different dosage forms, do not provide constant levels over a 24-h span.[8,11-13] Plasma concentrations of these drugs undergo large-amplitude circadian changes even with a continuous intravenous infusion. From the viewpoint of therapeutic optimization, however, maintaining a constant blood level of a drug is not always desirable. Recently, chronopharmacology has been extensively taken into account in clinical therapy. In particular, a tolerance to nitroglycerin released from a long-term- use transdermal patch with zero-order release kinetics has been found.[17]

According to the above considerations, combining homeostasis theory and chronopharmacology to design an ideal DDS seems to be an attractive and effective approach. The ideal DDS aims to improve the therapeutic efficacy by varying drug release in accordance with the requirements of a patient. It not only produces or pumps with constant or programmable delivery rates, but it also is possible to deliver a drug at a definite time responding to signals from the human body when physiologically needed. In order to achieve that purpose, several approaches using temporal-controlled DDSs have been studied by using different types of intelligent materials to change their structure and physical properties in response to external signals, such as pH, temperature, electric field, photo-irradiation, ultrasounds and specific chemical agents.[18-19] The intelligent materials may be used to prepare different dosage forms or devices with functions of rate control, site control and quantity control (Fig. 3). These mechanisms should be capable of modulating drug release from the exterior of the body by pulsatile release, self-regulations or auto-feedback. Since pulsatile drug release is similar to biological rhythms in the human body, it can empirically result in better drug therapy by avoiding toxicity of and tolerance to a drug.

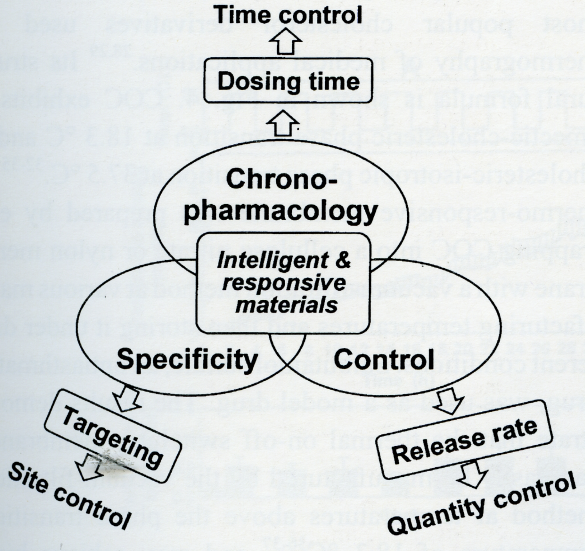

Fig. 3. Approaches to designing an intelligent drug delivery system.

It has been reported that pulsatile insulin administration can replace a continuous insulin infusion to reduce systemic hyperinsulinemia and insulin resistance after long-term infusion.[20] Therefore, the use of controlled-release preparations should be combined with a chronopharmacological approach to choose the best time for administration. This combination corresponds to pharmacological chronotherapy by the administration of medication according to biological rhythms to maximize pharmacological effects and minimize side effects. The percutaneous passage of drugs via transdermal patches also involves chronopharmacological phenomena; even this route still provides constant and continuous delivery of a drug.[13] Skin penetration of a eutectic mixture of lidocaine and prilocaine, reported to depend on the time of administration in children, is higher in the evening.[21] In addition, circadian dosing time has also been demonstrated to depend on the forearm skin penetration of methyl and hexyl nicotinate.[22]

Several marker rhythms in the human body, such as body temperature, heart rates and breathing, are well known. The circadian rhythm is particularly important to relate to the declining lung function of asthmatics at night, in which asthma symptoms and airway inflammation may increase. In these patients, dyspnea tends to worsen during the nighttime due to circadian rhythms in airway function.[23,24] However, the optimal effect of antiasthmatic drugs with late afternoon or evening administration indicates that by scheduling medication in relation to a specific biological rhythm, it is possible to enhance the efficacy of treatment and to reduce the incidence of adverse effects. For exam-