CITRIC ACID AS AN EFFECTIVE RELEASE RETARDING AGENT IN MATRIX TABLETS FORMULATION

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Introduction

Amoxicillin is a β- lactam antibiotic. Its sodium salt is found to has pH dependant solubility and also has a short half-life [1]. The development of controlled release formulation of amoxicillin sodium is therefore of therapeutic relevance and can be used to provide a consistent dosage through controlling the release for an appropriate level of the drug over time [2]. Hydrophilic matrices are an interesting option when formulating an oral controlled release dosage form. The dosage release properties of matrix devices may be dependent upon the solubility of the drug [3]. Organic acids can be used to control the solubility of drug by changing the pH of internal environment of the tablet [4]. Hydroxypropyl methylcellulose (HPMC) and xanthan gum are the dominant hydrophilic vehicles used for the preparation of oral controlled drug delivery systems [5]. The objective of the present study was to study the effect of citric acid and sodium citrate on release rate of amoxicillin sodium from hydrophilic matrix tablets.

Experimental

Materials

Amoxicillin sodium, HPMC K 100, xanthan gum, microcrystalline cellulose (MCC) and aerocil 200 were obtained from Oskar Remedies, Kala Amb (HP) India.

Preparation of matrix tablets

Controlled release matrix tablets of amoxicillin sodium were prepared separately with HPMC K 100 and xanthan gum in different polymer: salt ratio viz 1: 0 (without salt), 1: 0.1, 1: 0.5 and 1: 1. Here salt is indicating citric acid and sodium citrate, which were used as release retarding agents. Tablets were prepared by dry granulation method.

Evaluation of physical parameters

The compressed tablets were evaluated for uniformity of weight, hardness, thickness, friability and drug content. Drug content for amoxicillin sodium was carried out by measuring the absorbance of samples at 229 nm using Shimadzu 1700 double beam UV/ Vis spectrophotometer. The in vitro dissolution studies were carried out using USP 24 dissolution apparatus type II (paddle method) at 50 rpm using 1000 ml different dissolution mediums sequentially. Dissolution test was carried out for a total period of 12 h using 0.1 N HCl (pH 1.2) solution 37 ± 0.5˚ C for first 2 h, 4.5 acetate buffer solution for further 4 h and pH 6.8 phosphate buffer solution for the rest of the period. 10 ml of the sample was withdrawn at regular intervals and replaced with the same volume prewarmed (37 ± 0.5˚ C) fresh dissolution medium. The samples were filtered through 0.45 µ membrane filter, and drug content in each sample was analyzed after suitable dilution by UV/ Vis spectrophotometer.

Kinetic analysis of dissolution data

The *in vitro* drug release data were fitted in the exponential equation (known as Korsmeyer-Peppas equation).

Results and Discussion

The results of hardness and friability of the prepared matrix tablets ranged from 17.1 ± 0.24 to 18.9 ± 0.15 and 0.12 to 0.43 respectively (Table 1). The tablet formulations in all the prepared batches contained amoxicillin sodium within 100 ± 5% of labelled content. As such, all the batches of the fabricated tablets were of good quality with regard to hardness, friability and drug content. All tablets complied with pharmacopoeial specifications for weight variation and friability. The results of dissolutions studies of batches FC-I, FC-II, FC-III, FC-IV, FS-II, FS-III and FS-IV are shown in fig. 1. Drug release from the matrix tablets was found to decrease with increase in polymer: citric acid ratio. Formulation FC-I was formulated without using citric acid, failed to sustained the drug release beyond 3 h, while formulation FC-II composed of polymer: citric acid 1: 0.1, sustained the drug release only for 4 h, which was not satisfactory. Formulation FC-IV with polymer: citric acid ratio of 1: 1 gave slower and complete release of amoxicillin sodium over period of 12 h. On the other hand the batches formulated using sodium citrate failed to release the drug for required time period (12 h). Formulation FS-I was formulated without using the sodium citrate, failed to sustained the drug release even for one h. Formulations FS-II and FS-III were sustained the drug release only for 4 h. Formulation FS-IV sustained the drug release for 8 h. The batches formulated using xanthan gum with citric acid as well with sodium citrate (XC-I, XC-II, XC-III, XC-IV, XS-I, XS-II, XS-III and XS-

IV) were unable to hold the tablets in the dissolution medium for more the 4 h. It could happen due to high hydrophilicity of xanthan gum. The polymer enabled to form the matrix with the used concentration of citric acid and sodium citrate, whereas HPMC K 100 is a high viscosity grade polymer which sustained the drug release for 12 h in polymer: citric acid concentration 1: 1. The mechanism of release of amoxicillin sodium from batch FC-IV showed better linearity (R^2 value 0.999) and slope (n) value of 0.536. This n value appears to indicate a coupling of diffusion and erosion mechanism (known as anomalous non-fickian diffusion). Hence diffusion coupled with erosion may be the mechanism of amoxicillin sodium release from FC-IV.

Table 1 Properties of compressed amoxicillin sodium matrix tablets using HPMC K 100

Formulation	Weight (mg) ± S.D (n = 20)	Hardness (kg/cm^2) ± S.D (n =5)	Thickness (mm) ± S.D (n =5)	Friability (%)	Drug content (%) ± S.D (n =3)
FC-I	635 (1.65)	17.1 (0.24)	6.11 (0.07)	0.43	99.60 (0.74)
FC-II	635 (1.49)	18.7 (0.13)	5.11 (0.05)	0.16	99.28 (0.48)
FC-III	635 (1.62)	18.1 (0.28)	5.14 (0.05)	0.28	99.58 (1.04)
FC-IV	635 (1.75)	18.9 (0.15)	4.85 (0.07)	0.12	99.84 (1.12)
FS-I	635 (1.48)	17.5 (0.22)	5.19 (0.06)	0.38	99.52 (0.62)
FS-II	635 (1.44)	18.5 (0.17)	5.16 (0.07)	0.18	99.34 (0.68)
FS-III	635 (1.55)	18.6 (0.16)	5.15 (0.05)	0.26	99.58 (1.26)
FS-IV	635 (1.58)	18.8 (0.14)	5.11 (0.07)	0.42	99.78 (1.18)

Note: All figures in the parentheses represent ± S.D; n is specified in each column head

Table 2 Mathematical modeling and drug release mechanisms of amoxicillin sodium SR tablets

Formulations	n	R	Mechanism
FC-I	0.323	0.963	Quasi-Fickian diffusion
FC-II	0.443	0.900	Quasi-Fickian diffusion
FC-III	0.483	0.968	Quasi-Fickian diffusion
FC-IV	0.536	0.999	Anomalous (Non-Fickian)
FS-II	0.329	0.965	Quasi-Fickian diffusion
FS-III	0.402	0.972	Quasi-Fickian diffusion
FS-IV	0.422	0.988	Quasi-Fickian diffusion

Note: based on Korsmeyer-Peppas equation $M_t/M_\infty = Kt^n$

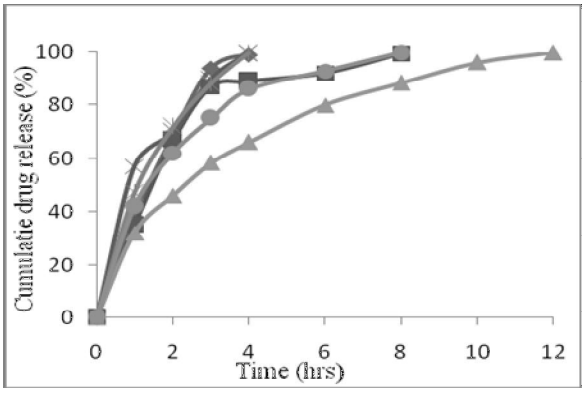

Fig. 1 Comparison of *in vitro* release profile of amoxicillin sodium from tablets of batches FC-II, FC-III, FC-IV, FS-II, FS-III and FS-IV. *In vitro* cumulative release of amoxicillin sodium from formulation FC-II (♦), FC-III (■), FC-IV (▲), FS-II (**x**), FS-III (+) and FS-IV (●).

Conclusion

It is concluded that citric acid is the better release retarding agent in polymer: citric acid ratio 1: 1 with HPMC K 100 as the matrix forming agent. Xanthan gum was unable to form the matrix with both citric acid and sodium citrate, which could be due to high hydrophilicity of xanthan gum due to which the tablets early disintegrated in the dissolution medium.

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