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Chronopharmaceutical drug delivery

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Conventional oral pharmaceutical formulations release drug in one of two ways, either as a bolus soon after the preparations are swallowed by the patient, (i.e. immediate release), or as a progressive release of the drug substance, (i.e. sustained release). It has been recognised that with many disease states, the symptoms or incidence of the disease do not occur evenly during the 24 hours of the day, but undergo significant daily variations. Circadian variations occur in the manifestation of asthma (Turner-Warwick 1988) with maximum incidence occurring in the nocturnal period around 4 a.m. and with heart disease (Willich et al. 1992) where death is most prevalent in the first 3 h after awakening.

To treat diseases that exhibit daily variations in their incidence, drug delivery scientists are engaged in the development of new types of formulations that release drugs after a defined delay period after being taken by the patient. This contrasts with current drug delivery strategies where drugs are given at times which may be convenient for the patient, but which may not be optimal for the disease to be treated.

Time-delayed tablets are being developed with barrier layers either coated or compressed around conventional tablet formulations. The barrier may be erodible (Pozzi et al 1994), gellable (Conte et al 1993), or act as a diffusion barrier to retard water entry into an expanding core (Ishino et al 1992). Covera-HS, based on an osmotic tablet releases the drug verapamil after a 4-h delay in the middle of the night (Gupta et al 1996).

Capsule delivery systems have been extensively studied and various mechanisms proposed to 'open' insoluble capsules after time-delays, including the use of swelling hydrogel plugs(McNeil et al 1994; Wilson et al 1997), erodible plugs (Stevens et al 1995) and expanding contents that cause separation of components (Wilding et al 1992). Pellet formulations that are coated to provide a barrier that then delays the entry of fluids into a 'explosive' core have been studied by Japanese researchers (Ueda et al 1994).

Chronopharmaceutical drug delivery offers a tantalising glimpse into a future where it will be possible to administer the right dose of drug at the optimal time. It may provide more effective treatment of certain diseases and permit less drug to be administered than is conventionally dosed. Challenges to today's clinical strategies of constant plasma levels over a 24-h period are being made possible by advances in the development of time-delayed drug delivery technologies.

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