

An Investigation into the Effect of Carbopols on the Release of Propranolol HCl from Tablet Matrices

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Abstract

In this study, attempts were made to evaluate the effect of various acrylic acid based Carbopols on the release profile of a beta-adrenoreceptor blocking drug, propranolol HCl, from matrix-type tablets invitro. For this purpose, tablets containing 160 mg of propranolol HCl along with various amounts of Carbopols 934 (C934), 971 (C971), 974 (C974) and Pemulen (Pem) were prepared using the wet granulation technique. Tablets prepared were placed in a USP apparatus I dissolution tester containing a pH 1.5 HCl solution for the first 2 h of this study and a pH 6.8 phosphate buffer for the next 10 h of the study. The amount of drug released was determined using the constructed calibration curves at 289 nm, using a uv-visible spectrophotometer. The results showed that tablets containing Pem are unsuitable for preparing tablets with desirable drug release profiles. In contrast, C971, C974 and C934 were all found to be suitable for this purpose at concentrations of 14, 16 and 12%, respectively. Tablets containing C971 were found to have the slowest profile of drug release, while C934 containing tablets had the greatest drug release profile among the Carbopols investigated. Hence, Carbopols 971, 974 and 934 are found to be suitable, when used alone, for the preparation of propranolol HCl hydrophilic matrix-type tablets.

Keywords: Propranolol HCl; Sustained release tablets; Carbopols; Drug release; Hydrophilic matrices.

Introduction

Propranolol HCl is a beta-adrenergic blocking drug, which is widely used in the treatment of cardiovascular diseases, particularly in the treatment of weak and moderate hypertension, angina pectoris, ventricular arrhythmia, hypertrophic subaortic stenosis, etc. (1-4).

Incorporation of propranolol HCl within tablet matrices containing a suitable polymer can form a slow release formulation, capable of releasing its drug content over an extended period of time. Among the various polymers which can be used in the preparation of such systems, are Carbopols. These polymers are long chains containing acrylic acid as the

monomer. Carbopols are white, hygroscopic and fluffy powders, which are amongst hydrophilic polymers. Among the most widely used and well known Carbopols are Carbopols 934, 974, 971, Pemulen and Polycarbophil (5-7). Because of the presence of acrylic acid moiety within Carbopol structure, it has an anionic and acidic nature, and hence is highly pH dependent.

Oral slow and sustained release drug delivery systems can release their drug content with a controlled manner, producing a desirable blood serum level which has little or no fluctuation, hence reducing the occurrence of drug toxicity and also improving patient compliance by prolonging dosing intervals (8-11).

Sustained release drug delivery systems can release their drug content via different

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mechanisms such as diffusion, dissolution, erosion, etc., usually producing a zero order or Higuchi model of drug release (12). Care must be taken to formulate a dosage form which can maintain a uniform blood concentration profile within the therapeutic window of the drug.

Various methods could be used for the preparation of oral sustained release dosage forms. Among these methods, the use of hydrophilic polymeric matrices is popular. The polymer used absorbs water from the surrounding medium, resulting in the formation of a swollen barrier which will gradually dissolve or erode, and through which drug molecules will be released (8). As mentioned before, Carbopols belong to this group of polymers.

Previous studies have been aimed in the use of hydrophilic matrices containing hydroxypropylmethyl cellulose, hydroxypropyl cellulose, or their combination with hydrophobic polymers such as ethyl cellulose for the preparation of sustained release matrix-type formulations and in particular propranolol HCl (13-20).

In this study, attempts were made to investigate the effect of Carbopols on the release of propranolol HCl from tablet matrices invitro.

Experimental

Materials

Propranolol HCl powder was purchased from Tolidaru Pharmaceutical Co., (Tehran, Iran). Various Carbopols including Carbopol 934 (C934), Carbopol 971 (C971), Carbopol 974 (C974) and Pemulen (Pem.) were obtained from B.F. Goodrich Co., (U.K).

Microfine cellulose (Elcema 100) was obtained from Degussa-Via Co.; polyvinylpyrrolidone (K-25) from ISP Technologie Inc.; chloroform, hydrochloric acid and phosphate buffer from Merck Chemical Co., (Germany). Talc powder and magnesium stearate were obtained as a gift by Tolidaru Pharmaceutical Co., (Tehran, Iran).

Methods

Preparation of tablets

Matrix-type tablets containing 160 mg of propranolol HCl powder along with various amounts of Carbopols C934, C974, C971 and

Pem were prepared by compression using a single punch tablet press, equipped with 9 mm shallow concave punches. In these studies the technique of wet granulation was used for the preparation of tablets. For this purpose chloroform was employed as the granulation solvent, and polyvinylpyrrolidone as the binder. The other inactive ingredients added to formulation for the preparation of tablets were microfine cellulose as filler and compression aid, talc powder as glidant and magnesium stearate as lubricant.

In order to prepare tablets, all the ingredients except magnesium stearate were passed through a 60 mesh sieve to obtain uniform particles. Next, they were completely mixed and granulated using a laboratory granulator equipped with a 1.25 mm sieve. Granules obtained were air dried at room temperature for 24 h, passed through a 35 mesh sieve and then a 60 mesh sieve, and finally compressed into tablets.

Construction of calibration curves

In order to determine the amount of drug released from tablets prepared, calibration curves of propranolol HCl in pH 1.5 hydrochloric acid and pH 6.8 phosphate buffer were constructed. For this purpose, solutions containing propranolol HCl in the range of 20-80 mg/l for pH 1.5 hydrochloric acid and 20-120 mg/l for pH 6.8 phosphate buffer were prepared and their absorbances were determined at 289 nm, using a uv-visible spectrophotometer. Both graphs were found to be linear and hence used to determine the amount of propranolol HCl released from tablets.

Drug release studies

The amount of propranolol HCl released from various tablet formulations prepared was determined using a USP apparatus I (rotating basket) dissolution tester set at 100 rpm and a temperature of $37 \pm 0.5^\circ\text{C}$. First of all, tablets were placed in 900 ml of a pH 1.5 hydrochloric acid solution for 2 h and 5ml samples were taken after 0.75 and 2 h, whilst keeping volume of the dissolution medium constant by replacing the volumes removed. After 2 h the dissolution medium was completely removed and replaced with 900 ml of pH 6.8 phosphate buffer solution. Again 5 ml samples were removed and the amount of propranolol HCl released, determined over a period of 10 h. The sampling

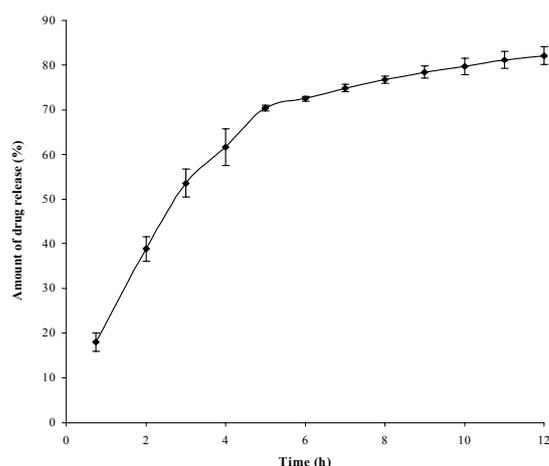


Figure 1. Propranolol HCl release profile from matrix-type tablets containing 14% C971 (n=3, mean \pm standard deviation).

interval was 1 h, and again the volume of the dissolution medium was kept constant throughout the study by replacing the 5 ml samples removed with equal volumes of pH 6.8 phosphate buffer.

Results and Discussion

Propranolol HCl is an important cardiovascular drug and the preparation of a sustained release formulation from this drug can be highly beneficial for patients using it.

As mentioned before, the use of hydrophilic polymeric matrices can provide a useful mean of retarding the release rate of drugs. Hence, this study was carried out to determine the effect of various acrylic acid based Carbopols, which are hydrophilic polymers, on the release of propranolol HCl from tablet matrices

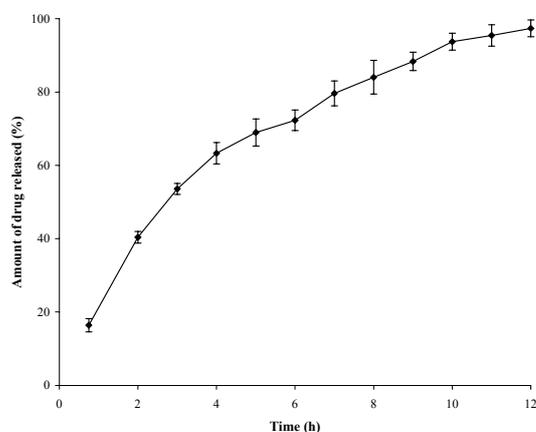


Figure 2. Propranolol HCl release profile from matrix-type tablets containing 16% C974 (n=3, mean \pm standard deviation).

containing various amounts of these polymers. In order to evaluate the amount of drug released at different time intervals, the monograph of extended release propranolol HCl capsules in USP (21) was used. The monograph of capsules was used since no monograph was mentioned in USP for its extended releases tablets. Based on this monograph, less than 30% of drug content (propranolol HCl) should be released after 0.75 h, 35-60% after 2 h, 55-80% after 4 h, 70-95% after 7 h and 82-110% after 12 h.

When investigating the influence of C971 on the release rate of propranolol HCl from tablet matrices, polymer concentrations ranging from 10-40% were used. At higher than 20% polymer content, the drug release rate was far too slow, falling outside the acceptable USP limits. On the other hand, at concentrations less than 10%, the release rate was too fast and tablets tended to dissolve quickly, making them unsuitable for use. Eventually it was found that tablets containing 14% C971 can provide desirable release profile (Figure 1).

Next, the effect of C974 on the release of propranolol HCl from matrix-type tablets was investigated. Tablets containing less than 12% polymer were found to release their drug content with a fast and undesirable rate. On the other hand, tablets containing more than 20% polymer were found to release their drug content too slow and again produced an undesirable drug release profile. A polymer concentration ranging from 15-18% was found to be suitable for producing a desirable drug release profile. Ultimately, tablets containing 16% C974 were found to produce the most suitable drug release profile (Figure 2).

When considering the effect of C934 on the release rate of propranolol HCl from matrix-type tablets, polymer concentrations less than 10% and over 15% were found to produce undesirable drug release profiles. Overall, polymer concentrations ranging between 12-15% were found to be suitable, capable of producing acceptable drug release profiles. Nevertheless, a C934 content of 12% was found to provide the best drug release profile and hence was chosen as the desirable formulation. The drug release profile obtained with this formulation (containing 12% C934) is shown in figure 3.

Finally, when examining the effect of Pem on the release rate and profile of propranolol

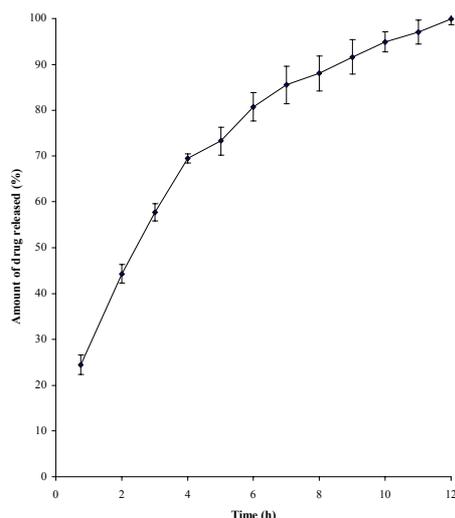


Figure 3. Propranolol HCl release profile from matrix- type tablets containing 12% C934 (n=3, mean \pm standard deviation).

HCl release, it was found that polymer contents above 15% resulted in relatively slow and unacceptable drug release profiles. Reducing the amount of polymer present within the formulation from 15% to 12% slightly improved the drug release profile, but still unsuitable in terms of the acceptable USP limits. Further reduction in the polymer content resulted in the formation of tablets with undesirable hardness, which disintegrated after a short period of time in the dissolution vessel. Hence, Pem was found to be unsuitable for use alone as a retarding agent for the preparation of matrix-type propranolol HCl tablets. However, it is possible that its use along with other Carbopols could provide a suitable base for drug release. Also, it should be noted that the use of Pem in quickly hydrating hydrophilic matrices could help to reduce their hydration rate, making them suitable as bases for sustained release formulations.

Overall, among the three Carbopols (C934, C971 and C974) found suitable for preparing matrix-type propranolol HCl tablets, C971 produced tablets with the slowest drug release rate over 12 h. On the other hand, C934 resulted in the fastest drug release rate among the three polymers studied. C974 containing tablets resulted in a drug release profile which was more than C971 containing tablets, but less than C934 containing tablets. Carbopols 971, 974 and 934 all contain acrylic acid as the monomer, but nevertheless, they have different chain lengths, cross-linking agents and

percentage of cross-linking agent. These rather important parameters could result in the differences observed in the drug releasing ability of these polymers.

The kinetic of propranolol HCl release from these tablets was also assessed. The kinetic models evaluated were zero order, first order and Higuchi model (drug release vs. $\sqrt{\text{time}}$). The results obtained by assessing the drug release profiles showed that over a period of 12 h, C934 containing tablets most likely follow a Higuchi profile of drug release ($r = 0.9906$). With the other two Carbopols (C971 and C974), the profile of drug release seems to be close to both the zero order (for C971 $r = 0.9888$ and for C974 $r = 0.9866$) and Higuchi model ($r = 0.9809$ for C971 and $r = 0.9861$ for C974). This means that the drug release profile could swing between these two models and does not follow a single distinct profile of drug release. Ideally, the profile of drug release is best to follow a zero order pattern. This is because a zero order pattern of drug release could minimize fluctuation within the blood serum levels of the drug. However, achieving a zero order pattern of drug release is not always easy to obtain and with a lot of sustained release oral tablet matrices, a Higuchi profile of drug release is obtained.

In conclusion, C971, C974 and C934 are found to be suitable, when used alone, as bases for preparing hydrophilic tablet matrices containing the drug propranolol HCl.

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