Pakistan Journal of Pharmacol. ISSN 0255-7088
Vol. 15(2), July 1998, pp.57-63

RELEASE KINETICS OF SALBUTAMOL SULFATE FROM HPMC BASED SUSTAINED RELEASE MATRIX: I EFFECT OF CETYL ALCOHOL AND BEES WAX

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ABSTRACT

In order to search better combination of water insoluble waxy materials with hydrophilic polymer, investigations have been carried out using cetyl alcohol (CA) and bees wax (BW) as additives to the hydrophilic polymer, HPMC. They were added in increasing amount (up to 40% of the waxy materials) to the HPMC based sustained release (SR) matrix tablets. Excellent correlation was found between the concentration of waxy materials and salbutamol sulfate (SS) release rate. Release pattern of SS from HPMC-CA combination matrics were found zero order and the release rate of SS decreases linearly with the increase in the concentration of CA in the matrics. On the other hand, release pattern of SS from HPMC-BW combination matrices were found to be bi-phasic. The first phase release was initially rapid, however, the extent of release both in the first and second phase were reduced with the increase of the BW concentration.

INTRODUCTION

Controlled release (CR) technology is being actively explored in the pharmaceutical industry due to its therapeutic, economic, and commercial advantages (Haan & Lerk, 1984). A matrix may be formed simply by compressing or fusing the drug and the matrix material together. Microfine pores within insoluble matrix effectively inhibits the passage of drug from the matrix to the depot fluid. The matrix tablet which incorporates the active ingredient in an inert material matrix has been well known to act as an effective sustained release medicament (Lazarus & Cooper, 1961).

It was found that the choice of matrix material, amount of drug incorporated in matrix, the hardness of the tablet, density variation and tablet shape could markedly effect the release rate of drug (Captan, 1989). Several other workers (Desai et al., 1965; Farhadieh et al., 1971) also reported that the rate of drug release from matrix is affected by the composition of the matrix, shape, pH of the dissolution fluid, drug solubility, external agitation, mass of drug and the porosity of the matrix. The objective of this research was to observe the influence of different concentrations of CA & BW in hydrophilic polymeric matrix tablets on the kinetics, rate and mechanism of drug release.

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EXPERIMENTAL SECTION

Materials and equipments:

Salbutamol Sulfate (Sigma), Cetyl alcohol (BDH, U.K.), Bees wax (BDH, U.K.), Hydroxy propyl methyl cellulose (HPMC 50 cps, Shin - Etsu chemical, Japan), Magnesium Stearate (BDH, U.K.). All other chemicals were of reagent or analytical grade. Electrolab Tablet Dissolution Tester U.S.P. (XXI) TDT-06, for dissolution, a mini drum mixer for mixing purpose, a double beam digital spectrophotometer SP8-400 PYE UNICAM for absorbance and Perkin- Elmer compressor machine for compression.

METHODS

Preparation of matrix tablet:

Thirteen batches of matrix tablets were prepared for this study. In batch A, waxy materials were not used for matrix formulation. CA and BW were used for matrix formulation in the batches C1 to C6 and B1 to B6 respectively. In batch A, SS and HPMC matrix tablets were prepared simply by dry mixing and compression in a Perkin-Elmer hydraulic press at 6 tons compression pressure. For the preparation of HPMC based matrix tablets containing BW, the batches B1-B6, SS was mixed well with HPMC in a container. In another container, BW was taken and heated on a Hot-Plate just o melt the wax. The mixer of the drug and HPMC was then just to melt the wax. The mixer of the drug and HPMC was then incorporated into the molten wax and mixed well while hot and finally cool. Congealed mass was then passed through sieve (mesh # 20) to obtain granules. The prepared granules were compressed to matrix tablets in a Perkin-Elmer hydraulic press at 3 tons pressure. Magnesium Stearate was used as lubricant for the matrix tablets preparation. The same procedure was followed for the preparation of matrix tablets containing CA instead of BW in the batches C1-C6. The amounts of each ingredients are shown in the table 1.

Dissolution studies

The dissolution studies were carried out using 6 matrix tablets from each formulation using a "Electrolab Tablet Dissolution Tester USP (XXI) TDT-06". One litre of distilled water was used in each vessel as dissolution medium. The temperature of dissolution medium was set at $37^{\circ} \pm 2^{\circ}C$ and paddle rotation was set at 100 rpm. Time was recorded as soon as the tablets were put into dissolution vessels. 5 ml sample solution were withdrawn from each vessel at time to time (5, 10, 20, 30, 40, 60, 120, 150, 180, 210, 240, 270, 300, 330 and 360 min) for analysis and were replaced with freshly prepared distilled water. The dissolution study was carried out for 240 minutes for cetyl alcohol and 360 minutes for bees wax.

Drug content of the sample solution, i.e. the quantity of drug released, was determined by spectrophotometric analysis at the absorbance measured at 276 nm using a Pye-Unicam SP8-400 spectrophotometer. Distilled water was used as a blank. The average value of absorbance was used for data analysis.

RESULTS AND DISCUSSIONS

It was found that drug release from matrix tablets containing CA followed zero order mechanism (fig. 1) and it also showed that the release of drug was highest in the absence of CA. When the percent of CA was slowly increased, the release of drug from the hydrophilic matrix tablets became slowly decreased. This was due to the tacky nature of the hydrophobic character of CA. CA prohibits the wetting and penetration of the dissolution fluid into the hydrophilic matrices. It has been reported that the drug-wax combinations are strictly physical and the release of the drug from the waxy matrix is influenced by the hardness and composition of the core and drug particle size (Schroeder et al., 1978).

The release of SS from the matrix tablets containing BW was found bi-phasic, with an initial large and fast release followed by a much slower release (fig. 2). The initial phase of release was very rapid and the quantity of drug release decreased with an increase of BW concentration. The quantity of drug released in this phase was due to greater diffusion of drug from the vicinity of tablet surface, where wetting and dissolution took place from a very large surface area. At lower concentration of BW, the initial phase release was highest. But with an increase in BW concentration the wetting and penetration of dissolution fluid into the matrix became slowly impeded. The time for initial phase was only 40 minutes.

Time required for 50% release of drug from all matrixes were calculated from fig. 1 and fig. 2 and when these values were plotted against percentage of waxy materials, a straight line was obtained in case of CA, but in case of BW a non linear curve was found as shown in fig. 3.

Release rates of drug from all matrices were calculated from the slope values of fig. 1 and fig. 2 and the values were plotted against percentage of waxy materials as shown in fig. 4 which showed a decrease in release rate with the increase of CA. It indicated that the drug release from hydrophilic matrices was influenced by the hydrophobic nature of the CA. But in case of BW when release rates of the 1st phase were plotted against percentage of BW it indicated a linear decrease in release rate with the increase of BW in the hydrophilic matrices. Similarly when the release rate value of the 2nd phase was plotted against BW concentration it showed that drug release from the hydrophilic matrices gradually impeded by the drug release from the

hydrophilic matrices gradually impeded by the hydrophobic nature of the BW, thereby reducing the diffusion and subsequent dissolution of the drug in to the bulk. The reason behind this bi-phasic pattern may be due to the number of drug-HPMC granules and the percentage of BW. With the increase of BW more surface area of the granules was covered and hence gradual decrease of release rate was observed upto the end point of 1st phase. The drug release in this phase occurred through both uncovered and covered surface of the granules. Complete covering of the granule surfaces abruptly change the release pattern producing 2nd phase, since drug was released only by diffusion through the waxy film around the granules. Further increasing the concentration of BW makes the film of surface uniform and thicker which slowly reduces the release of the drug from the matrices.

When percent release of drug in first phases of both cases were plotted against percentage of waxy materials as shown in fig. 5, it was found that the percent release of the drug was linear with the percentage of the CA. But in case of BW the drug release was more or less same upto 25% of BW and further increase of BW substantial reduction of the drug release was observed.

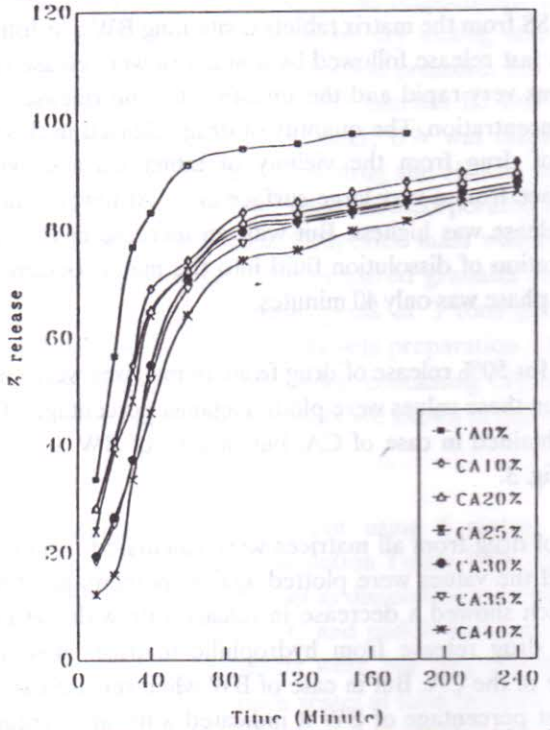

Fig. 1: Zero order plot of SS release from CA & HPMC combination matrices. SS = Salbutamol Sulfate, CA = Cetyl Alcohol, HPMC = Hydroxy Propyl Methyl Cellulose.

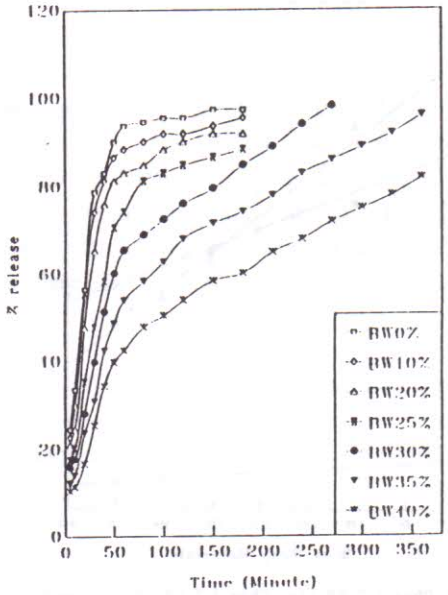

Fig. 2: Zero order plot of SS release from BW & HPMC combination matrices. BW = Bees Wax.

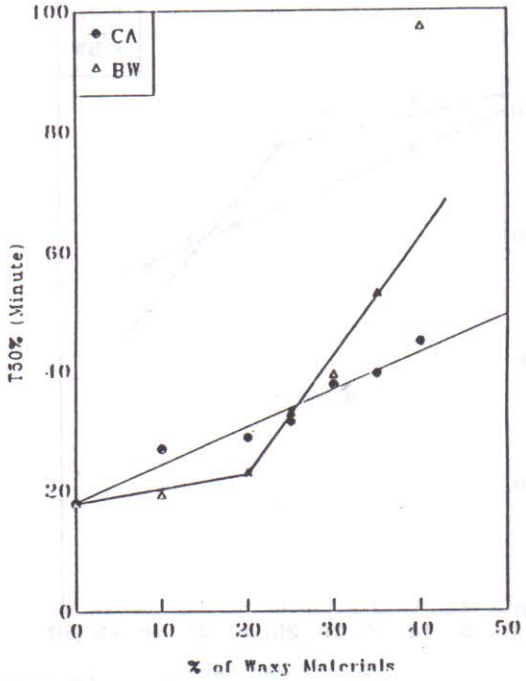

Fig. 3: A plot of T50% release of SS from CA & BW matrices.

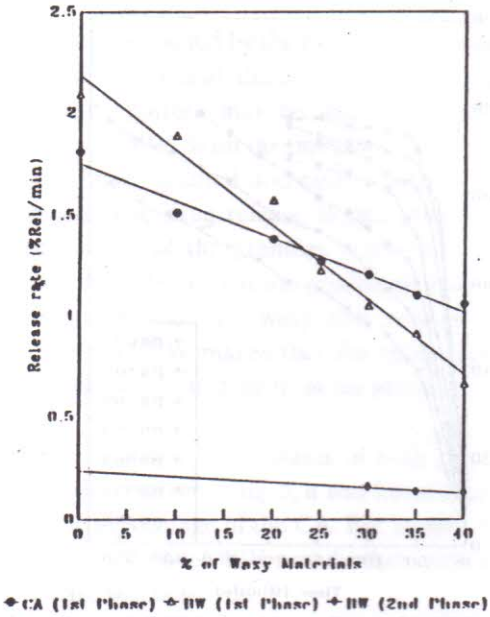

Fig. 4: Zero order release rate plot of SS from CA & BW matrices.

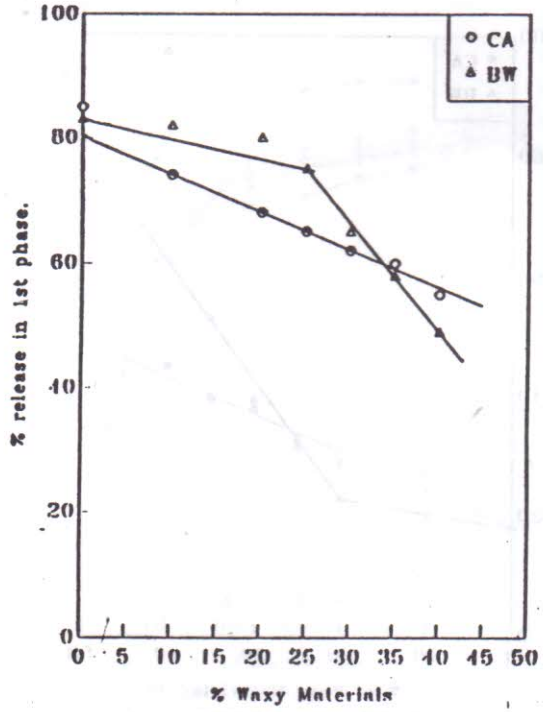

Fig. 5: A plot of percent release of Salbutamol sulfate in first phase from cetyl alcohol and bees wax matrices.

CONCLUSION

Matrix tablets were prepared with an aim to study the release kinetics of SS and the effect of BW and CA on the HPMC based matrices. With the addition of hydrophobic waxy materials (BW & CA) to the hydrophilic polymers (HPMC) a substantial reduction of release rate was occurred. The release mechanism followed zero order and bi-phasic pattern and the observed result indicates that this technology could be used to formulate SR matrix tablets.

Table 1
Proportion of each ingredients in different batches of matrix tablets

Batch no.	Amount of SS (mg)	Amount of HPMC (mg)	Amount of CA (mg)	Amount of BW (mg)
A	10	90	0	0
B1	10	80	0	10
B2	10	70	0	20
B3	10	65	0	25
B4	10	60	0	30
B5	10	55	0	35
B6	10	50	0	40
C1	10	80	10	0
C2	10	70	20	0
C3	10	65	25	0
C4	10	60	30	0
C5	10	55	35	0
C6	10	50	40	0

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