RESEARCH PAPERS

Accepted 17 August 1997
Received 26 November 1996
Indian J. Pharm. Sci., 1997, 59(6)pp. 312-315

Formulation of Multilayered Sustained Release Tablets using Insoluble Matrix System

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In an attempt to provide sustained release of ephedrine hydrochloride, the multilayered tablet concept was utilized having a loading dose of 20 mg and a maintenance dose of 40 mg formulated in an insoluble matrix system. Several formulations having ethyl cellulose and Eudragit RS 100 were tried. Eudragit RS 100 alone did not yield good results. However, a combination of ethyl cellulose and Eudragit RS 100 retarded the release considerably. Drug release from all the tablets followed first order kinetics.

SUSTAINED release dosage forms are becoming popular as these have a number of advantages over conventional preparations viz., reduction of the dosing frequencies, less fluctuations in circulating blood levels, increased patient compliance and more uniform effect. For sustained release systems, the oral route of administration has received the most attention[1].

Several approaches are available to add the loading dose to the maintenance dose such as simple addition of a non-sustained dose of a drug to the sustained portion and placement of initial dose in a tablet coat with the sustaining portion in the core, as in compression coated tablets.

An alternative approach for having the loading dose had maintenance dose in a tablet is the formulation of drug in a multilayered tablet system. This multilayered approach is a convenient method in that it contains the loading dose sandwiched between two outer matrix layers. The central layer releases the dose required for immediate onset of action whereas the matrix layers release the drug in a sustained manner, which helps to maintain the blood level initially reached. Thus the multilayered tablet appears to be an ideal method for achieving sustained release of drugs.

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Ephedrine hydrochloride, a sympathomimetic amine which is used in the treatment of bronchial asthma, has a half life of about 3-6 hours. The usual dose of ephedrine hydrochloride is 15-60 mg to be taken 3 to 4 times a day. Thus, it was thought that developing a sustained release multilayered tablet of ephedrine hydrochloride would eliminate some of the problems such as frequent dosing, patient compliance and fluctuations in circulating blood levels, which are associated with conventional tablet dosage forms. Hence a systematic study comprising the formulation and release pattern of ephedrine hydrochloride from multilayered tablet was taken up.

Materials and Methods

Ephedrine hydrochloride IP (Hansa Chemical Works, Bombay), ethyl cellulose (Robert Johnson, Bombay), dicalcium phosphate (Sarbhai Chemicals, Bombay). Eudragit RS 100 (Rohm Pharma, Germany) and ethyl alcohol (locally distilled) were used through out the study.

Production of tablets:

Direct compression:

The raw materials were first passed separately through sieve #80. Then the required amount of each ingredient was weighed accurately. They were then

Table-1: Tablet formulations showing the outer : inner layer ratios of different excipients

	Formulation A		Formulation B		Formulation C		Formulation D		Formulation E		Formulation F		Formulation G		Formulation H	
	Outer layer mg	Inner layer mg	Outer layer mg	Inner layer mg	Outer layer mg	Inner layer mg	Outer layer mg	Inner layer mg	Outer layer mg	Inner layer mg	Outer layer mg	Inner layer mg	Outer layer mg	Inner layer mg	Outer layer mg	Inner layer mg
Ethyl cellulose	60	10	70	10	80	10	90	10	100	10	50	10	60	10	70	10
Ephedrine HCl	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Dicalcium Phosphate	-	110	-	90	-	70	-	50	-	30	-	70	-	70	-	70
Eudragit RS 100	-	-	-	-	-	-	-	-	-	30	-	20	-	10	-	-
Av. Wt.	0.300 g		0.300 g		0.330 g		0.300 g		0.330 g		0.260 g		0.270 g		0.280 g	

Hardness - 8 kg/sq. cm for all formulations

mixed thoroughly in geometric progression one after the other. After mixing, the powders for individual layers were packed separately, with each layer calculated to contain 20 milligram of ephedrine hydrochloride, that is 20 milligram of ephedrine hydrochloride from central layer for loading dose and 40 milligram of ephedrine hydrochloride from two outer layers for maintenance dose.

Wet granulation:

The raw materials were first passed separately through sieve number 80. Calculated amounts of ethyl cellulose and ephedrine hydrochloride were weighed accurately and transferred to a China dish. Ethyl alcohol was added dropwise till the powder acquired a dough like consistency. It was then air dried till the ethyl alcohol evaporated off and sieved. Then Eudragit RS 100 was weighed accurately and mixed with the granules formed. After thorough mixing, the granules for each layer were packed separately with quantity equivalent to 20 milligram of ephedrine hydrochloride.

Tablet compression:

The tablet compression was carried out in a single punch tablet compression machine. Individually packed layers were introduced directly into the itself, with the lower layer first, then the middle layer and finally the upper layer. After adding each layer, a slight pre-compression was made so that the layers were uniformly distributed. After the final layer was added, a final compression was made. Hardness was adjusted to the requirements that is 8 kg/sq cm. Tablets of different formulations (Table-1) were prepared as mentioned above.

Dissolution Studies

In the dissolution study, the paddle method[2] was followed for studying the release pattern in order to suit the UV sensitivity of the drug.

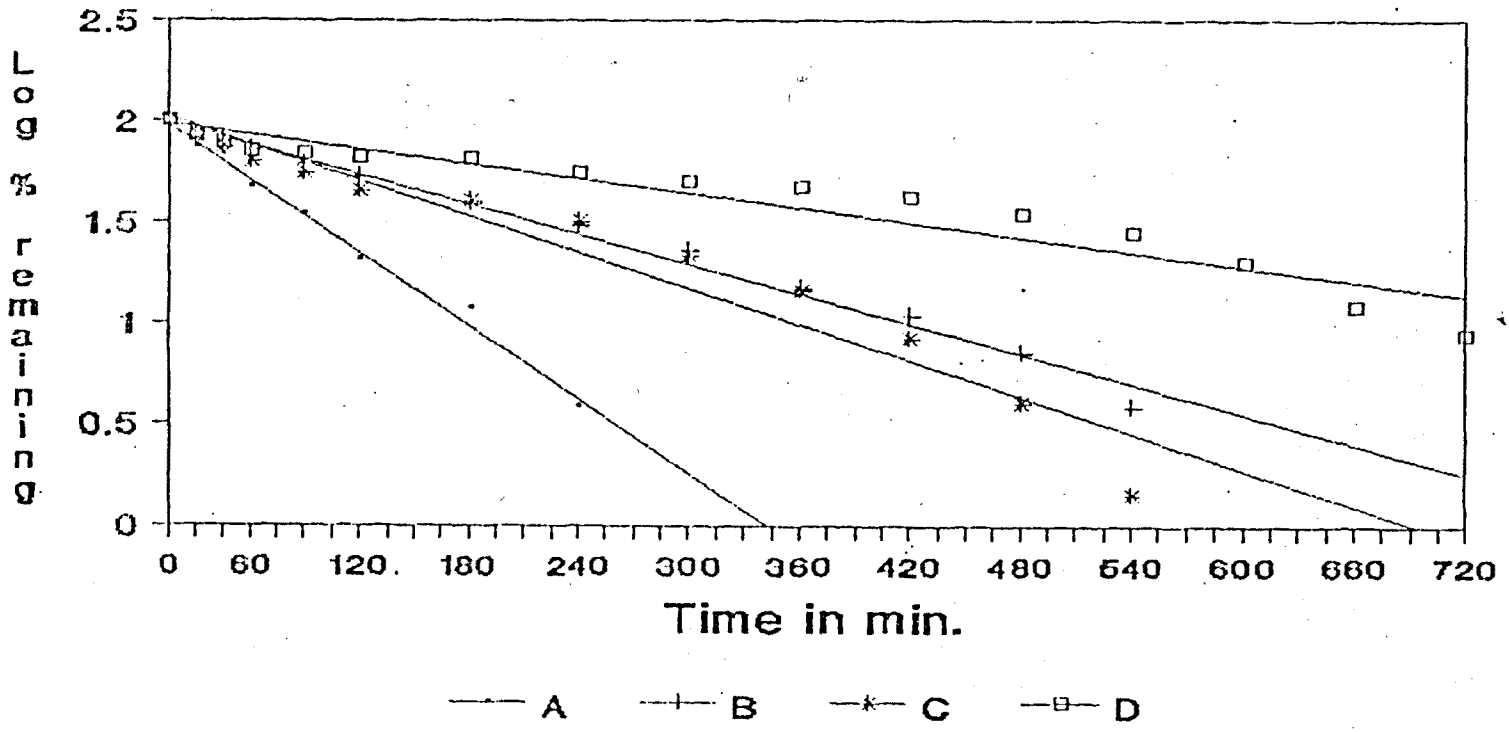

Fig. 1: Release of Ephedrine HCl from Formulation, A, B, C and D

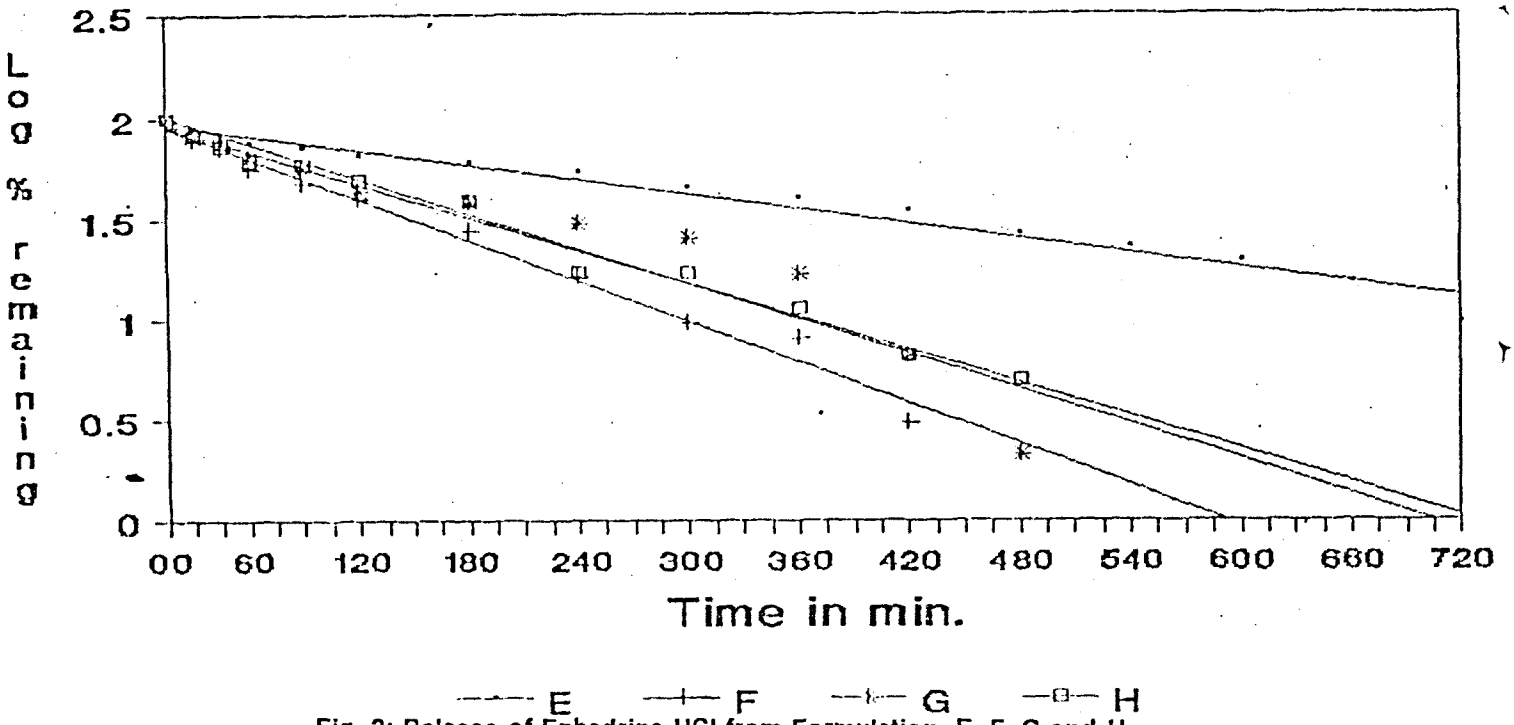

Fig. 2: Release of Ephedrine HCl from Formulation, E, F, G and H

RESULTS AND DISCUSSION

In an attempt to provide sustained release of ephedrine hydrochloride, the multilayered concept was utilized having a loading dose of 20 mg and a maintenance dose of 40 mg formulated in an insoluble matrix system. In this study, several formulations having ethyl cellulose and Eudragit RS 100 were tried, and those which sustained the drug release atleast for 3 hours and above were taken for further investigation.

Tablets prepared were flat faced having three distinct visible layers. Even after complete release of drug (12 hours), the tablets retained their shape. Friability remained within 0.75% to 1% showing that the tablet can withstand the mechanical shock during shipment and usage.

In case of direct compression technique with ethyl cellulose as the matrix material, it was observed that the release rate was generally inversely proportional to the drug: ethyl cellulose ratio. A total of five formulations were made with drug: ethyl cellulose ratio of 1:3 to 1:5. At and above 1:4.5, the release was extended to 12 hours and more.

In the case of Eudragit RS 100, direct compression method was not successful and even at a drug : matrix ratio of 1:4, complete release was observed within 2 hours. Granulation of the matrix with ethyl alcohol was also tried for these formulations without any significant improvement of the results. So the study with this material alone was abandoned.

Combinations of ethyl cellulose and Eudragit RS 100 in various ratios were tried with direct compression but did not yield encouraging results. So the drug was granulated with alcoholic solution of ethyl cellulose as granulating agent and Eudragit RS 100 was then mixed with these granules and compressed. By this method, the release was considerably retarded compared to the previous methods. Several formulations were prepared containing different ratios of ethyl cellulose and Eudragit RS 100. Drug release was extended over a period of 9 hours with these formulations.

The dissolution rate studies were carried out in distilled water only, since there was not much variation in the drug release in the three media tried that is distilled water, pH 1.2 buffer and pH 7.4 buffer. However, definite conclusion could not be drawn as further investigations are in progress.

Drug release from all the tablets followed first order kinetics. This was observed from the plot of Log % drug remaining vs time. It shows a straight line (Figure 1 and 2).

From the data, this appears to be a good technique for prolonging the release of highly water soluble drugs.

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