Review Article

Novel Technologies of Oral Controlled Release Drug Delivery System

Patel RR, Patel JK

Department of Pharmaceutical Technology, Nootan Pharmacy College, Visnagar – 384 315, Mehsana, Gujarat, India

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ABSTRACT

Novel oral drug delivery technologies have emerged and expanded into different drug delivery systems with different drug release mechanisms in the last few decades. Sophisticated instrumentation, modern mathematical models and computational power have revolutionized the entire process of formulation and development of drug delivery systems and advanced the concept of drug delivery from a simple pill to a programmable, time controlled smart system. *In situ* forming oral controlled release formulation is a new technology in the field of oral controlled release delivery systems. The concept of *in situ* forming devices (ISFD) entered the pharmaceutical field in the early 1980s as parenteral controlled release dosage forms. In the last decade, this technology has grown significantly due to its potential advantages compared to the traditional parenteral controlled release dosage forms. However, a review of literature revealed that there are not many publications describing the usage of this technology for oral controlled release formulations.

Introduction

In 1895, a reputed British Pharmaceutical Journal predicted "Tablets have had their day and will pass away to make room for something else." More than 100 years after this statement, today, oral solid dosage forms are the leading drug delivery systems in the market, and they are not going to perish in next 30 years. The oral route is still the preferred route of drug administration due to its prominent advantages compared to the other routes. However, the sophisticated instrumentation, modern mathematical models and computational power have revolutionized the entire process of all the aspects of formulation and development of drug delivery systems in last few decades. Novel drug delivery technologies have emerged and advanced the concept of drug delivery from a simple pill to a programmable, time controlled smart system.

The concept of Novel Controlled Drug Delivery System (NCDDS) developed with the "Spansules", the first controlled drug delivery system of dexedrine produced by Smith Kline and French Laboratories in 1952.[1] After that, it expanded into different drug delivery systems with different drug release mechanisms. The controlled release drug delivery systems can be broadly classified based on 1) the route of drug administration, for example, oral, parenteral, or transdermal controlled release systems, and 2) drug release mechanisms like diffusion-controlled, membrane-controlled, osmotic pressure-controlled, etc.[2] The NCDDS has improved patient compliance and efficacy of the dosage regimen. In addition, it has also given a second life to various old drugs with improved therapeutic effect. This is especially important now because there are less and less numbers of new drugs coming to market.[3] As shown in Figure 1, the number of new molecular entities entering into the market has decreased significantly in the last 10 years. However, the funding for pharmaceutical research has doubled in the last 20 years, and as a result, the research in the field of novel controlled release drug delivery systems has continuously grown over the years [Figure 2]. Formulation scientists have developed various novel controlled release formulations. According to the SciFinder Scholar database, more than 20,000 publications can be found using "controlled drug delivery" as keywords.[4,5] Examples of a few notable oral controlled released technologies are described below.

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Correspondence:
Prof. Ravikumar R Patel; E-mail: raviptl_84@yahoo.co.in

Osmotic controlled release oral delivery system technology

Osmotic controlled release oral delivery system (OROS) is a unique oral drug delivery system that releases the drug at a "zero

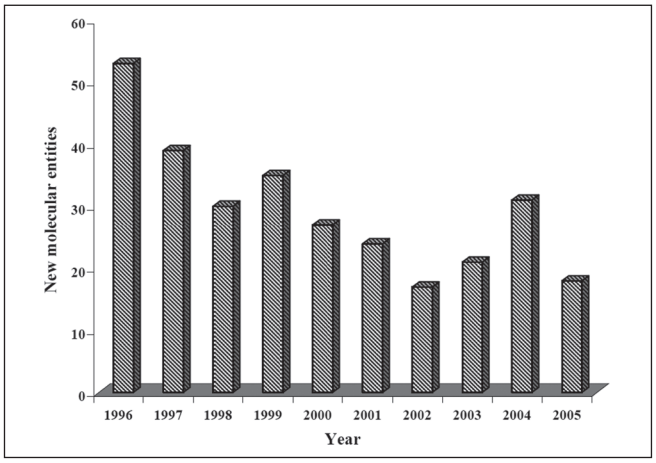

Figure 1: Number of new molecular entities coming to the market in last decade

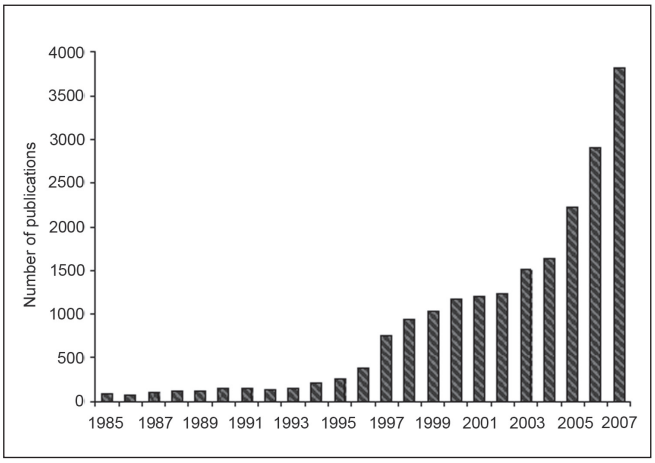

Figure 2: Number of publications on controlled drug delivery systems over the years

order" rate. It is a complex system, which consists of a tablet core containing a water soluble drug and osmotic agents such as NaCl, mannitol, sugars, PEGs, Carbopol, Polyox, etc. The tablet core is coated with a semipermeable polymer such as cellulose acetate. This semi-permeable coating is permeable to water but not to the drug. A laser-drilled hole, 100-250 μm in size, is created as a drug delivery orifice. The osmotic pressure of the body fluid is 7.5 atm, whereas the osmotic pressure in an OROS tablet is around 130–140 atm. As a result, aqueous fluid present in the gastrointestinal (GI) tract enters into the OROS tablet through the semipermeable membrane and pushes the drug out through a delivery orifice. The osmotic pressure of the GI fluid remains constant throughout the GI tract, and as a result, the OROS tablet provides controlled drug release at a constant zero order rate. However, the drugs suitable for this delivery system should be highly water soluble (>100 mg/mL). Poorly soluble drugs cause insufficient osmotic pressure and prevent complete drug release. To overcome this limitation, Alza Corporation came up with "OROS Pull-Push technology" in which, tablets are made with multiple drug layers and a push layer at the bottom. The push layer contains a water-swellable polymer, osmotic agents and other excipients.[6] As water permeates inside the tablet, the hydrophilic polymer absorbs the water and swells. The swelled layer pushes solution from the upper drug layers out of the system through the delivery orifice [Figure 3].

L-OROS™ was developed for highly insoluble drugs, polypeptides such as hormones, steroids, etc., and for liquid drugs. L-OROS™ consists of a liquid filled softgel coated with multiple layers such as osmotic push layer and a semipermeable layer. The internal osmotic layer pushes against the drug compartment and forces the liquid drug formulation from the delivery orifice present in the outer layers of a coated capsule. Glucotrol XL® and Procardia XL® are classical examples of OROS tablets.

Glucotrol XL® is a once a day tablet formulation of glipizide, a blood-glucose lowering drug for diabetic patients, whereas Procardia XL® is a controlled release formulation of nifedipine, a calcium-channel blocker for the treatment of hypertension. Pfizer launched Glucotrol XL® in 1984 and Procardia XL® in 1989.[7] Since then, they have both become the top selling drug products on the market.

TIMERx™ technology

Penwest Pharmaceuticals introduced different drug delivery systems based on slowly eroding matrix platform technology called TIMERx™ technology. This technology consists of two polysaccharides, namely, xanthan gum and locust bean gum. Xanthan gum consists of two β-D-glucose units linked through the 1 and 4 positions, with side chains consisting of two mannose and one glucuronic acid units. Interaction between two of these chains give a double helix like structure to the xanthan gum, which swells in the presence of water. The locust bean gum works synergistically with the xanthan gum and forms a tight gel structure, which retards water penetration into the dosage form, and as a result, controls the release of the active ingredient.[8]

TIMERx™ controlled release tablet formulation forms a hydrophilic matrix in the aqueous media and controls the drug release for 24 hours. It is a cost-effective technology, which is easy to manufacture and improve patient compliance. It is suitable for a wide variety of active ingredients with different drug loading and drug solubility. The different release profiles such as zero order, first order and burst release can be achieved with this technology. Penwest Pharmaceuticals and Mylan Laboratories, Inc. have developed an oral controlled release dosage form of nifedipine using the TIMERx technology. It was the first Food and Drug Administration (FDA) approved generic product that matched the release profile of OROS technology based Procardia XL®.[8]

Multiparticulate system

Multiparticulates as dosage forms have been known since the 1950s when the first product was introduced to the market. Since then, these dosage forms have gained considerable popularity because of their distinct advantages such as ease of capsule filling, better flow properties of the spherical beads, ease of coating, sustained, controlled or site-specific delivery of the drug from coated beads, uniform packing, even distribution in the GI tract, and less GI irritation. In addition, beads are less susceptible to dose dumping, which results in reduced peak plasma fluctuations, thus minimizing the potential side effects without appreciably lowering drug bioavailability.[9]

Multiparticulate dosage forms can be prepared by a number of techniques such as drug layering on non-pareil sugar or microcrystalline cellulose beads, spray-drying, spray congealing, rotogranulation, hot-melt extrusion and spheronization of low melting materials or extrusion-spheronization of a wet mass. Beads can also be either coated with rate-limiting polymers or compressed into tablets to obtain slow-release, target-release or controlled-release profiles. Multiparticulate dosage forms with different dose strengths can also be prepared from the same batch of drug-loaded pellets without any formulation or process changes.[9] Moreover, beads with two incompatible bioactive agents and/or with different release profiles, which need to be delivered to the same or different sites in the body, can also be prepared.[10,11]

Elan's multiparticulate technologies such as Spheroidal Oral Drug Absorption System (SODAS), Intestinal Protective Drug Absorption System (IPDAS), Chronotherapeutic Oral Drug Absorption System (CODAS), and Programmable Oral Drug Absorption System (PRODAS) are designed on the need of the individual drug. SODAS technology consists of coated and uncoated beads, which are combined to get the desired drug release profile. Ritalin LA® and Focalin XR®, controlled release formulations of central nervous system stimulants to treat attention-deficit hyperactivity disorder (ADHD) in children, are based on SODAS technology in which immediate release and controlled released beads are mixed together to obtain a pulsatile drug release profile.[12] IPDAS technology is meant for GI irritant drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) in which high density multiparticulte beads are compressed into tablet formulations to obtain a controlled release profile. Controlled release formulation of naproxen, Naprelan®, uses the IPDAS technology.[13] Naprelan® tablet disintegrates into multiparticulate beads that disperse throughout the GI tract and prevent dose dumping of naproxen, a GI irritant drug. The PRODAS technology consists of mini-tablets, which are filled into capsules to get benefits of both tablets and multiparticulate dosage forms [Figure 4].

Researchers have found that certain diseases are affected by the rhythmic changes of human body. For example, the risk of heart attack appears to be greatest during the early morning hours compared to evening.[14] CODAS drug delivery system is tailored to give drug release according to circadian pattern of the disease. Verelan® PM is sustained release formulation of verapamil HCl, a blood pressure lowering drug. After taking Verelan® at bedtime, it gives a higher drug release during the early morning hours when the chances of heart attacks are higher. Chronotherapeutic drug delivery system gives maximum health benefits with great patient compliance.

Compression coated tablets

Compression coating is an old concept, which has been recently renewed as a novel technology due to advances in tablet-press technologies. This technique requires specific tablet press with compression coating capabilities. Compression coated tablets have two layers, an inner core and an outer shell. First, the inner core is compressed as a small tablet, and then the inner core is dry coated with rate controlling materials such as controlled release polymers and fillers.[15] The drug release rate is dependent on various factors such as thickness and porosity of the outer shell, types of material used to compress inner core and outer shell, particle size of the excipients, compression force used to compress both the layers and position of the inner core in the tablet [Figure 5].

Penwest's SyncroDose™ technology is a classical example of compression coated tablets. These tablets contain an immediate release inner core and compression coating outer layer of xanthan gum and locust bean gum. The lag time and rate of drug release is controlled by the modulating the concentrations of the two polysaccharides.[8]

Melt-extrusion technology

In the melt-extrusion technology, the active pharmaceutical ingredient is mixed with low melting point excipients such as waxes or polymers, and the resulting mixture is extruded as beads or granules. The resulting granules are compressed into tablets. Kaletra®, an anti-HIV drug formulation, was developed by Abbott laboratories to decrease the number of tablets to be ingested, and to increase the patient compliance, it uses the melt-extrusion technique.[16]

Layered tablets or RingCap™ tablets

Bi-layer, tri-layer and dual release tablet technology gives different release profiles of one or more drugs. This technique is very useful for combination products in which two different release profiles of

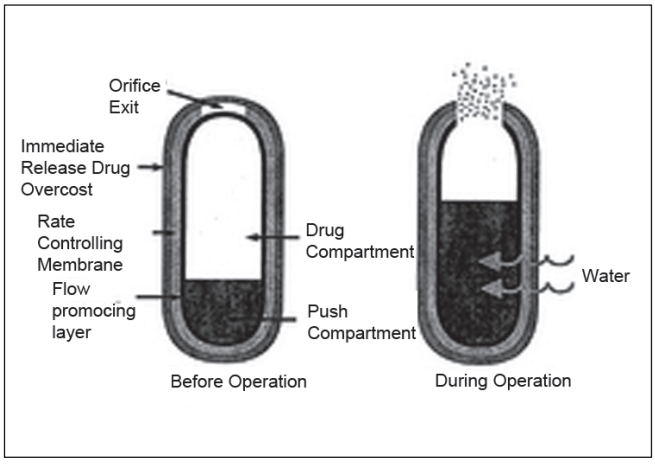

Figure 3: OROS push stick design

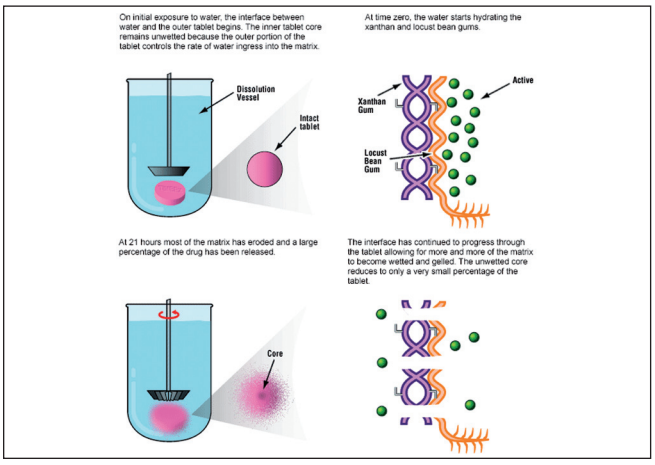

Figure 4: Mechanism of the TIMERx system at the molecular level

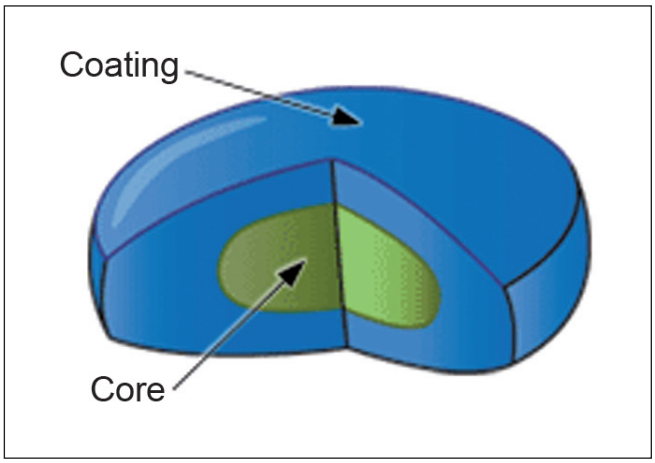

Figure 5: Illustration of compression coated tablet

two different drugs can be achieved from a single tablet. In addition, this technology can also be used for controlled release and abuse resistant drug delivery systems. Geomatrix® (SkyePharma), London, UK and Geminex™ (Penwest Pharmaceutical) Danbury, Connecticut, USA technologies are based on this concept and give dual drug delivery profiles from a single multilayer tablet. Madopar DR® is a three-layered gastro-retentive matrix tablet of L-dopa for the treatment of Parkinson's disease. The outer layers release the L-dopa in high concentration for quick onset of effect, whereas the inner sustained release layer is made up of hydrophilic water swellable polymer (HPMC), which swells in the presence of water and increases the gastric retention time of the tablet. The swelled tablet releases the maintenance dose slowly up to 6 hours [Figure 6].

RingCap™ is a new oral controlled release technology which incorporates several insoluble polymeric rings around a tablet. These rings control erosion of the tablet, thus modulating the release of drug in the GI tract. Unlike the currently available matrix tablets which release decreasing amounts of drug over time, RingCap™ systems can deliver the total dose evenly over an extended period. Drugs that are suitable for this type of delivery system may include traditional small molecules, for example, calcium channel blockers, angiotensin-converting enzyme inhibitors, NSAIDS and vitamins.[17]

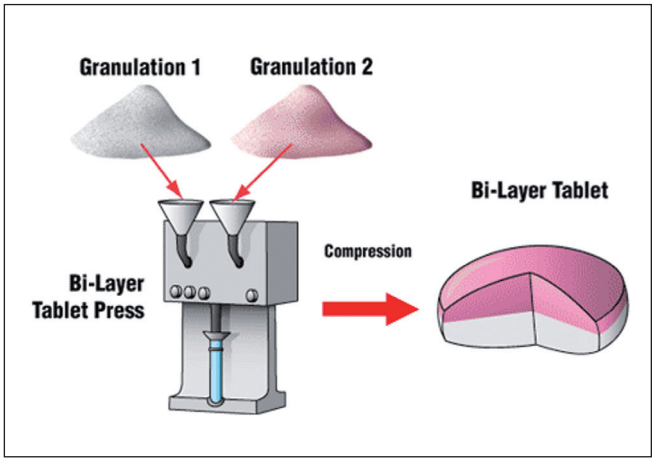

Figure 6: Geminex compaction illustration

Ion exchange resins as drug delivery systems

Formulators have used ion exchange resins as drug delivery systems. Ion exchange resins are basically insoluble polymers such as polystyrene or polymethacrylate polymers that contain non-ionizable groups. They have been widely used as adsorbents for water purification. In the 1950s, Saunders and Srivatsava suggested that ion exchange resins may be used for sustained/controlled release formulations.[18] The drug release rate from the resinate (drug–resin complex) is dependent on the ionic strength and pH of the drug delivery site. That is why the resinate releases the drug in a controlled manner. There are less chances of drug dumping from ion exchange resin drug delivery systems. Resinates can be filled into capsules, coated with controlled release polymers, compressed into tablets, and dispersed in liquids. In the last few years, resinates have also been used to formulate abuse-resistant drug delivery systems. The drug bound to the ion exchange resin cannot be easily extracted in water and alcohol, and is hard to crush or sniff.[19]

Delsym®, dextromethorphan cough syrup, and Phentuss®, codeine and chlorpheniramine syrup are marketed formulations of ion exchange resin sustained release drug delivery systems. In these formulations, polyethylene glycol treated resinates are coated with hydrophobic polymers to control the release of drugs. This particular technology is known as Pennkinetic™ system, which was originally patented by Pennwalt Corporation.[20]

Gel-Cap™ technology

The major drawbacks of controlled release oral formulations are dose dumping, drug diversion, abuse or accidental misuse by patients. The unintentional deaths due to drug overdose have also increased in the last decade. Pain Therapeutics in alliance with King Pharmaceuticals, Inc. has developed the Gel-Cap™ technology as abuse resistant sustained release dosage forms for controlled substances. Gel-Cap™ technology is based on highly viscous material called sucrose acetate isobutyrate (SAIB), which is insoluble in water, but soluble in alcohol. Formulations prepared with SAIB are difficult to crush, break, freeze and snort due to its high viscosity. In addition, because it is insoluble in water, extraction of drug out of the dosage form is difficult. After oral administration of the Gel-Cap™ formulation, the gelatin capsule and solvents dissolve, and the drug is released in a controlled manner from the adhesive SAIB matrix.[21] Dosage forms prepared with this technology are still under clinical trials.

Liquid formulations which form a solid depot after a subcutaneous injection are common for parenteral use, and they are known as *in situ* forming parenteral dosage forms. Some examples of *in situ* forming devices (ISFDs) parenteral formulations are listed below.

In situ forming devices

The concept of ISFDs entered the pharmaceutical field in the early 1980s. In last decade, this technology has grown significantly due to their potential advantages compared to the traditional parenteral controlled release dosage forms. Some of these advantages are that the ISFDs are less painful compared to implants, they have less dosing frequencies, and they do not require any surgical procedures for parenteral administration. In addition, the ISFDs are also suitable as drug delivery systems for protein and peptide molecules. Since

the biotech industry has grown considerably in the past few years, the researchers are seriously considering ISFDs as future drug delivery systems as protein/peptide therapies.

Packhaeuser *et al*. have subdivided this technology into four different groups based on their mechanism of depot formation: 1) Polymer precipitation technology, 2) Thermoplastic pastes, 3) Cross-linked polymer system or hydrogels, and 4) Thermally induced gelling system.[22]

In the polymer precipitation technique, a biodegradable polymer and an Active pharmaceutical ingrediant are dissolved in an appropriate solvent or a mixture of solvents. Upon injection of this formulation, the solvents disperse from the injection site and leave the embedded polymer mass with entrapped drug at the injection site through which the drug releases out in a controlled manner for several days or months. This technology is also known as "Atrigel™ Technology" since it was developed by Atrix Laboratories in the 1980s.[23] In 1989, Lupron® Depot, monthly intramuscular injection of luprolide acetate, was approved by the FDA. Luprolide acetate is a luteinizing hormone-releasing hormone (LHRH) agonist, which reduces the testosterone production and treats prostate cancer.[24] Eligard™, the current subcutaneous injection of leuprolide acetate for 6 months was approved by the FDA in 2002. Eligard™ contains PLGA 75/25, as the biodegradable polymer, and N-methyl-2-pyrrolidone (NMP) as the solvent, and the release mechanism of the formulations is diffusion and erosion controlled.[25] Thermoplastic pastes are melted polymer formulations which form a solid depot at body temperature. This system is suitable for local drug delivery at the surgical or resection site. Researchers have used polyanhydrides, polycaprolactones, and polyorthoesters as low melting polymers for preparing thermoplastic pastes.[22] Cross-linked polymers are also used to formulate ISFD systems for protein and peptides. However, the major concerns with these formulations are inflammatory response at the administration site due to the free-radicals initiation of *in situ* cross-linking. In addition, the cross-linked polymers are not biodegradable and hence require surgical removal of the depot after treatment.

Thermally induced gelling system is a promising technique in which thermosensitive polymers are used to form the gel depot immediately after the injection. These formulations are liquids below room temperature, and upon injection at the body temperature, the polymer precipitates as a hydrophobic depot and controls the drug release. MacroMed is actively involved in developing this technology. MacroMed's ReGel® technology is based on thermosensitive tri block copolymers, PLGA-PEG-PLGA, system. Oncogel®, a controlled release formulation of paclitaxel, is an example of ReGel® technology. Oncogel® formulation is free flowing liquid at room temperature, and after intra-tumor injection, it forms solid depot at body temperature and controls the paclitaxel release up to 6 weeks.

Scientists have successfully used ISFD technology for controlled release parenteral dosage forms. However, a review of literature revealed that there are not many publications describing the usage of this technology for oral controlled release formulations. Therefore, the objective of this study was to develop novel *in situ* forming oral controlled release formulations (ISFOF) that can control the drug release up to 24 hours after oral ingestion. ISFOF formulations are liquids or semisolids at room temperature, and upon ingestion, they convert into solid masses that control the drug release for 12–24 hours. As a unit dosage form, liquid or semisolid formulations are filled into hard or soft gelatin capsules for oral administration.

References

1. Perrin JH. Drugs and Pharmaceutical Sciences In: Robinson JR, editor. Sustained and Controlled Release Drug Delivery Systems. Vol. 6. New York, NY 10016, 1978.
2. Pillai O, Dhanikula AB, Panchagnula R. Drug delivery: An odyssey of 100 years. Curr Opin Chem Biol 2001;5:439-46.
3. Economist T. Fixing the drugs pipeline. Available from: http://www.economist.com/printedition/displayStory.cfm?Story_ID=2477075 [last cited on 2004 Mar 11] [last accessed on 2008 Jan 13].
4. Rocca JG, Park K. Oral drug delivery: Prospects and challenges. Drug Deliv Technol 2004;4:52-4, 7.
5. Database SS. Available from: http://www.cas.org/support/scifi/index.html [last accessed on 2010 Mar 8].
6. Bhatt PP. Osmotic drug delivery systems for poorly soluble drugs: The drug delivery companie w report autumn/winter 2004. 2004.
7. Pfizer. Available from: http://www.pfizer.com/about/history/1951_1999.jsp. Timeline 1951-1999 [last accessed on 2010 Mar 8].
8. Penwest. Drug delivery technologies. Available from: http://www.penwest.com/drug_del_tech.html [last accessed on 2010 Mar 8].
9. Isaac Ghebre-Sellassie AK. Pelletization Techniques. Encyclopedia of Pharmaceutical Technology. London, UK, 2002. p. 2067-80.
10. Erkoboni DF. Extrusion/spheronisation. Drugs and the Pharmaceutical Sciences (Pharmaceutical Extrusion Technology). Vol. 133. Informa Healthcare, London, UK, 2003. p. 277-322.
11. Bechgaard H, Nielsen GH. Controlled-release multiple-units and single-unit doses: A literature review. Drug Dev Ind Pharm 1978;4:53-67.
12. Elan. Oral Controlled release technologies. Available from: http://wwwelancom/EDT/oral_controlled_release_technology/ [last accessed on 2010 Mar 8].
13. Naprelan. Available from: http://www.naprelan375.com/home.html [last accessed on 2010 Mar 8].
14. Mangione RA. Chronotherapeutics and Pharmaceutical Care. US Pharmacist. 22:7. Available from: http://www.uspharmacist.com/oldformat.asp?url=newlook/files/Feat/ACF2F15.cfmand pub_id=8andarticle_id=48 [last accessed on 2008 Feb 11].
15. Lin SY, Lin KH, Li MJ. Formulation design of double-layer in the outer shell of drycoated tablet to modulate lag time and time-controlled dissolution function: Studies on micronized ethylcellulose for dosage form design (VII). AAPS J 2004;6:e17.
16. Breitenbach J. Melt extrusion: From process to drug delivery technology. Eur J Pharm Biopharm 2002;54:107-17.
17. Rathbone MJ, Hadgraft J, Roberts MS. Modified-Release Drug Delivery Technology. Weimar, Texas 78962. 2003.
18. Anand V, Kandarapu R, Garg S. Ion-exchange resins: Carrying drug delivery forward. Drug Discov Today 2001;6:905-14.
19. Oshlack B, Wright C, Haddox JD. Tamper-resistant oral opioid agonist formulations. February 24, 2004(US Patent 6696088).
20. Raghunathan Y. Prolonged release pharmaceutical preparations.;US Patent 4,221,778(1980).
21. Webster LR. PTI-821: Sustained-release oxycodone using gel-cap technology. Expert Opin Investig Drugs 2007;16:359-66.
22. Packhaeuser CB, Schnieders J, Oster CG, Kissel T. *In situ* forming parenteral drug delivery systems: An overview. Eur J Pharm Biopharm 2004;58:445-55.
23. Sartor O. Eligard: Leuprolide acetate in a novel sustained-release delivery system. Urology 2003;61:25-31.
24. Wikipedia. Leuprolide acetate. Available from: http://www.enwikipediaorg/wiki/Eligard [last accessed 2008 Mar 31].
25. Ravivarapu HB, Moyer KL, Dunn RL. Parameters affecting the efficacy of a sustained release polymeric implant of leuprolide. Int J Pharm 2000;194:181-91.

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