of drug release from pharmaceutical systems [12,] namely:

(i) Zero order: $m = k_0 t$ (2)
(ii) First order: $\log m_1 = \log m_0 - 0.432 k_1 t$ (3), and
(iii) Huguchi square root of time relationship [13]: $Q = k_H \sqrt{t}$ (4)

where m and Q are the percentages (%) amount of drug released in time t, m_1 is the amount of drug remaining (%) at time t, m_0 is the initial amount of drug (100%) at the beginning of the first order release, and k_0, k_1, and k_H are the kinetic constants for the zero order, first order and the Higuchi release respectively.

Results

Tablet Friability

Values of the friability index are presented in Table 1, which shows that the tablets became less friable with increase in binder concentration in the tablets. The tablets generally displayed a low friability index; the maximum recorded for tablets with the lowest binder content was 2%.

Tablet tensile strength

The T values are also presented in Table 1. The tablets became harder as binder content increased, reaching a maximum at a binder content of 11.25% w/w. In other words there

was no statistical difference in T values when binder content was further increased above 11.25% w/w. Hence, the binder content 11.25% w/w may be considered optimal for the tablet formulation.

Tablet disintegration time

The tablets did not disintegrate at all binder concentrations even after 3h, which was also the time course of the dissolution test. The binder thus conferred a matrix property on the tablets.

Dissolution profile

The amounts (%) of drug released were plotted versus time (Figure 1). The plots were curvi-linear, the slopes decreasing with time, suggesting that the dissolution rate at any instant decreased with time, which is a feature of matrix release [14]. Furthermore, an increase in binder content from 0.75% w/w to 11.25% markedly retarded the dissolution rate.

The R^2 values (Table 1) showed that the release profile followed the Higuchi release kinetic ($R^2 \geq 0.95$), thus confirming a matrix release. The values of the Higuchi dissolution constant (k_H) dropped sharply with increase in the binder content (0.75% w/w to 11.25% w/w).

Table 1: Effect of binder concentration on the mechanical strengths and the release kinetics of the tablets

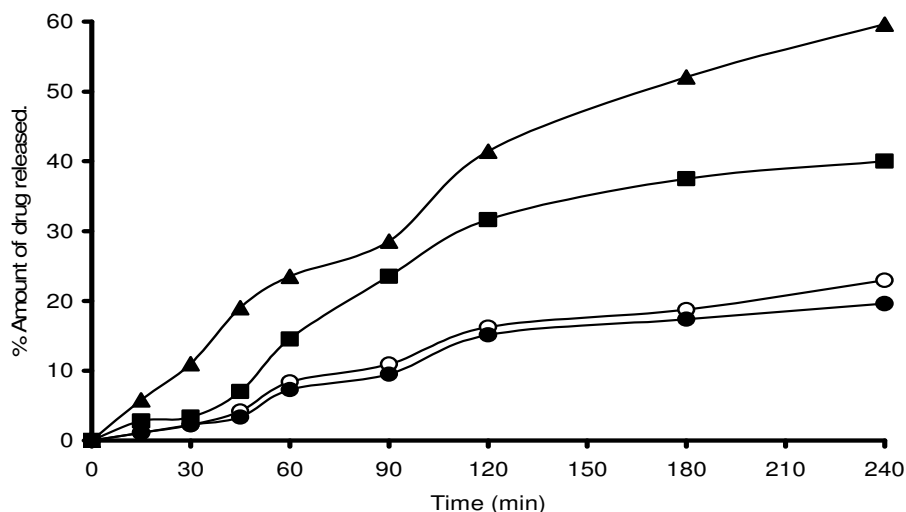| Binder conc. In the tablet (% w/w)	Tensile strength (T) (MNm-^{2})	Friability % (F)	K_H (min$^{-1/2}$)	Regression coefficient (R^2 Values)		
				Zero order	First order	Higuchi
0.75	1.04	2.27	30	0.765	0.873	0.979
3.75	1.17	2,07	15	0.798	0.896	0.969
7.5	1.51	1.12	11	0.784	0.88	0.916
11.25	2.01	085	9	0.816	0.803	0.935

Figure 1: Effect of binder compositions on the drug release profile from matrix tablets; (binder concentration. in the tablet %w/w): 0.75% (▲), 3.5% (■), 7.5% (○) and 11.25% (●)

Discussion

The aqueous dispersion of the AMA at various concentrations employed in the study were non-viscous fluids, yet they were effective binders forming hard tablets with low friability tendency even at low binder composition of 0.75% w/w. This finding suggests that the AMA copolymer imparted plasticity to the tablet formulations. The AMA thus promoted the plastic deformation of the particles during compression with subsequent formation of solid bonds in the tablets. A plastic material will deform readily without fracture under an applied load, thus increasing the area of particle-particle contact during tableting. Thus the increase in plasticity as the binder content increased accounted for the increase in tablet hardness and the decrease in their friability.

The tablets did not disintegrate throughout the time course of the disintegration and dissolution tests. Drug release was therefore due to slow diffusion of dissolved drug molecules via aqueous filled channels in the polymeric matrix. The decrease in dissolution rate with increase in polymer content of the matrix tablet can be associated with increase in the totuorsity of the diffusion path length as more polymer strands are now involved in the formation of the polymeric matrix. The systems displayed a Higuchi release kinetic, the amount of drug release being linearly related to the square root of time. Such systems are usually characterized by an initial zone of depletion, i.e. the surface layers are depleted of their drug content due to rapid leaching into the dissolution medium. The depletion zone will recede inwards in the course of the dissolution experiment, with the implication that the diffusion pathlength for the drug molecule increases with time. This increase in diffusion pathlength accounted for the decreasing release rate with time generally in the course of the dissolution experiment.

Conclusion

Hitherto, the AMA copolymers have been used as drug release retardants by spray coating of drug particles with organic solution of the polymer or by formation of drug – polymer coacervates [15-16], followed by compression to matrix tablets. Results of the present study have shown that simple granulation of drug powder with aqueous dispersions of the water – insoluble copolymer is a less expensive, less complicated method of obtaining retard release. The release rate from such systems can be controlled by variation in the polymeric binder content in resulting matrix tablets.

Acknowledgement

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