Compliance is a major problem in the treatment of schizophrenia. Several oral second-generation antipsychotics (AP2G) were introduced in clinical practice the position of depot AP1G dramatically changed. Thirty years later, when oral second-generation antipsychotics (AP2G) were introduced in a localized mass and stored in the muscle and gradually absorbed by surrounding tissue. Formulators formulated these depot preparations in an oil base, which slowly move out of the muscle into the bloodstream. Based on pharmacokinetic studies which demonstrated that the rate of release of drugs from oil vehicles is, at least partly, related to the pH-dependent oil vehicle-water distribution coefficient or in case of non-electrolytes to the partition coefficient. From 1960s, first-generation long-acting injectable (depot) antipsychotics emerged in clinical practice. There use for the treatment of schizophrenia not only resulted in a significant decrease in the number of patient’s relapses, but also reduces the frequency of hospitalizations. Thirty years later, when oral second-generation antipsychotics (AP2G) were introduced in clinical practice the position of depot AP1G dramatically changed. Despite the benefits of APIG, psychiatrists started preferably prescribing AP2G for long-term treatment of schizophrenia as they were seen as more efficient and well tolerated. This trend persisted for many years, despite evidence to suggest from meta-analyses and naturalistic studies that depot AP1G were more effective in minimising schizophrenic relapses than oral AP2G. The same finding was later logically applied also for long-acting injectable (LAI) AP2G. Although patients with schizophrenia are often prefer to use depot or LAI antipsychotics, these formulations are today prescribed only for approximately 20% of them. In a survey of psychiatrists were asked the preference of AP2G over LAIs and they only prefer long-acting injectable antipsychotics to one in every three schizophrenic patients. A list of Commercially Available first-generation antipsychotic (APIG) LAIs are illustrated in table 1.
3. Second-generation long-acting antipsychotic injections

From 1990 onwards, the use of classical depot antipsychotics medication declined, because of a development and introduction of the second-generation ("atypical") antipsychotic drugs which shows higher efficacy especially with respect to the treatment of negative symptoms of schizophrenia apart from the positive symptoms and reduced liability for motor side effects.

However, these atypical drugs were initially available as oral formulations only. By the first years of the new millennium, psychiatrists started taking additional measures for using those atypical drugs as well with long-acting formulations being the natural choice keeping in mind that, although patients treated with second-generation antipsychotics showed moderately better therapy compliance than those treated with older drugs [10].

The slow and controlled release pharmacokinetics of these long-acting injectable (LAI) drugs [11] made it possible to deliver stabilized but potentially non-compliant patients who would then have to return only once per month to receive their next LAI injection [12].

In the US, there are several long-acting injectables (LAIs) available in the market, including two first-generation antipsychotics haloperidol and fluphenazine (more first-generation LAIs available worldwide) and four second-generation antipsychotics risperidone, paliperidone, olanzapine, and Aripiprazole LAIs [11] as illustrated in table 2.

In August 2002 onwards, Risperidone (Risperdal Consta®) was the first second generation LAI became available in Europe, and in December 2003 it was launched in the US market [40].

In 2013, the second second generation LAI, Abilify MyCana was approved by the FDA for the treatment of schizophrenia [44]. Comparison among available LAIs in the US is illustrated in Table 3 [42].

4. Long-Acting Drug Delivery Technology

4.1 Medisorb Microspheres Technology

Medisorb microsphere technology is Alkermes proprietary technology that allows novel and advance formulations of pharmaceuticals by providing controlled, long acting release of drug over time.

This technology, utilizes biodegradable polylactide co-glycolide (PLG) in which drug is encapsulated in microspheres. The size of each microsphere is about one-tenth of a millimeter, roughly equivalent to the diameter of a human hair. PLG is a common, biodegradable polymer with a history of safe human use in sutures, bone plates and extended-release pharmaceuticals.

PLG polymer is a biodegradable polymer which over time, breaks down into lactic acid and glycolic acid, which are completely metabolized by the body and eliminated as carbon dioxide and water, thereby releasing the drug from the microspheres.

The mechanism of drug release form the PLG based microspheres is depicted in Fig. 1 where upon administration of injection, the microspheres (A) begin to absorb water almost immediately, leading to a swelling mass of the microspheres (B). This process begins a stage in which a small amount of drug at or near the surface of the microspheres is released.

Over time water slowly breaks down the PLG polymer structure allowing drug to release, resulting in an extended supply of drug (C). The PLG polymer matrix eventually breaks down and is eliminated.
from the body as carbon dioxide and water (D) as it is illustrated in Fig. 1.

![Diagram of drug particle and polymer matrix]

**Fig. 1: Schematic representation of the Medisorb Microspheres Technology**

Risperidone Long acting injection (Risperdal Consta) uses Alkermes’ Medisorb PLG polymer-based microsphere technology to deliver and sustaining therapeutic plasma drug levels in the body through just one injection every two weeks. Risperdal Consta is exclusively manufactured by Alkermes and is marketed and sold by Janssen worldwide. In May 2009, FDA approved Risperdal Consta as both monotherapy and adjunctive therapy to lithium or valproate in the maintenance treatment of bipolar I disorder. Risperdal Consta is also approved for the maintenance treatment of bipolar I disorder in Canada, Australia and Saudi Arabia.

Although formulators has applied similar experimental drug delivery systems for chlorpromazine and haloperidol, no such formulation of any classical antipsychotic drugs has ever reached the pharmacy shelves and Risperdal Consta was the first atypical antipsychotic to become available as a LAI version using Medisorb microspheres technology.

**4.2 NanoCrystal Technology**

Alkermes’s NanoCrystal technology is applicable to poorly water-soluble compounds and involves formulating and stabilizing drugs into particles that are nanometers in size. A drug in NanoCrystal form can be apipled into a range of common dosage forms and administration routes, including oral such as tablets, capsules, inhalation devices and parenteral dosage form such as for injection, with the potential for enhanced oral bioavailability, increased therapeutic effectiveness, reduced/eliminated fed/fasted variability, and sustained duration of intravenous/intramuscular release as it is illustrated in Fig. 2.

![Diagram of NanoCrystal process]

**Fig: 2. Schematic representation of the NanoCrystal® process**

Under Alkermes license agreement with Janssen Pharmaceutical, Alkermes granted Janssen a worldwide exclusive license under Alkermes NanoCrystal technology to develop, commercialize and manufacture Invega Sustenna/Xeplion and related products.

Paliperidone palmitate long-acting injection (Invega Sustenna) uses Alkermes nanoparticle injectable extended-release technology for once-monthly intramuscular administration. In 2009, FDA approved Invega Sustenna for the acute and maintenance treatment of schizophrenia in adults. Paliperidone palmitate extended-release for injectable suspension is also approved in the European Union ("EU") and other countries worldwide, and is marketed and sold in the EU under the trade name Xeplion. Invega Sustenna/Xeplion is manufactured and commercialized worldwide by Janssen.

On May 18, 2015, US FDA approved Invega Trinza™, a three-month injection, for the treatment of schizophrenia. Patients must be adequately treated with Invega Sustenna (one-month paliperidone palmitate) for at least four months before starting Invega Trinza™.

**4.3 FluidCrystal Injection Depot Technology**

FluidCrystal technology is based on Lipid liquid crystal (LLC) phase formation, which is presented as a low-viscosity mixture of long-chain lipids—for example, a soy phosphatidyl choline (SPC) and glycerol dioleate (GDO), together with small amounts of solvent which forms LLC phases. The mechanism of encapsulation is based on LLC phase, which upon contact with small quantities of aqueous fluids present in the tissue, the FluidCrystal delivery system self-assembles in a controlled manner into one or more reverse LLC phases, thereby effectively encapsulating dissolved or dispersed drugs and restricting diffusive transport to the surrounding tissue as it is illustrated in Fig. 3. The use of a two-component lipid system, such as SPC and GDO where each component favours a different phase structure, the release of the dissolved drug can be optimise by tuning the phase behaviour of composition. By using these LLC phases which are thermodynamically stable in excess aqueous water, a controlled extended-release reservoir is assured, which is slowly degraded in vivo with the help of endogenous enzymes, and releases the drug.

The viscosity of the phase can be adjusted using small amounts of co-solvent, such as ethanol or propylene glycol. The reversed cubic and/or reversed hexagonal LLC phases formed when PC and GDO are mixed in around equal proportions and added to an aqueous environment, which have been shown to be suitable for extend-ed-release applications.

The FluidCrystal system is a liquid compatible with, for example, prefilled syringes, which ensures not only easy handling prior to administration but also straightforward manufacturing.

On May 18, 2015, US FDA approved Invega Trinza™, a three-month injection, for the treatment of schizophrenia. Patients must be ade-

**Fig: 3. Schematic representation of the FluidCrystal® process**

**4.4 Monosphere™ Technology**

The microsieve technology developed by Nanomi allows for the production of monodisperse microspheres in a large scale. Micro-sieves are silicone-based membranes with uniform pore size and shape, which are fabricated using a photolithographic technique widely utilized in the semiconductor industry. A monodisperse emulsion is generated by forcing an organic solvent containing the dissolved polymer and drug through the microsieve into an aqueous solution. The droplet size of the emulsion is solely controlled by the membrane and independent of the formulation. The solvent is subsequently removed by evaporation resulting in uniformly sized solid microspheres. The process is capable of producing microspheres in the size range of 1-50 μm. It is also compatible with both single and double emulsion methods for microsphere manufacture.
The microsieve emulsification process is readily scaled up by increasing the number and surface area of the membranes. The technology also allows continuous and close operations which make aseptic processing feasible.

Monosphere™ technology brings the precision and reliability of semiconductor technology to the process of microsphere manufacture. Silicon microsieves™ with uniform pores size used in an emulsification process provide uniform microspheres of very uniform and predictable size as it is illustrated in Fig. 4.

The uniform particle size of microspheres together with its robustness, reproducibility and straightforward scalability make Monosphere™ a valuable technology for the development and manufacture of microspheres for long-acting injectables.

The Monosphere™ technology provides a uniform, controlled microspheres particle size which allows for less painful injection through very thin needles.

Fig. 4. Schematic representation of the microsieve™ emulsification process.

4.5 CriticalMix™ Injectable Technology

CriticalMix™ technology is used for the development of long-acting injectable preparation, which uses supercritical carbon dioxide to encapsulate drugs in a biodegradable regulatory approved polymers for extended release applications. CriticalMix™ technology enables the development of highly active extended release depot products for bimonthly, monthly or less frequent injection.

Supercritical carbon dioxide (scCO2) with its unique ability to plasticize polymers and diffuse through solids has served as an excellent alternative to organic solvents in the fabrication of microspheres containing biological molecules. Furthermore, its low critical point (31.1°C at 73.8 bar) makes it a very attractive processing medium for heat labile drugs. Rapid expansion of supercritical solutions (RESS) process is an organic solvent-free method that has been used to produce microspheres for drug delivery applications. The RESS process uses scCO2 to plasticize polymers (e.g., PLGA or PLA) allowing effective incorporation of solid drug particles into the liquefied polymer at near ambient temperature without the use of an organic solvent. The subsequent spraying of the drug polymer mixture through a nozzle results in rapid expansion of the CO2 and formation of drug loaded microspheres.

Supercritical carbon dioxide can also be used as an antisolvent for the preparation of microspheres. In a typical process with scCO2 as an antisolvent, the polymer and drug are dissolved in an organic solvent followed by atomizing the solution through a nozzle into a vessel containing scCO2. Rapid extraction of the organic solvent into scCO2 causes precipitation and formation of drug-loaded microspheres. Greater drug entrapment is feasible with this method. Various ways of introducing the solution into the supercritical fluid have been explored, including the use of an ultrasonic atomizer to the spray to produce monodisperse particles and ultrasonic vibration to produce smaller particles leading to increased mass transfer rate between the solvent and the scCO2.

The process involves in the CriticalMix™ technology, where the biodegradable polymer/polymer mix and the drug are placed in a high-pressure chamber and filled with CO2 under pressure resulting in the formation of supercritical carbon dioxide (scCO2). The formed scCO2 homogeneously mixed the polymer and the required drug using a rotor blade situated within the chamber. The scCO2 acts as a plasticizing agent, the resulting liquefied drug-polymer mixture is then rapidly released through a nozzle causing rapid depressurization and thus solidification resulting in a fine spray of drug-loaded microparticles.

Critical Pharmaceuticals uses this technology for the preparation of long acting injectables which they use a range of FDA approved biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) and polylactic acids (PLA) in novel combinations with a selection of plasticizers and solubilizers such as Polyethylene glycol (PEG), Poloxamers and PEGylated derivatives. The final extend release microparticle products are injected through a 25G fine gauge needle.

Critical Pharmaceuticals is developing a long-acting injection of risperidone (CP018) as a once every two week injection that uses CriticalMix™ Injectable technology.

4.5 LinkeRx™ Technology

LinkeRx™ platform technology is Alkermes’s long-acting technology which is designed to allow the creation of extended-release injectable versions of antipsychotic drugs and may also be useful in other disease areas in which long action may provide therapeutic benefits. This technology uses proprietary linker-tail chemistry to create New Molecular Entities (NMEs) derived from known approved drugs. These NMEs are designed to have improved clinical utility, manufacturing and ease-of-use compared to other long-acting drugs.

Alkermes has developed this LinkeRx platform technology that allows the preparation of prodrugs from parent drugs which lack hydroxyl functional groups. The modified prodrugs using linker-tail chemistry to drugs allow made for use in extended-release injectable formulations based on useful physicochemical properties. These modified prodrugs are preferably crystalline in nature with low aqueous solubility and efficient formed to the parent drug in presence of biological systems. The most desired extended-release formulation is an aqueous suspension of a crystalline prodrug. The mechanism of drug release is based on the rate-limiting dissolution of the prodrug from a depot followed by rapid absorption of the prodrug into systemic circulation with concomitant enzymatic breakdown to provide sufficient plasma levels of the parent drug and negligible plasma levels of the prodrug.

Aripiprazole lauroxil is a long acting injectable of atypical antipsychotic with one-month formulations for the treatment of schizophrenia. Once in the body, aripiprazole lauroxil converts into aripiprazole, which is commercially available under the name Abilify. As a long-acting investigational medication based on Alkermes’s proprietary LinkeRx™ technology, aripiprazole lauroxil is designed to have multiple dosing options and to be administered in a ready-to-use, pre-filled product format. Aripiprazole lauroxil is a first product candidate to use Alkermes proprietary LinkeRx™ technology.


4.6 SABER™ Depot Technology

SABER depot technology generally used in parenteral application uses a high viscosity base component, such as sucrose acetate isobutyrate (SAIB), to provide extended release of a drug.
When the high viscosity SAIB is formulated with drug, solvent and other additives, the resulting formulation is easily injectable with standard syringes and needles. After injection of a SABER formulation, the solvent diffuse away, leaving a high viscous depot which provides controlled extended release of drug [64].

In the simplest case, the high-viscosity SAIB is mixed with pharmaceutically acceptable solvent to prepare a low-viscosity liquid. The drug to be delivered is dissolved or dispersed in the SAIB/solvent solution to prepare low viscous SAIB/drug fluid that may administered either subcutaneously or intramuscularly. The more water soluble solvent, such as ethanol is chosen, the more solvent will diffuse out of the injected volume leaving a high viscous depot of SAIB and drug. The use of a more hydrophobic solvent such as benzyl benzoate gives a less viscous depot with slower solvent diffusion. Extended drug release occurs over a period from several hours to several weeks by diffusion [65]. In some applications, an additive is used to affect release kinetics, drug stability, or other performance parameters. SAIB degradation follows drug release. Once administered these low viscous SAIB/Drug formulation solidify into a semisolid or solid depot post solvent diffusion. Thus it turns into a ‘solid’ dosage form as it is illustrated in Fig. 5 for a thermally-induced gelling system [66].

Relday® is being developed to address unmet clinical needs in this large patient population. A marketed long-acting injectable of risperidone (Risperdal Consta®) product, require twice monthly, intramuscular injections and drug reconstitution prior to administered, which achieved global net sales of $1.3 billion in 2013. Relday® if approved will be the first long acting depot once-monthly, subcutaneous antipsychotic preparation that may have advantage over marketed product with respect to pharmacokinetic profile, reduction in injection volume as well as simplified dosing regimen. Relday® will not only provide a new treatment option but also address unmet clinical needs for patients. In 2011, the combined market for oral and injectable antipsychotic products is estimated at more than $17 billion [64].

![Image](https://via.placeholder.com/150)

**Fig.5. In situ gel forming system (1 epidermis and dermis, 2 subcutis, 3 muscle)**

**Conclusion**

Since the introduction of long-acting first generation antipsychotics, the better more improved outcome in the management of schizophrenia have been tried by clinicians. The entry of second-generation antipsychotics has led to further progress with the introduction of atypical drug that minimises the development of adverse effects, as well as broader risk benefit ratio. Second-generation long-acting injectables extend the favourable outcomes, improved compliance obtained with for better long-term schizophrenia management.

The various marketed long-acting drug delivery technology product has come a long way and will continue to grow at an impressive rate. Today's various long acting depot technologies enable the incorporation of drug molecules into different delivery systems with required release profile for a desired period of time, thus providing numerous therapeutic and commercial advantages. A large number of companies are focusing more on novel long acting technology and also involved in the development products using novel long acting technology, which is evident by an increased number of products in the market and the number of patents granted in the recent past. Tomorrow's drug definitely will be more challenging in terms of the development of technology, and pharmaceutical scientists will have to be ready for a difficult task ahead. Future long-acting second-generation antipsychotics clinical trials should include outpatient functioning, and preferably be of longer duration to address unmet clinical need as well as cost-effectiveness.
REFERENCES