Research Paper

Volume : 4 | Issue : 12 | December 2015 • ISSN No 2277 - 8179

New-Generation Antipsychotics Long-Acting Injectable Formulations and Drug-Delivery Technologies

Pharma

KEYWORDS : Schizophrenia, Long acting injectable, First-generation antipsychotic, Second-generation antipsychotic, Long-Acting Drug Delivery Technology

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ABSTRACT

Compliance is a major problem in the treatment of schizophrenia. Several oral second-generation antipsychotics drugs are available for schizophrenia management. Non-compliance and limited availability as oral drugs limits the benefits. Second-generation antipsychotics long-acting injectable (LAIs) shows more controlled treatment of negative symptoms of schizophrenia and better therapy adherence as compared to first-generation LAIs. Various new innovative technologies that utilize fully bioresorbable/biodegradable polymers as a long acting polymers which allow for increased performance of new and existing pharmaceutical drugs for the development of LAIs, which includes Medisorb®, Monospheres®, and SABER™ depot technologies.

1. Introduction

Schizophrenia a chronic, disabling and progressive disease covering 0.8% to 1% of the general population [1]-[2]. Relapsing of schizophrenia is due to non-compliance where even brief periods of non-compliance can increase the risk of hospitalization [3]-[5]. Approximately 50% of patients as estimated escape taking about 30% or more of their medications for schizophrenia [6]-[8]. The major side effects of antipsychotics including extrapyramidal symptoms, weight gain and cognitive impairment contribute to non-compliance [9]-[11].

Long acting injectable (LAI) formulations of antipsychotic drugs were developed to allow the drugs to be delivered in a controlled or modified form, over time, following administration. This has the advantage over tablets as it maintained a steady state therapeutic concentration of the drug, with less fluctuation of peaks and troughs concentration and therefore minimising some of the side effects and variable effects. The achievement of a steady state therapeutic concentration from regular immediate release injections also affords protection from relapse beyond the time the last injection was received. From a treatment point of view, long-acting injectable of antipsychotics are frequently seen as an intervention to improve compliance [12].

Even during the early times of antipsychotic drug therapy, formulators realized that long-acting injectable formulations of antipsychotic drugs which can maintain therapeutic plasma concentration for several weeks after a single intramuscular injection not only minimise side effects but also could offer a way to partially overcome the problem of noncompliance in the therapy of schizophrenia [13]. It was estimated that 28.8%–80% of patient's poor compliance is observed across both first-generation and second-generation antipsychotics drugs [14]-[17]. Almost 54.9% versus 50.1% compliance is observed with oral second-generation antipsychotics versus first-generation antipsychotics [18].

Many actions have been tried to improve compliance. These include specific treatments such as electronic reminders [19], actions taken that are tailored to the patient [20], more focusing on mental status examination of patient[21]-[22], improving oversight by friends or relatives [23]-[25], or focusing on the relationship between the patient and care taker or provider [26]-[28].

As will be outlined, medication compliance is a major problem a patient with schizophrenia face. Therefore, the development of long-acting injectable second-generation antipsychotic drugs with limited adverse effects and which allows excellent medication compliance is an important issue for the long-term management of schizophrenia. This review article focus on (1) Comparison among available first-generation long acting antipsychotic injectable and second generation long-acting antipsychotic injectables and (2) Summarizes the available drug-delivery technologies on long-acting antipsychotic injections with ongoing clinical studies on long-acting injectable formulations. The various long-acting drug-delivery technologies have attracted worldwide interest among pharmaceutical/drug delivery companies, which led to the development of commercial therapeutic products for a wide range of clinical applications.

2. First-generation antipsychotic long-acting injections

First-generation antipsychotic (AP1G) long-acting injectables are commonly called 'depot' injections. Depot refers to the way the drug is deposited 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 [13]. 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 [29]. 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 [30]. 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 AP1G, psychiatrists started preferably prescribing AP2G for long-term treatment of schizophrenia as they were seen as more efficient and well tolerated [31]. 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 [32]. 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 [33]-[35]. In a survey [5] psychiatrists were asked the preference of AP2G over LAIs and they only prefer long-acting injectable antipsychotics to one in every three schizophrenic patients [36]. A list of Commercially Available first-generation antipsychotic (AP1G) LAIs are illustrated in table 1 [37]-[39].

Table 1: Commercially Available Long-acting First-generation antipsychotics injectables

Molecules	Prodrug	Brand	Vehicles	Company
Fluphenazine	Fluphenazine decanoate	Modecate®	Sesame oil	Sanofi-aventis
Haloperidol	Haloperidol decanoate	Haldol®	Sesame oil	Janssen-Cilag
Zuclopenthixol decanoate	Zuclopenthixol decanoate	Cloxipol®	Sesame oil	Lundbeck

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 [40]. The slow and controlled release pharmacokinetics of these long-acting injectable (LAI) drugs [41] 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 [42].

In the U.S. 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 [43] as illustrated in table 2.

Table 2: Commercially Available Long-acting Second-generation antipsychotics injectables

Molecules	Brand	Market approval	Patent protection	Company
Risperidone	Risperdal Consta®	2003 (US)	US 6,667,061 US 6,596,316	Janssen Pharma
Paliperidone palmitate	Invega Sustenna®	2009 (US)	US 6,555,544 US 6,077,843	Janssen Pharma
Olanzapine pamoate monohydrate	Zyprexa Relprevv®	2009 (US)	US 6,169,084	Eli Lilly
Aripiprazole	Abilify Maintena®	2013 (US)	US 7,807,680 US 8,338,427	Otsuka Pharm

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].

Aripiprazole (Abilify Maintena®) is the fourth second-generation long-acting injectable suspension is an intramuscular (IM) depot formulation of oral aripiprazole. Abilify Maintena® was approved in February 2013 as a once-monthly injection for the treatment of schizophrenia [44]-[45]. Other second and third-generation LAIs are in development [13]. Comparison among available LAIs in the US is illustrated in Table 3 [43].

Table 3: Comparison among available Long-acting Injectables in the United States

	Fluphenazine decanoate	Haloperidol decanoate	Risperidone microspheres	Paliperidone palmitate	Olanzapine pamoate	Aripiprazole monohydrate
Dosage strengths	25 mg/mL (variable dose)	50 mg/mL, 100 mg/mL (variable dose)	12.5 mg, 25 mg, 37.5 mg, 50 mg	39 mg, 78 mg, 117 mg, 156 mg, 234 mg	39 mg, 78 mg, 117 mg, 156 mg, 234 mg	300 mg, 400 mg
Dose range	12.5 to 100 mg	20 to 450 mg	12.5 to 50 mg	39 to 234 mg	150 to 405 mg	160 to 400 mg
Maximum recommended dose	100 mg every 2 weeks	450 mg every 4 weeks	50 mg every 2 weeks	234 mg every 4 weeks	300 mg every 2 weeks or 405 mg every 4 weeks	400 mg
Injection site	Deltoid or gluteal	Deltoid or gluteal	Deltoid or gluteal	Deltoid or gluteal	Gluteal only	Gluteal only
Injection technique	Z-Track	Z-Track	Standard	Standard	Standard	Standard
Solubilization and vehicle	Ester in sesame seed oil	Ester in sesame seed oil	Microsphere matrix in aqueous suspension	Nanoparticles in aqueous suspension	Nanoparticles in aqueous suspension	Lyophilized powder reconstituted with sterile water to form an injectable suspension
Initiation or loading	Loading possible	Loading possible	None	Initiation required	Initiation required	None
Time to peak	8–24 hours	3–9 days	4–5 weeks	13 days	<1 week	5–7 days
Overlap with oral	1 week	4 weeks (none if loading)	3 weeks	None	None	2 weeks
Time to steady state	2–3 months	2–3 months	6–8 weeks	36 days	3 months	3–4 months

4. Long-Acting Drug Delivery Technology

4.1 Medisorb® Microspheres Technology

Medisorb microsphere technology is Alkermes's 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

Volume : 4 | Issue : 12 | December 2015 • ISSN No 2277 - 8179

from the body as carbon dioxide and water (D) as it is illustrated in Fig. 1 [46].

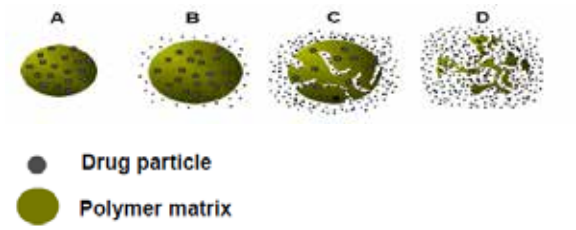

Fig. 1: Schematic representation of the Medisorb® Microspheres Technology

Risperidone Long acting injection (Risperdal Consta®) uses Alkermes' Medisorb PLG polymer-based microsphere technology to deliver and sustained 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 [47].

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 [40].

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 applide 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 [48].

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 [47].

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™ [49].

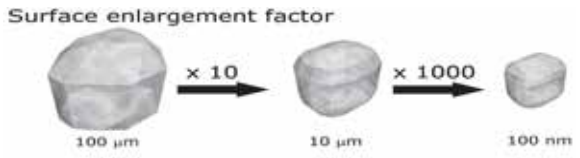

Fig: 2. Schematic representation of the NanoCrystal® process

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 extended-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 [50]-[51].

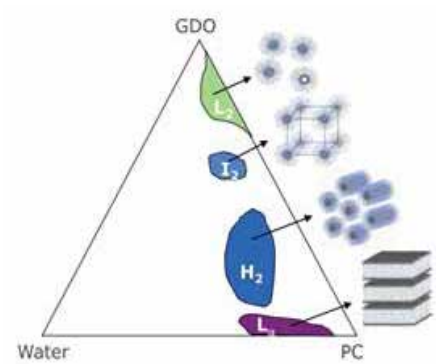

Fig: 3. Schematic representation of the FluidCrystal® process

4.4 Monosphere™ Technology

The microsieve technology [52] developed by Nanomi allows for the production of monodispersed microspheres in a large scale. Microsieves are silicone-based membranes with uniform pore size and shape, which are fabricated using a photolithographic technique widely utilized in the semiconductor industry. A monodispersed 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 [53].

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 which 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 [51].

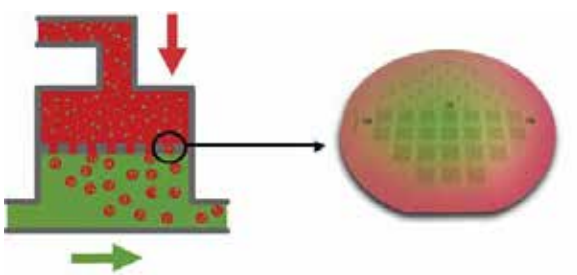

Fig: 4. Schematic representation of the microsieve™ emulsification process

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 [54]. Rapid expansion of supercritical solutions (RESS) process is an organic solvent-free method that has been used to produce microspheres for drug delivery applications [55]-[57]. 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 [58]-[59]. 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 component to the spray to produce monodisperse particles [60] and ultrasonic vibration to produce smaller particles leading to increased mass transfer rate between the solvent and the scCO2[53].

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 CO_2 under pressure resulting in the formation of supercritical carbon dioxide ($scCO_2$). The formed $scCO_2$ homogeneously mixed the polymer and the required drug using a rotor blade situated within the chamber. The $scCO_{2\ a}$cts 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 injectable which they uses 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 extende 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 [61].

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 of 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 [62].

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 [11].

On Oct 05, 2015, US FDA approved aripiprazole lauroxil (Aristada™) extended release injectable suspension for the treatment of schizophrenia [63].

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.

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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 for patients. In 2011, the combined market for oral and injectable antipsychotic products is estimated at more than $17 billion [64].

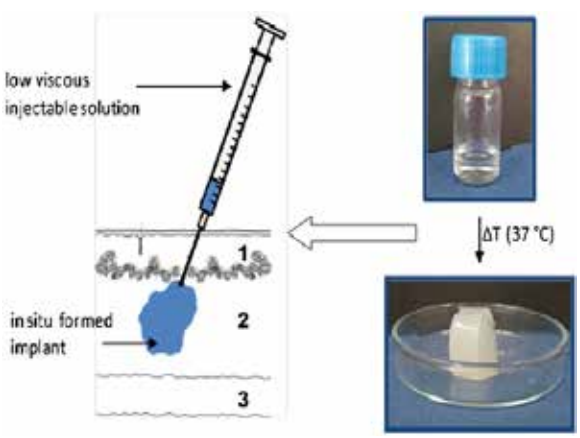

Fig.5. In situ gel forming system (1 epidermis and dermis, 2 subcutis, 3 muscle)

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.

REFERENCE

References | [1] Messias E, Chen CY, Eaton WW. Epidemiology of schizophrenia: review of findings and myths. Psychiatr Clin N Am. 2007; 30:323–338. | [2] McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008; 30:67–76. | [3] Masand PS, Roca M, Turner MS, Kane JM. Partial adherence to antipsychotic medication impacts course of illness in patients with schizophrenia: a review. Prim Care Companion J Clin Psychiatry. 2009; 11:147-154. | [4] Weiden PJ, Mackell JA, McDonnell DD. Obesity as a risk factor for antipsychotic noncompliance. Schizophr Res. 2004; 66:51-57. | [5] Heres S, Hamann J, Kissling W, Leucht S. Attitudes of psychiatrists toward antipsychotic depot medication. J Clin Psychiatry. 2006; 67(12):1948-1953. | [6] Velligan DI, Lam YW, Glahn DC, Barrett JA, Maples NJ, Ereshefsky L, et al. Defining and assessing adherence to oral antipsychotics: a review of the literature. Schizophr Bull. 2006; 32:724-742. | [7] Kamali M, Kelly BD, Clarke M, Browne S, Gervin M, Kinsella A, et al. A prospective evaluation of adherence to medication in first episode schizophrenia. Eur Psychiatry. 2006; 21:29-33. | [8] Goff DC, Hill M, Freudenreich, O. Strategies for improving treatment adherence in schizophrenia and schizoaffective disorder. J Clin Psychiatry. 2010; 71(2):20-26. | [9] Ascher-Svanum H, Zhu B, Faries D, Lacro JP, Dolder CR. A prospective study of risk factors for nonadherence with antipsychotic medication in the treatment of schizophrenia. J Clin Psychiatry. 2006; 67:1114-1123. | [10] DiBonaventura M, Gabriel S, Dupclay L, Gupta S, Kim E. A patient perspective of the impact of medication side effects on adherence: results of a cross-sectional nationwide survey of patients with schizophrenia. BMC Psychiatry. 2012; 12:20. | [11] Turncliff R, Hard M, Du Y, Risinger R, Ehrich EW. Relative bioavailability and safety of aripiprazole lauroxil, a novel once-monthly, long-acting injectable atypical antipsychotic, following deltoid and gluteal administration in adult subjects with schizophrenia. Schizophr Res. 2014; 159:404-410. | [12] Motiwala FB, Siscoe KS, El-Mallakh RS. Review of depot aripiprazole for schizophrenia. Patient Prefer Adherence. 2013;7. | [13] Crowley J, Hardy GS, Vincent M, White J, Voyce A. Administration of Depot and long-acting antipsychotic injections, mental health practice. Vol.12, 2008:2. | [14] Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication non adherence in patients with schizophrenia: a comprehensive review of recent literature. J Clin Psychiatry. 2002; 63:892-909. | [15] Byerly M, Fisher R, Whatley K, Holland R, Varghese F, Carmody T, et al. A comparison of electronic monitoring vs clinician rating of antipsychotic adherence in outpatients with schizophrenia. Psychiatry Res. 2005; 133:129-133. | [16] Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM. Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatry Res. 2010; 176:109-113. | [17] Alene M, Wiese MD, Angamo MT, Bajorek BV, Yesuf EA, Wabe NT. Adherence to medication for the treatment of psychosis: rates and risk factors in an Ethiopian population. BMC Clin Pharmacol. 2012; 12:10. | [18] Dolder CR, Lacro JP, Dunn LB, Jeste DV. Antipsychotic medication adherence: is there a difference between typical and atypical agents. Am J Psychiatry. 2002; 159:103-108. | [19] Granholm E, Ben-Zeev D, Link PC, Bradshaw KR, Holden JL. Mobile Assessment and Treatment for Schizophrenia (MATS): a pilot trial of an interactive text-messaging intervention for medication adherence, socialization, and auditory hallucinations. Schizophr Bull. 2012; 38:414-425. | [20] Staring AB, Van der Gaag M, Koopmans GT, Selten JP, Van Beveren JM, Hengeveld L. Treatment adherence therapy in people with psychotic disorders: randomised controlled trial. Br J Psychiatry. 2010; 197:448-455. | [21] Schennach R, Meyer S, Seemüller F, Jäger M, Schmauss M, Laux G, et al. Insight in schizophrenia-course and predictors during the acute treatment phase of patients suffering from a schizophrenia spectrum disorder. Eur Psychiatry. 2012; 27:625-633. | [22] Trevisi M, Talamo A, Bandinelli PL, Ducci G, Kotzalidis GD, Santucci C, et al. Insight and awareness as related to psychopathology and cognition. Psychopathology. 2012; 45:235-243. | [23] Farley JF, Hansen RA, Yu-Isenberg KS, Maciejewski ML. Antipsychotic adherence and its correlation to health outcomes for chronic comorbid conditions. Prim Care Companion CNS Disord. 2012; 14: pii: PCC.11m01324. | [24] Farooq S, Nazar Z, Irfan M, Akhter J, Gul E, Irfan U, et al. Schizophrenia medication adherence in a resource-poor setting: randomised controlled trial of supervised treatment in out-patients for schizophrenia (STOPS). Br J Psychiatry. 2011; 199:467-472. | [25] Glick ID, Stekoll AH, Hays S. The role of the family and improvement in treatment maintenance, adherence, and outcome for schizophrenia. J Clin Psychopharmacol. 2011; 31:82-85. | [26] McCabe R , Bullenkamp J, Hansson L, Lauber C, Martinez-Leal R, Rössler W, et al. The therapeutic relationship and adherence to antipsychotic medication in schizophrenia. PLoS One. 2012; 7:e36080. | [27] Misdrahi D, Petit M, Blanc O, Bayle F, Llorca PM. The influence of therapeutic alliance and insight on medication adherence in schizophrenia. Nord J Psychiatry. 2012; 66:49-54. | [28] McCann TV, Boardman G, Clark E, Lu S. Risk profiles for non-adherence to antipsychotic medications. J Psychiatr Ment Health Nurs. 2008; 15:622-629. | [29] Fredholt K, Larsen DH, Larsen C. Modification of in vitro drug release rate from oily parenteral depots using a formulation approach. Eur J Pharm Sci. 2000; 11(3):231-7. | [30] Davis JM, Metalon L, Watanabe MD, Blake L. Depot antipsychotic drugs. Place in therapy. Drugs. 1994; 47(5):741-73. | [31] Patel MX, Nikolaou V, David AS. Psychiatrists' attitudes to maintenance medication for patients with schizophrenia. Psychol Med. 2003; 33(1):83-89. | [32] Tiihonen J, Walhbeck K, Lönnqvist J, Klaukka T, Loannidis JPA, Volavka J, Haukka J. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. BMJ. 2006; 333(561):224-227. | [33] Sim K, Su A, Ungvari GS, Fujii S, Yang SY, Chong MY, Si T, Chung EK, Tsang HY, Chan YH, Shinfuku N, Tan CH. Depot antipsychotic use in schizophrenia: an East Asian perspective. Hum Psychopharmacol. 2004; 19(2):103-109. | [34] Nasrallah HA. The case for long-acting antipsychotic agents in the post-CATIE era. Acta Psychiatr Scand. 2007; 115(4):260-267. | [35] Ahn J, McCombs JS, Jung C, Croudace TJ, McDonnell D, Ascher-Svanum H, et al. Classifying patients by antipsychotic adherence patterns using latent class analysis: characteristics of non-adherent groups in the California Medicaid (Medi-Cal) program. Value Health. 2008; 11(1):48-56. | [36] Prikryl R, Ku˚cerova HP, Vrzalova M, Ceskova E. Role of Long-Acting Injectable Second-Generation Antipsychotics in the Treatment of First-Episode Schizophrenia:A Clinical Perspective. Schizophr Res Treatment. 2012; 2012:7. | [37] http://www.medicines.org.uk/emc/medicine/6956/SPC/Modecate+Injection+25mg+ml (accessed on March 24, 2015) | [38] http://www.medicines.org.uk/emc/medicine/904 (accessed on March 25, 2015) | [39] http://home.intekom.com/pharm/lundbeck/clopixdp.html (accessed on March 25, 2015) | [40] Rainer MK. Risperidone long-acting injection: a review of its long term safety and efficacy. Neuropsychiatr Dis Treat. 2008; 4(5):919-927. | [41] Jann MW, Ereshefsky L, Saklad SR. Clinical pharmacokinetics of the depot antipsychotics. Clin Pharmacokinet. 1985; 10:315-333. | [42] McEvoy JP. Risks versus benefits of different types of long-acting injectable antipsychotics. J Clin Psychiatry. 2006; 67(5):15-18. | [43] Gopalakrishna G, Aggarwal A, Lauriello J. Long-Acting Injectable Aripiprazole: How Might It Fit In Our Tool Box?. Clin Schizophr Relat Psychoses. 2013; 7(2):87-92. | [44] Kane JM, Sanchez R, Perry PP, et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2012; 73(5):617-624. | [45] Abilify Maintena (Aripiprazole) US Prescrition Information http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202971s000lbl.pdf (Accessed on August 05, 2015) | [46] Ramstack M, Grandolfi GP, Mannaert E, D'Hoore P, Lasser RA. Long-acting risperidone: Prolonged-release injectable delivery of risperidone using medisorbò microsphere technology. Schizophr Res. 2003; 60:314. | [47] http://www.alkermes.com/ (accessed on October 05, 2014) | [48] Junghanns JUAH, Müller RH. Nanocrystal technology, drug delivery and clinical applications. Int J Nanomedicine. 2008; 3(3):295-310. | [49] Invega Trinza (Paliperidone Palmitate) US Prescribing Information http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207946s000lbl.pdf (Accessed on May 20, 2015) | [50] Burgess DJ, Wright JC. An Introduction to Long Acting Injections and Implants. Springer, US, 2012, pp 1-9. | [51] www.ondrugdelivery.com (Accessed on October 04, 2014) | [52] Veldhuis G, Girones M, Bingham D. Monodisperse microspheres for parenteral drug delivery. Drug Deliv Technol. 2009; 9(1):24-31. | [53] Mao S, Guo C, Shi Y, Li LC. Recent advances in polymeric microspheres for parenteral drug delivery-part 2. Expert Opin Drug Deliv. 2012; 9(10):1209-1223. | [54] Davies OR, Lewis AL, Whitaker MJ, Tai H, Shakesheff KM, Howdle SM. Applications of supercritical CO2 in the fabrication of polymer systems for drug delivery and tissue engineering. Adv Drug Deliv Rev. 2008; 60(3):373-387. | [55] Baxendale A, van Hooff P, Durrant LG, Spendlove I, Howdle SM, Woods HM, et al. Single shot tetanus vaccine manufactured by a supercritical fluid encapsulation technology. Int J Pharm. 2011; 413(1-2):147-154. | [56] Whitaker MJ, Hao J, Davies OR, Serhatkulu G, Stolnik-Trenkic S, Howdle SM, Shakesheff KM. The production of protein-loaded microparticles by supercritical fluid enhanced mixing and spraying. J Control Release. 2005; 101(1-3):85-92. | [57] Jordan F, Naylor A, Kelly CA, Howdle SM, Lewis A, Illum L.Sustained release hGH microsphere formulation produced by a novel supercritical fluid technology: in vivo studies. | J Control Release. 2010; 141(2):153-160. | | [58] Bahrami M, Ranjbarian S. Production of micro- and nano-composite particles by supercritical carbon dioxide. J Supercrit Fluids. 2007; 40(2):263-283. | [59] Reverchon E, Adami R, G. Caputo G, Marco ID. Spherical microparticles production by supercritical antisolvent precipitation: Interpretation of results. J Supercrit Fluids. 2008; 47(1):70-84. | [60] Mishima K. Biodegradable particle formation for drug and gene delivery using supercritical fluid and dense gas. Adv Drug Deliv Rev. 2008; 60(3):411-432. | [61] http://www.criticalpharmaceuticals.com/technology (Accessed on December 14, 2014) | [62] Blumberg LC, Zeidan TA, Maddaford A, Blumberg LC, Zeidan TA, Maddaford A, et al. Novel N-5-(acyloxyalkoxy) carbonyl prodrugs of olanzapine with physicochemical properties for extended-release. RSC Adv. 2013; 3:16270. | [63] Aristada ((aripiprazole lauroxil) US prescription information http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207533s000lbl.pdf (Accessed on Oct 10, 2015) | [64] www.durect.com/saberdrugdeliverysystem (Accessed on December 28, 2014) | [65] Pandya Y, Sisodiya D, Dashora K. Atrigel, implants and controlled released drug delivery system. Int J Biopharmaceutics. 2014; 5(3):208-213. | [66] Kempe S, Mäder K, In situ forming implants-an attractive formulation principle for parenteral depot formulations. J Controlled Release. 2012; 161:668-679. | | |