PRELIMINARY STUDIES ON CONTROLLED RELEASE OF ACETYLSALYCILIC ACID FROM MEMBRANE MODULE

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Diffusion through membranes is often used as a means of controling the rate of drug release from solid dosage forms. The unique performance of these specialized drug delivery systems is a means of regulating the input of drug to the body and thereby maintaining desired blood levels. Since the delivery of drug from the dosage form to the gastrointestinal tract is the rate limiting step in the drug absorption and distribution process, in vitro dissolution is a key factor in predicting the performance of the delivery system (Imanidis G, et al., 1998; Carro RC, et al., 1985; Tao WV, et al., 1998). A specific experimental system, based on a membrane module, which was earlier developed for controlled release of antibiotics from liposomes (Boltic Z., et al., 2002; Boltic Z, et al., 2003), was used in order to investigate release of acetylsalycilic acid from cristalline and tablet form. Comparison of obtained data was done using known dissolution–controlled and diffusion–controlled release models (Smart J D, et al., 1992; Colombo P, et al., 1995; Higuchi T, 1963; Hixson A.W., et al.,1931; Roseman TJ, et al., 1970; Ritger PL, et al., 1987).

MATERIALS AND MODELS

Materials

Acetylsalycilic acid (ASA) was Ph. Eur. 1997 grade. Midol (ASA) tablets were from Panfarma (Serbia&Montenegro). Water was obtained from Hemofarm (Serbia&Montenegro) and hydrochloric acid was from Fluka (Swiss).

Methods

The rate of release of ASA from crystalline and tablet form was determined using aparatus given in Figure 1. The apparatus was concieved of the membrane module, sumberged in the well–stirred 0.1 M solution of HCl (1000 cm^3) at 37±0.5°C. The membranes were cellulose–acetate disc membranes (ϕ142 mm) and

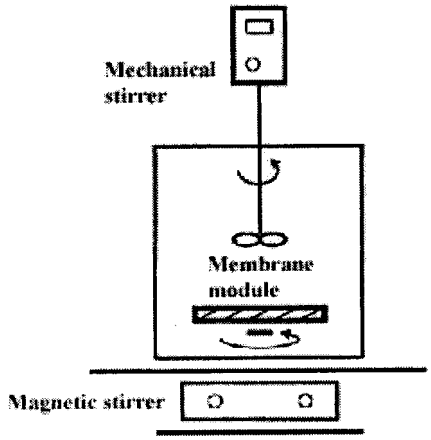

Figure 1. Apparatus for experiments

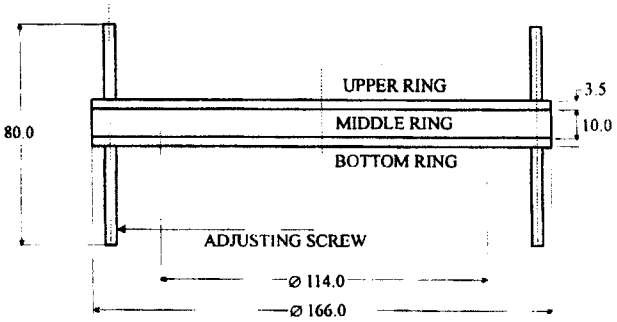

Figure 2. The membrane module

were obtained from Sartorius AG (Germany). Homogenisation of the medium was achieved using magnetic stirrer (Janke–Kunkel, IKAMAG REC–6) and mechanical stirrer (IKA/WERK, RW 20 DZM), both at 500 rpm. The drug concentration in the dissolution medium was monitored using UV spectrophotometer (Shimadzu UV–160A) at a wavelength of 277 nm in predetermined time intervals.

The construction of membrane module is presented in Figure 2. It consisted of three concentric steel rings (114 mm i.d.). Width of the module, i.e – distance between the two membranes was δ = 10 mm.

3 g of crystalline ASA and 10 tablets of Midol each containing 300 mg of ASA, placed in the membrane module, were used in each experiment. The used Midol

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Paper presented as a poster.

tablets were commercially available and were formulated as conventional, fast desintegrated, immediate–release tablets.

RESULTS ANS DISCUSSION

The dissolution experiments in which the membrane module was used include: permeation of water across the membrane, dissolution of the drug core, and exudation of the solution. The transport and transformation of water can be tracked as it goes through the dissolution process, since it is the only component common to all of the mentioned steps. In a dissolution experiment, second step can be taken as a rate limiting one.

Figure 3. shows the release of ASA from crystalline and tablet form from the membrane module. The obtained data clearly show the prolonged release of ASA from tablet in comparison to release of ASA from crystalline form. Even the release of ASA from crystaline form is prolonged in comparison to the results (Parojcic J, et al., 2001) obtained from standard dissolution experiments.

The obtained data for the release of ASA from crystalline and tablet form from the membrane module were fitted using well known dissolution–controlled and diffusion–controlled release models. Six different models were used including Roseman&Higuchi model (model designated for diffusion controled drug release from non–erodible cylindrical matrices under sink conditions), Hixson&Crowell model (model designated for dissolution controlled drug release for systems that do not dramaticaly change in shape) and Ritger&Peppas model (model designated to describe the general solute release behaviour of controlled release polymeric devices). Tables 1 and 2 give the goodness of fit and

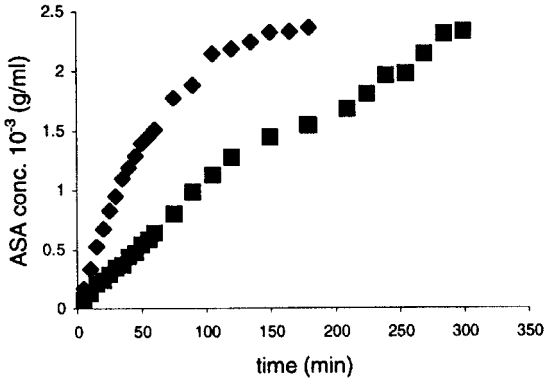

Figure 3. The dissolution curves for crystaline (♦) and tablet ASA (♦)

standard error for the used models. This models better describe the drug release from pharmaceutical systems when it results from a simple phenomenon or when that phenomenon, by the fact of being the rate–limiting step, conditions all the other processes (Costa P, et al., 2001).

The comon method to choose the "best model" to study drug dissolution/release phenomena uses the coefficient of determination, R^2, or the correlation coefficient (R), to assess the "fit" of a model equation. Used models discribe the release of ASA from tablet form better in comparison to the release of ASA from crystalline form regarding to the goodness of fit.

The best correlation was obtained using Ritger&Peppas model for tablets. The diffusion exponent for Ritger&Peppas model was also determined and n is for crystalline form 0.70 and for tablet n is 0.84. Very good correlations were also obtained using zero order, first order and Hixson &Crowell models for tablets, while for the crystalline form the best correlations were obtained using first order and Higuchi model.

Table 1. The goodness of fit and standard error for dissolution of ASA from crystaline form

Model		R	S
Zero order	$M_t/M_\infty = kt$	0.9416	0.081
First order	$\ln (1 - M_t/M_\infty) = -kt$	0.9844	0.090
Higuchi	$(1 - M_t/M_\infty)^2 = -kt$	0.9895	0.1260
Roseman & Higuchi (1970)	$M_t/M_\infty + (1 - M_t/M_\infty \ln(1 - M_t/M_\infty)) = kt$	0.8160	0.130
Hixson & Crowell (1931)	$(1 - M_t/M_\infty)^{1/3} = -kt$	0.9739	0.029
Ritger & Peppas	$\ln M_t/M_\infty = \ln k + n \ln t$	0.9794	0.146

Table 2. The goodness of fit and standard error for dissolution of ASA from tablet form

Model		R	S
Zero order	$M_t/M_\infty = kt$	0.9927	0.030
First order	$\ln (1 - M_t/M_\infty) = -kt$	0.9907	0.064
Higuchi	$(1 - M_t/M_\infty)^2 = -kt$	0.9224	0.260
Roseman & Higuchi (1970)	$M_t/M_\infty + (1 - M_t/M_\infty \ln(1 - M_t/M_\infty)) = kt$	0.9347	0.100
Hixson & Crowell (1931)	$(1 - M_t/M_\infty)^{1/3} = -kt$	0.9958	0.011
Ritger & Peppas	$\ln M_t/M_\infty = \ln k + n \ln t$	0.9981	0.059

CONCLUSION

It is evident, on the basis of obtained results, that the release of acetylsalycilic acid membrane modul can be well described using known dissolution–controlled and diffusion–controlled release models. Used models discribe the release of ASA from tablet form better in comparison to the release of ASA from crystalline form regarding to the goodness of fit.

ACKNOWLEDGMENT

The authors are grateful to the Ministry of Science and Environmental Protection of Serbia for financial support.

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