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STUDIES ON THE RELEASE OF OXOLAMINE CITRATE FROM MATRIX TABLETS PREPARED WITH EUDRAGIT®

EUDRAGIT® İLE HAZIRLANAN MATRİKS TABLETLERDEN OKSOLAMİN SİTRAT SALIMI ÜZERİNDE ÇALIŞMALAR

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The release of oxolamine citrate (OXC) from matrix tablets prepared with direct compression and wet-granulation method was evaluated. Eudragit® RS PM as polymer was used. The release of drug from matrix tablets prepared at different drug-polymer ratios (1:0.5, 1:0.75, 1:1, 1:1.5, 1.2) was examined using USP rotating paddle dissolution method. Drug-polymer ratio was found to be effective on the release of oxolamine citrate from matrix tablets. The matrix tablets prepared with direct compression technique released the drug faster than the matrix tablets prepared with wetgranulation method. Since the granules of matrix tablets at the highest drug-polymer ratio (1:2), were not clamped to each other during the production of the tablets, they release the drug rapidly by disintegrating in the dissolution medium. It was also observed that the release rate of oxolamine citrate could be decreased by heating the matrix tablets prepared both by direct compression an wet-granulation method in an oven at 150°C for five minutes.

Bu çalışmada oksolamin sitrat'ın direkt basım ve yaş granülasyon yöntemiyle hazırlanan matriks tabletlerinden salım kinetiği incelendi. Polimer olarak Eudragit RS PM tipi kullanıldı. Farklı ilaç-polimer oranlarında (1:0.5, 1:0.75, 1:1, 1:1.5, 1:2) hazırlanan matriks tabletlerden oksolamin sitrat salımı USP XXII palet metoduyla incelendi. Söz konusu matriks tabletlerden salım hızında ilaç-polimer oranının etkili olduğu gözlendi. Direkt basım ile hazırlanan matriks tabletler yaş granülasyon yöntemi ile hazırlananlara göre çok daha hızlı olarak etken maddeyi saldı. Yüksek ilaç-polimer oranında (1:2) matriks tabletlerin granülelerinin iyi kenetlenmemesinden dolayı diğer 4 ilaç-polimer oranından farklı olarak polimer içeriğinden bağımsız bir şekilde hızlı salım elde edildi. Hem direkt basım hem de yaş granülasyon yöntemiyle hazırlanan Eudragit matriks tabletlerin ısıtılıp daha sıkı kenetlenmesiyle oksolamin sitratın salım hızının değiştirilebileceği gözlendi.

Introduction

Matrix tablets can be made in two principle ways from acrylic resins, namely by granulation or by direct compression. Neutral poly(meth) acrylic acid esters are pharmacologically inactive. Pharmacologically active substances can be embedded in water-insoluble polymers as a means of retardation, e.g. by tabletting together with polymer powder or by extrusion at the softening temperature of the polymers in the range of 120-200°C. Poly(meth)acrylates are used mainly to regulate the drug release.

There are many kinds of poly(meth)acrylates (Eudragit®) which are used for different aims. Eudragit® RS PM (PM=powder masses) is used for delayed-release porous matrix structures. Eudragit® RS PM is a powder of medium finess which is intended for direct incorporation into drug formulations and has low permeability. Its swelling characteristics and permeability are unaffected by the pH conditions. Its field of application is a filler for embedding active substances in the construction of matrix structures-so-called depot or rated formulations(1). Oxolamine

[1] Correspondence

citrate (OXC) known as one of the synthetic derivatives of 3,5-disubstituted-1,2,4-oxadiazole, is used particularly for its antitussive activity. The usual dose of the drug is 200 mg given four times daily. Its use was limited by side-effects as nausea and vomiting(2). There is no sustained release dosage form of OXC in market and the number of studies are also limited (3). The aim of this study was to prepare the matrix tablets of oxolamine citrate using Eudragit® RS PM at different drug-polymer ratios and to investigate the effect of content of active substance on the release rate. The effect of direct compression, wet-granulation methods and heating of the prepared matrix tablets on the realese of the drug were also researched.

Materials and Methods

1- Preparation of marix tablets

Sustained release matrix tablets of OXC were formulated at different drug-polymer ratios (1:0.5, 1:0.75, 1:1, 1:1.5, and 1:2). Direct compression and wet granulation methods were employed. In the wet granulation method acetone was used as solvent. Tablets containing 100 mg oxolamine citrate were compressed in 9 mm diameter. No diluents an lubricants were used when compressing the matrix tablets. Then, some of the matrix tablets prepared with wet-granulation method were heated in an oven at 150°C for five minutes in order to investigate the effect of heating process on the release of OXC.

2- In vitro release of OXC from matrix tablets

The manufactured matrix tablets were tested for dissolution rate in 500 ml of 0.1 N HCl by using the USP XXII paddle method at 50 rpm. Since OXC is more stable in acidic medium, 0.1 N HCl was used as the dissolution medium (4,5). Samples withdrawn at appropriate time intervals were filtered and assayed using a UV-visible spectrophotometer (Shimadzu Double-Beam UV-150-02) at 239 nm.

Results and Discussion

The results of drug percent of the matrix tablet formulations, prepared with wet-granulation method, concerning different drug-polymer ratios are given in Table 1. Hardness of the tablets (except 1:2) were within the range of 4.25-6 kg according to Monsanto hardness tester. The mean dissolution profiles of these formulations of sustained release matrix tablets are shown in Fig.1. Where the release rates from the matrix tablets were proportionally related with drug-polymer ratio. When the drug percent in the matrix tablet decreases, the release rate decreases. For the matrix tablets prepared at 1:2 drug-polymer ratio, since the tablets could not be compressed in sufficient hardness (3.5 kg), the granules could not clamp to each other. In these tablets, the dissolution rate was as fast as the matrix tablets prepared with 1:0.5 drug-polymer ratio. Here, whole drug was released in four hours. The dissolution period of 8 hours was obtained only by using the matrix tablets prepared at 1:1 and 1:1.5 drug-polymer ratios.

Table 1. Drug contents of the matrix tablets formulated with wet-granulation method at different ratios and *direct compression technique at 1:1 ratio.

Drug-polymer ratio	Drug content %±SD	
	Predicted	Observed
1:0.5	66.6	64.3±0.105
1: 0.75	57	53.2±0.38
1:1	50	49±0.285,*51±0.24
1:1.5	36.7	33.8±0.145
1:2	33.3	34±0.263

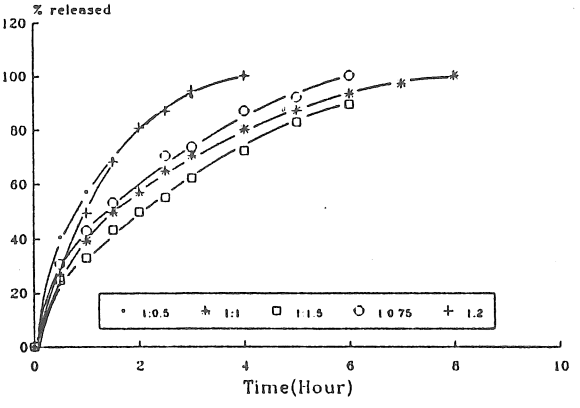

Fig.1. The dissolution plots of the OXC matrix tablets prepared at different drug-polymer ratios

On the other hand, a linear relationship between the logarithm of the released amount of the drug from the matrix tablets and the drug percent was observed (Fig 2). We have tried to form a general equation including the drug content, percentage release and time, which could allow us the estimation of the drug contcent to be calculated for a desired dissolution time. The equation obtained by using Minitab 5.1 statistical analysis package programme was; ($r^2 = 0.97$)

log%release=1.29+0.00678(drug content%)+0.474log t

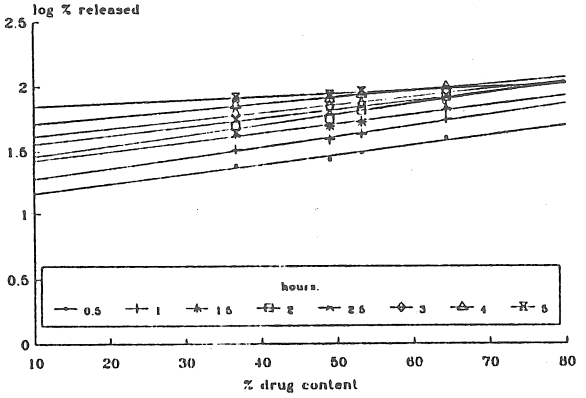

Fig.2. The relationship between the logaritm of the released amount of OXC and drug content in the matrix tablets

Using this equation, for each dissolution time intervals, release percentage of drug was calculated and thus the predicted results were compared with the observed ones. A good correlation was found between these results (Fig.3).

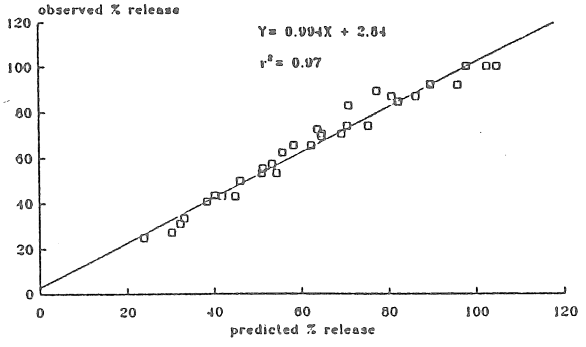

Fig.3. The correlation between the observed and predicted results

The matrix tablets which were prepared at 1:1 drug-polymer ratio by applying direct compression and wet granulation were compared and it was found that the release rate from the matrix tablets prepared with direct compression was faster. Almost whole drug in the tablet was released in one hour by disintegrating, the release time corresponding to the tablets prepared with wet-granulation was about 8 hours and these tablets did not disintegrate. But, when the matrix tablets prepared at 1:1 drug-polymer ratio with direct compression technique was heated for 5 min. in an oven, the release time of OXC was observed to prolonge. The tablets did not disintegrate like the matrix tablets prepared with wet-granulation method(Fig.4).

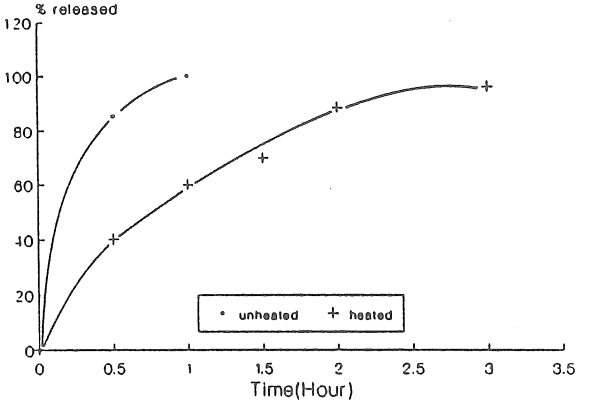

Fig.4. The effect of heating on the release of OXC from the matrix tablets prepared at 1:1 drug-polymer ratio with direct compression technique

In this study, it was also thought to heat the formulated matrix tablets in an oven for a short time. Firstly, the stability of OXC at 150°C for five minutes was carried decrease of the pore diameter in the matrix tablets could be investigated. For this aim, the matrix tablets prepared at 1:0.5, 1:1 and 1:2 drug-polymer ratios by using wet-granulation method and the matrix tablets prepared at 1:1 drug-polymer ratio by using direct compression were kept in an oven of 150°C for five minutes. After this process, it was observed that the matrix tablets clamped more firmly. Although the matrix tablets prepared with direct compression

method released the drug in one hour by disintegrating, after heating process, the matrix tablets were observed to remain as intact during dissolution studies. In addition, the release rates from the heated matrix tablets were observed to decrease significantly. It was observed that the matrix tablets formulated at 1:2 drug-polymer ratio with wet-granulation and being at unsufficient hardness were also clamped firmly after heating. They released about 63 percent of the drug in 7 hours due to softening of Eudragit® RS PM after the heating process. The plots of these findings are shown in Fig. 5.

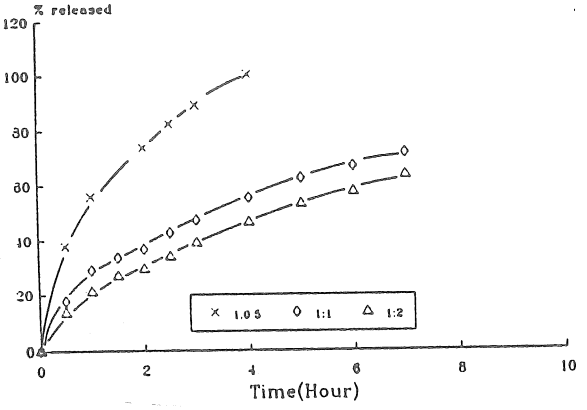

Fig.5. The effect of heating on the release of OXC from the matrix tablets prepared at different drug-polymer ratios with wet-granulation method

As a result, the present study indicates that the release time of OXC from the matrix tablets prepared by using Eudragit® RS PM can be prolonged and by heating the formulated matrix tablets, the release rate can be changed significantly and also by using the proposed equation describing the desired release time, experimental desing can be made.

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