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Research paper

Controlled release of tramadol hydrochloride from matrices prepared using glyceryl behenate

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Abstract

An inert matrix to control the release of tramadol HCl was prepared using glyceryl behenate as a matrix-forming agent. The matrices were prepared by either direct compression of a physical mixture of the drug and the matrix-forming agent or by compression of granules prepared by hot fusion of the drug and the matrix-forming agent. The hot fusion method was found to be more effective than compression of physical mixtures in retarding the release of the drug from the matrix. Drug release was adjusted by using release enhancers, such as microcrystalline cellulose and lactose, and the results showed that higher release rates were obtained using lactose. However, the release of the drug was independent of the compression force and the pH of the dissolution medium. This study showed that glyceryl behenate is an appropriate waxy material that can be used as a matrix-forming agent to control the release of a water-soluble drug such as tramadol HCl. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Tramadol HCl; Glyceryl behenate; Lactose; Microcrystalline cellulose; Controlled release; Waxy material

1. Introduction

Waxy materials have major applications in sustained-release systems, especially for highly water-soluble drugs. Examples of waxy materials include hydrogenated oils, glyceryl stearates, fatty alcohols and microcrystalline wax. Such materials provide several advantages ranging from good stability at varying pH values and moisture levels to well established safe applications in humans. Matrix delivery systems utilizing waxy materials usually employ a core of drug embedded in the wax or a compressed physical blend of drug and matrix-forming agent. As the system passes through the gastrointestinal tract (GIT), the active ingredient is slowly released and absorbed [1]. Since they are water-insoluble and non-swellable, waxy materials have been introduced to eliminate the effects of food present in the GIT on the matrix tablets. These effects range from shearing the hydrated polymer gel layer leading to ‘dose dumping’ to blocking the pores of the matrix and inhibiting drug release [2].

Glyceryl behenate (Compritol®) is a waxy material, originally introduced as a lubricant in compressing tablets, which has recently had a wide application as a sustained-release agent [3]. It is commonly used as a lubricant and binding agent for tablets in concentrations of 1–3% and a sustained-release excepient in concentrations above 10%. A recent study by Barthelemy and coworkers [4] investigated the use of glyceryl behenate as a hot-melt coating agent to prolong the release of theophylline. Their study confirmed a satisfactory coating potential by this agent and a potential in sustaining the release of theophylline over an extended period of time.

Tramadol is a centrally acting analgesic with a low affinity for opioid receptors where it has selectivity for μ-receptors [5]. Its limiting side-effects in the treatment of acute and chronic pain are reported to be less intense and less frequent than with other opioids [6,7]. A slow drug delivery system is particularly suitable for the formulation of an analgesic agent. An evident advantage of such a formulation is the reduction in the frequency of administration while maintaining the analgesic effect, for example, overnight. Therefore, tramadol is a good candidate drug to be formulated in a sustained-release dosage form.

The objective of this study was to prepare oral controlled-release tramadol HCl matrix tablets utilizing a simple technique that uses glyceryl behenate as a matrix-forming agent and which would provide an extended duration of therapeutic effect with minimum potential for side-effects. We

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studied the release of tramadol HCl from matrices prepared using glyceryl behenate both by compression of granules prepared by hot fusion and direct compression of physical mixtures of the drug and glyceryl behenate. The effect of some release enhancers such as lactose and microcrystalline cellulose on the release of tramadol HCl was also investigated.

2. Materials and methods

2.1. Materials

Tramadol HCl was a gift from the Advanced Pharmaceutical Industries Co. Ltd. (Amman-Jordan). Glyceryl behenate (Compritol®) was obtained from Gattefosse Corp. (St. Priest, France). Lactose and microcrystalline cellulose (Avicel®) were from FMC Corp., USA. Freshly distilled and deionized water was used in all experiments. All materials were used as supplied without any further purification.

2.2. Methods

2.2.1. Preparation of matrices by hot fusion method

Glyceryl behenate was melted with continuous stirring in a porcelain dish on a water bath maintained at 75°C. The drug (tramadol HCl) was added with continuous stirring (glyceryl behenate and the drug were used in the required ratios for each preparation). Then, the molten mass was allowed to cool down and solidify. Tramadol HCl was present in its solid form within the molten mass. The mass was ground and screened, and the granules retained on 1.25 mm sieve were used. These granules were compressed into flat-faced tablets using a Carver press. In order to study the effect of lactose and microcrystalline cellulose on the release of the drug from such matrices, other granules were mixed with lactose or microcrystalline cellulose at specified ratios and were compressed into flat-faced tablets.

2.2.2. Preparation of matrices by direct compression of physical mixtures

Different ratios of tramadol HCl, glyceryl behenate, and lactose or microcrystalline cellulose were mixed using a Turbula mixer (Type T2A, Bachofen, CH) for 30 min at 50 revs./min. Samples from these mixtures were directly compressed using a Carver press.

2.2.3. In-vitro drug release

A standard USP XXII rotating paddle (method II) apparatus (Erweka, Germany) was employed in the release studies with a stirring rate of 100 ± 2 revs./min and maintained at 37 ± 0.5°C. The dissolution medium was 1000 ml of either 0.1 N HCl or phosphate buffer adjusted to the pH of interest. At predetermined time intervals, 5 ml aliquot samples were withdrawn from the dissolution medium and immediately replaced by the same volume of fresh dissolution medium. The samples were filtered through a 0.45 μm membrane filter (Millipore) and measured spectrophotometrically at 271 nm for the content of tramadol HCl using an ultraviolet spectrophotometer (UV-vis Shimadzu model UV 1201). It is worth noting that none of the additives used in the matrices interfered with the assay. The results were expressed as the percentage of released drug as a function of time. Each release determination was carried out in triplicate and the mean values were plotted versus time with a standard deviation of <3 of the percentage released which indicated the reproducibility of the results.

3. Results and discussion

Granules prepared with different ratios of glyceryl behenate were studied to examine the effect of increasing the amount of glyceryl behenate on the release of tramadol HCl. The size of the granules used in this study was in the range of 1–2 mm since the size of the granules is known to affect the release of the drug. Fig. 1 shows the effect of increasing the ratio of glyceryl behenate in the granules on the release of the drug. All of the examined granules exhibited a considerable retardation effect on the release of the drug. However, increasing the ratio of glyceryl behenate in the granules resulted in a further decrease in the release of the drug. Therefore, the dissolution medium will slowly penetrate the granules resulting in a sustained or slow release of the drug. Granules prepared with a ratio of 1:3 (tramadol HCl/glyceryl behenate) gave sustained release of the drug over 8 h.

As it can be seen from Fig. 1, the differences between the three formulations examined regarding the initial release of the drug were not significant. This result was expected due to the formation of a solid dispersion of the drug in the waxy material. In this case, there will be no uniform coating of the drug particles by the polymer [8]. Therefore, fast dissolution of the drug particles from the surface of the granules is expected, and this was relatively similar in the three formulations studied. This resulted in a rapid initial release rate of the drug from the surface of the granules, while the drug

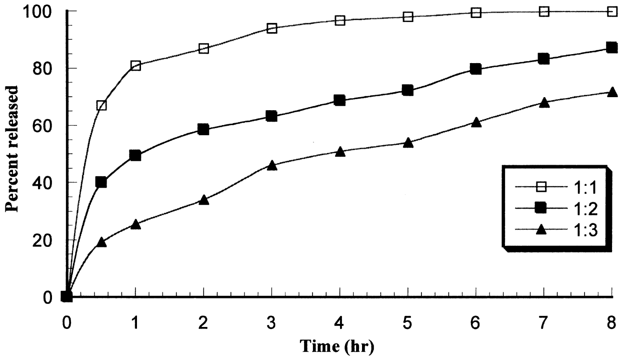

Fig. 1. Effect of increasing the ratio of glyceryl behenate on the release of tramadol HCl from granules prepared by the hot fusion method (pH 7.4; $n = 3$).

present in the deeper interstices of the granules was released at a slower rate.

The effect of compression of the granules on the release of the drug was examined. This effect was examined on tablets prepared by compression of granules prepared by the hot fusion method and on tablets made by direct compression of physical mixtures of the drug and glyceryl behenate. It was found that the compression of the granules prepared by both methods had a significant and marked effect on decreasing the release of the drug in comparison with the release from uncompressed granules.

Fig. 2 shows release profiles from matrices made by direct compression of physical mixtures and from matrices made by compression of granules made by the hot fusion method. Although the release is low and sustained from these matrices, it was higher from the matrices made by direct compression of physical mixtures relative to matrices prepared by compression of granules prepared by the hot fusion method. The slower release from the latter matrices is due to complete coating of the drug particles by the polymer melt in the case of hot fusion. In this case, it is expected that the penetration of the dissolution medium to the matrix will be low compared with matrices prepared by direct compression, and hence, the dissolution and release of the drug occurs at a slower rate.

In either case, both of these matrices will be highly hydrophobic and would be expected to release the drug at a very slow rate, as indeed was found to be the case (Fig. 2). However, in the case of matrices prepared by direct compression of physical mixtures, it seems that the dissolution of drug particles at the surface of the matrices allowed the establishment of channels through which the drug was released. Therefore, the release rate was higher compared with matrices containing granules prepared by the hot fusion method.

Variations in the compression force did not produce considerable variations in the release profiles from the matrices. All tablets showed a relatively rapid initial drug release during the first hour, followed by a slower release rate irrespective of the compression force. Although there are differences in the release profiles between matrices prepared by the two methods, there were no differences within the same type of matrices due to different compression forces. Therefore, it can be concluded that the compression force is not a major factor affecting drug release from such matrices. It is assumed that a minimal force of compression would result in melting and fusion of the waxy material and that would produce a slow release of the drug. This offers an advantage of using glyceryl behenate as a sustained-release agent where the release of the drug is independent of the compression force. Based on these results, an intermediate compression force of 5 tons was used in further experiments.

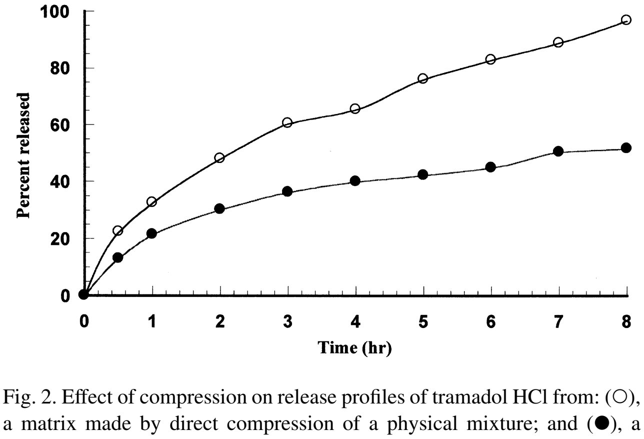

Fig. 2. Effect of compression on release profiles of tramadol HCl from: (○), a matrix made by direct compression of a physical mixture; and (●), a matrix made by compression of granules prepared by the hot fusion method. The formulation contains tramadol HCl and glyceryl behenate in a ratio of 1:3. The compression force was 5 tons and the dissolution experiments were run in a phosphate buffer with a pH of 7.4 ($n = 3$).

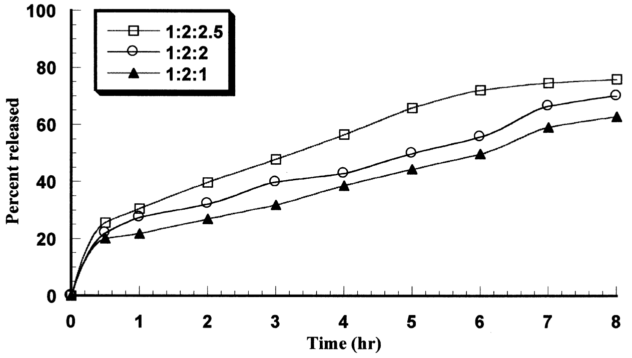

Fig. 3. Effect of microcrystalline cellulose on the release of tramadol HCl. The inset shows the ratios of tramadol HCl, glyceryl behenate, and microcrystalline cellulose, respectively (pH 7.4; $n = 3$).

Since the release from compressed granules was low, the effect of some release enhancers was investigated. The release enhancers studied were microcrystalline cellulose and lactose. They were used in different ratios within the matrices to study their effect on the release of the drug. Lactose produces its effect by the formation of pores in the matrix since it has rapid and high solubility in water unlike microcrystalline cellulose, which works by swelling in water, and eventually, disintegration of the matrix. Fig. 3 shows the effect of microcrystalline cellulose in different ratios in the matrix on the release of the drug. In this experiment, the ratios of drug and glyceryl behenate were kept constant, while the ratio of microcrystalline cellulose was varied. As it can be seen from Fig. 3, increasing the ratio of microcrystalline cellulose in the matrix resulted in a significant increase in the release of the drug.

Fig. 4 shows the effect of lactose on the release of the drug. It was found that using lactose produces a higher initial release as well as a higher release of the drug over the time range of the experiment compared with using microcrystalline cellulose. This result was expected due to the rapid water solubility of lactose compared with microcrystalline cellulose. Such rapid solubility of lactose will produce channels in the matrix that will allow the dissolu-

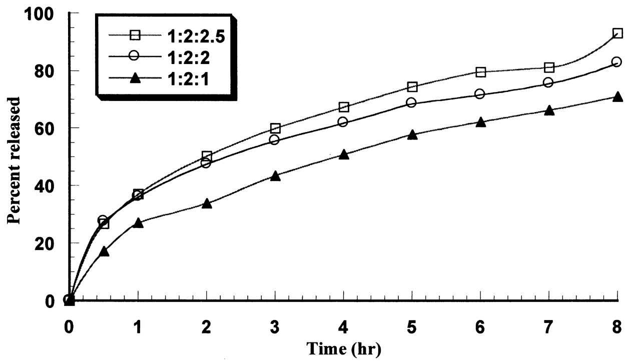

Fig. 4. Effect of lactose on the release of tramadol HCl. The inset shows the ratios of tramadol HCl, glyceryl behenate, and lactose, respectively (pH 7.4; $n = 3$).

tion medium to penetrate the matrix and dissolve the drug more rapidly. In order to clarify the effect of lactose and microcrystalline cellulose on the release of the drug, a kinetic parameter was used. This parameter is the T-50, and that is the time required for 50% of the drug to be released from the formulation.

Table 1 shows the T-50 values for a formulation containing similar ratios of lactose and microcrystalline cellulose. It is evident from the table that when using lactose as the release enhancer, the value of T-50 was shorter than when using microcrystalline cellulose. The effect of additives on the release of drugs from matrices has been well established and is known to control the release of drugs over the desired time period [9]. Studies showed that by including a water-soluble diluent such as lactose, a near zero-order release can be obtained from a matrix system [10].

The release from all the formulations prepared was studied under different pH values. It was observed that the release of tramadol HCl from such matrices is independent of the pH since the release rates were almost similar under the studied pH values. This result was expected since tramadol HCl is a salt of a basic drug with a pKa of 9.3. Therefore, it is ionized over the pH range of interest and soluble at all pH values used in this study, and it can be concluded that the matrix is inert towards changes in pH.

Table 1
Effect of lactose and microcrystalline cellulose in terms of T-50[a] on the release of tramadol HCl from a matrix made by constant ratios of tramadol HCl and glyceryl behenate[b] and various ratios of lactose and microcrystalline cellulose[c]

Ratio of release enhancer in the formulation	T-50 (h)
Lactose	
1	3.8
2	2.2
2.5	2.0
Microcrystalline cellulose	
1	6.0
2	5.0
2.5	3.2

[a] Time required for 50% of the drug to be released.

[b] Ratio, 1:2.

[c] Matrices were made by compression of granules prepared by the hot fusion method.

The mechanism of release of the drug from glyceryl behenate matrices appeared to be a diffusion-controlled mechanism. The data of drug release were fitted to the Higuchi's square root of time model. A good fitness was obtained for times greater than 1 h, and this was not affected by the compression force or the amounts of different ingredients in the matrix. This evidence indicated that the prepared tablets behaved as inert matrices. Visual observation of the tablets during the dissolution studies revealed that the tablets remained intact without any significant change in their shape. These observations support our conclusion that the release of the drug is mainly due to diffusion through the channels formed in the matrix. These channels are formed due to rapid dissolution of the drug particles on the surface of the matrix and the presence of the water-soluble release enhancers. Then, the dissolution medium would penetrate these channels allowing for more dissolution of the drug present in the deeper sites of the matrix.

In conclusion, this study showed that glyceryl behenate is an appropriate waxy material that can be utilized as a matrix-forming agent to control the release of a water-soluble drug such as tramadol HCl. Preparation of the matrices by compression of granules made by the hot fusion method was more effective than compression of physical mixtures in controlling the release of the drug. However, it was possible to adjust drug release from such matrices by using release enhancers like lactose and microcrystalline cellulose.

Acknowledgements

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