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REVIEW ARTICLE

Controlled Parenteral Formulations: An Efficacious and Favourable Way to Deliver the Anti-psychotic Drugs

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Abstract: The current paradigm of pharmaceutical formulations is focused on the controlled & sustained delivery of a drug for the management of chronic impairments. Since these diseases need daily and multiple intakes of the drug (*i.e.*, twice or thrice a day) and missing a single dose, leads to the poor therapeutic window which governs unpleasant pharmacological response and ultimately patient in-compliance. All over the world, millions of patients are suffering from life-threatening diseases; one of which is "psychosis", which immensely requires prolong and sustain release of the drug. Moreover, mainstay lacuna with antipsychotic medication is the reoccurrence of the symptoms, and patient adherence on the therapy has been observed. These issues attract scientists to formulate the Controlled Parenteral Antipsychotic (CPA). As per the literature search, significant work has been performed on the development of Novel Controlled Parenteral Formulations (CPFs) for the treatment of psychosis and especially focus has been given to microsphere, esterification, nanoformulation, and salt-based formulation. Reports revealed that all of the above-mentioned formulations have shown enormous potential to enhance the duration of a drug in the body for a longer period in a controlled manner. The development of a drug in any form has shown a great impact on the patient's life, with tremendous productivity in the Pharma Market. As well as, this has raised the hope to get more efficacious results of both the categories *i.e.*, typical & atypical antipsychotics and limiting the drawbacks of conventional antipsychotic drug delivery. Controlled formulations have also shown the prominent solutions to handle one of the major obstacles that arises due to the Biopharmaceutical Classification System (BCS). Drugs belonging to any of the BCS class can be utilized now with the idea of CPF. In this context, the current paper relies on CPA's strengths, weaknesses, opportunities, and challenges followed by a compilation of attempt made by scientists on its formulations (microspheres, salt-based, and nanoformulation) which will be one-stop-shop for the researchers working globally in this field to make better improvement on the existing options for psychosis. In summary, this review explains the concept of CPA as a promising option to treat psychosis.

Keywords: Controlled parenteral antipsychotic, biopharmaceutical classification system, controlled parenteral formulation, long-acting parenteral, microspheres, nanoparticle, salt formation.

1. ROLE OF CONTROLLED RELEASE PARENTERAL AS ANTIPSYCHOTICS

We are aware that the parenteral route of administration is one of the most fascinating routes to deliver the drug because of its rapid action & magnificent bioavailability [1, 2]. But, some major areas still remain to modify, for instance, prolongation of action, avoidance of frequent administration, and enhancement of the efficacy of the drug; which highly motivate the scientists to look forward to developing Controlled Parenteral Formulation (CPF) [3-12]. There are a plethora of diseases (psychosis, Parkinson, Alzheimer, depression, viral, hormonal imbalance, epilepsy, asthma) that highly distresses the life of a person due to their life-long characteristics. Countless patients are suffering across the world with such types of diseases and their complete cure is not possible till date [13].

For better utilization of a drug in the body, the conventional system was furnished and accepted as a controlled and novel drug delivery system [5, 14]. Furthermore, labs investigation has shown crystal clear importance of the psychotic parenteral medication over oral route. Therefore, it is utilized due to its valuable impact on the accurate delivery of drugs as it avoids the pre-systemic metabolism as well as its onset of action [15]. CPF is more popularly termed as

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'depot, prolong or long-acting formulation' [16]. The literature says that in terms of efficacy and tolerability both conventional & CPF have shown excellent characteristics [17-22]. Many associated advantages like- it serves good option for the drugs having low aqueous solubility, short half-life, & less bioavailability are the keen points of CPF for gaining the abundant popularity [9, 10, 23-25]. The following table illustrates various depot formulations available in the market for different ailments (Table **1**).

These prominent consequences and successful market of the above-mentioned formulations has paved a way for the researchers to look for the betterment of other diseases; one of which is "psychosis" as the proportion of psychosis suffering is high it belongs to the top 15 listed disorder which largely contributes to affect the worldwide population [26].

In acute psychosis, the treatment with conventional drug delivery is the primary choice. Psychosis is a complex neurodegenerative disorder of the Central Nervous System (CNS). It is a Greek word, composed of 'psyche' meaning 'mind' and 'oasis' meaning 'abnormal condition'. It is a mental situation when a person behaves out of control, unable to take the decision and communicate, and suffers from delusions & hallucinations. Psychosis can result in the form of schizophrenia *i.e*. chronic psychosis, or any mood-related disorders, for instance, depression or mania *i.e*. acute psychosis. The actual cause of the psychosis condition is still not clear. On the basis of data, genetic variations (Neuregulin-1, Dysbindin, Proline Dehydrogenase, and G72 are the prominent gene molecules) and environmental factors have been reported to play a key role in the psychotic condition. Additionally, dopamine is a well-known neurotransmitter, widely present in the autonomic, somatic and Central Nervous System (CNS) areas. The high amount of dopamine content in the limbic segment of the forebrain (temporal & prefrontal areas) and low concentration of serotonin neurotransmitter *i.e*. (5-Hydroxytryptamine, and Noradrenalin), causes the imbalance of brain activities and resulted in the psychosis condition.

Electroconvulsive therapy (ERT) is also an option to treat psychotic patient especially catatonic schizophrenia but nowadays this has been replaced by another alternative. In fact, only primary affective disorder required ERT (Montgomery, 2007).

Drugs are classified as First-Generation Antipsychotic (FGA), having weak potency for D2 (Dopamine) receptor and Second-Generation Antipsychotic (SGA), which showed excellent 5-Hydroxytryptamine (5-HT2) agonistic activity. Drugs which came earlier in the market were having a potent affinity to antagonize dopamine receptor D2, but less effective for the D3, D4, and D5. To confirm the affinity of a drug molecule with dopamine receptor, radio-ligand binding and autoradiographic assay have been done (Baldessarini and Tarazi, 1996). Reserpine is an active phytoconstituent present in *Rauwolfia* plant extract, very first used as an antipsychotic agent in 1950. With its good efficacy, the number of side effects has been observed such as hypotension, diarrhoea, and depression, *etc*. Later, an introduction of chlorpromazine and its confirmation regarding the positive clinical outcome gave a path to the scientist working on Antipsychotic area. Chlorpromazine and flupenthixol come under the phenothiazines and thioxanthenes class respectively, both are potent and most prescribed drugs. There is continuously research going on antipsychotic compounds in various labs with an idea to introduce new molecules or to modify the existing moiety. As per clinical data, SGA'S have shown less extrapyramidal side effects than FGA'S that have increased demands of SGA in the market and became the primary choice for psychosis treatment. Even in the concern of adherence, SGA has been used preferably. However, for the management of acute or chronic psychotic condition any

Table 1. Illustration of some marketed formulations.

Injectable Depot	Formulation	Therapeutic Area
Penicillin G-procaine	Suspension	Antibacterial
Cyanocobalamin-Zn-tannate	Suspension	Vitamin B12
Medroxyprogesterone acetate	Suspension	To prevent pregnancy
Fluphenazine enanthate and decanoate in oil	Solution	To treat Schizophrenia
Adenocorticotropin-Zn-tannate gelatine preparations	-	Antidiarrheal
Microcrystalline desoxycorti--costerone pivalate in oleaginous	Suspension	Hypoadrenocorticism
Testosterone enanthate	-	To balance the level of Testosterone
Testosterone enanthate-estradiol valeate in ethyl oleate BP	-	As anabolic steroid
Nandrolone decanoate	Injection	As anabolic steroid
Insulin Zinc	Suspension	To maintain sugar level
Lenovorgestrel releasing sub Dermal	Implant	As contraceptive
Goserelin acetate-releasing Biodegradable	Implant	For prostate cancer

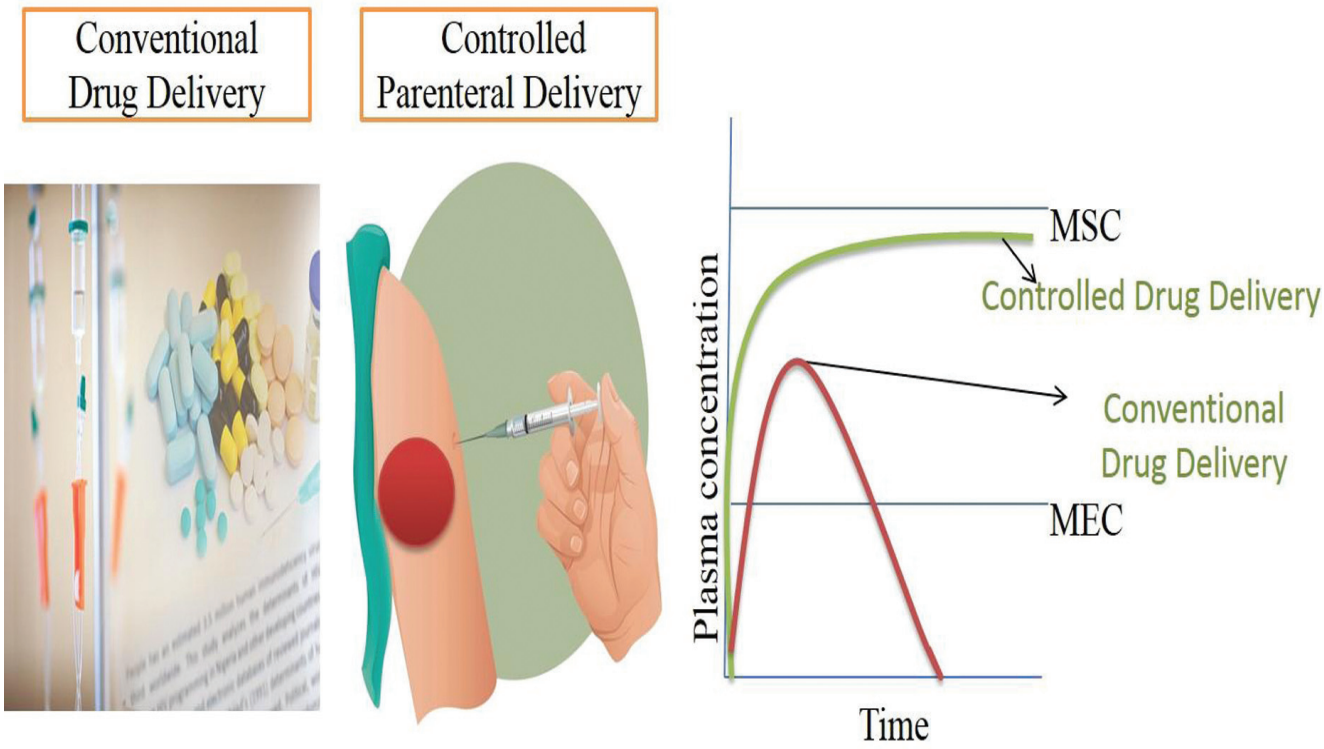


Fig. (1). Comparison of conventional & controlled parenteral drug delivery.

class of compound can be used. But it's true, even after the existence of these many treatments, till date complete cure of disease is not achieved.

Psychotic patients under oral therapy are advised to take the medicines at least three times a day to maintain the dosage regimen [27]. Failure of any dose leads to poor drug plasma concentration. Moreover, reoccurrence of this situation (once patient stop medications) and recalling the dosing schedule is a big factor for the patient non-compliance [28-32]. In some cases, hospitalization is also required, which results in a very costly treatment. The dose of antipsychotic drugs is very high that is responsible for major side effects such as diabetes, weight gain, *etc*. To minimize these adverse effects, the demand for lower dose increases and the implementation of nano-formulation has significantly strengthened the psychotic treatment. There is detailed information available in "The Clinical Antipsychotic Trials of Intervention Effectiveness" (CATIE) regarding the demerits of conventional parenteral drug delivery [17, 33-40]. The following image throws light on the comparison of both the drug deliveries (Fig. **1**). Upon administration of conventional drug delivery, rapid elimination of the drugs has been observed on the other hand controlled delivery has sustained effect for a predefined time.

In the same manner, to overcome the above-discussed challenges of conventional drug delivery, Controlled Parenteral Antipsychotic (CPA) has come into the picture in the era of 1966 [41]. Scientists have reported that around 11 controlled antipsychotic formulations are available in the market. One report says that in the UK, Denmark and Sweden almost <20% psychotic patients are under the depot therapy [33, 42, 43].

However, a lot of research has been done on CPA for the proper management of the Psychosis disorder up till now but loopholes are still there. Burst release and proper selection of drug dose are one of the major prerequisites in order to develop any depot. In spite of massive attention gained by the controlled formulations, burst release is the main reason for the failure of drugs even after the successful development of a formulation. Notwithstanding, many reports have also highlighted the lack of support from the regulatory bodies to come up with the CPF [44, 45].

Controlled and sustained kinds of formulations have the main advantage that patients can obviate from the daily intake of drugs. In correspondence to this, there are numerous approaches used by the researchers to sustain the drug from day to a week, administered by the parenteral route as shown in Fig. (**2**). Besides it, Fig. (**3**) illustrates the techniques employed to prepare nano formulations [46].

2. IMPORTANCE OF CONTROLLED FORMULATIONS IN BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

As we are familiar, the classification of any API is done on the basis of the Biopharmaceutical Classification System (BCS), dividing into the four classes (BCS-1, 2, 3, and 4). Solubility and permeability are the two primary aspects on which this classification is based on. The maximum ratio of acceptable Active Pharmaceutical Ingredient (API) falls into

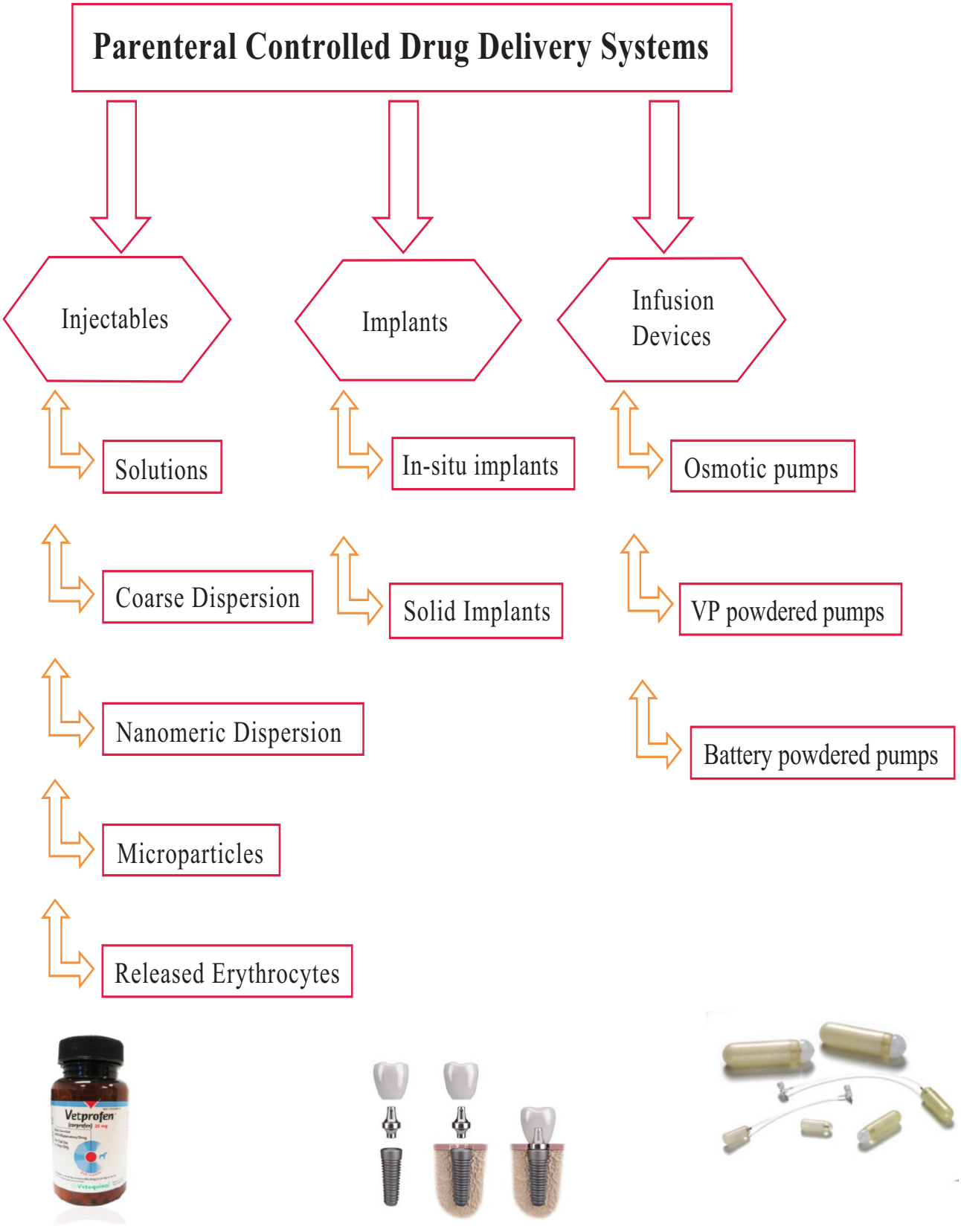


Fig. (2). Classification of controlled parenteral drug delivery.

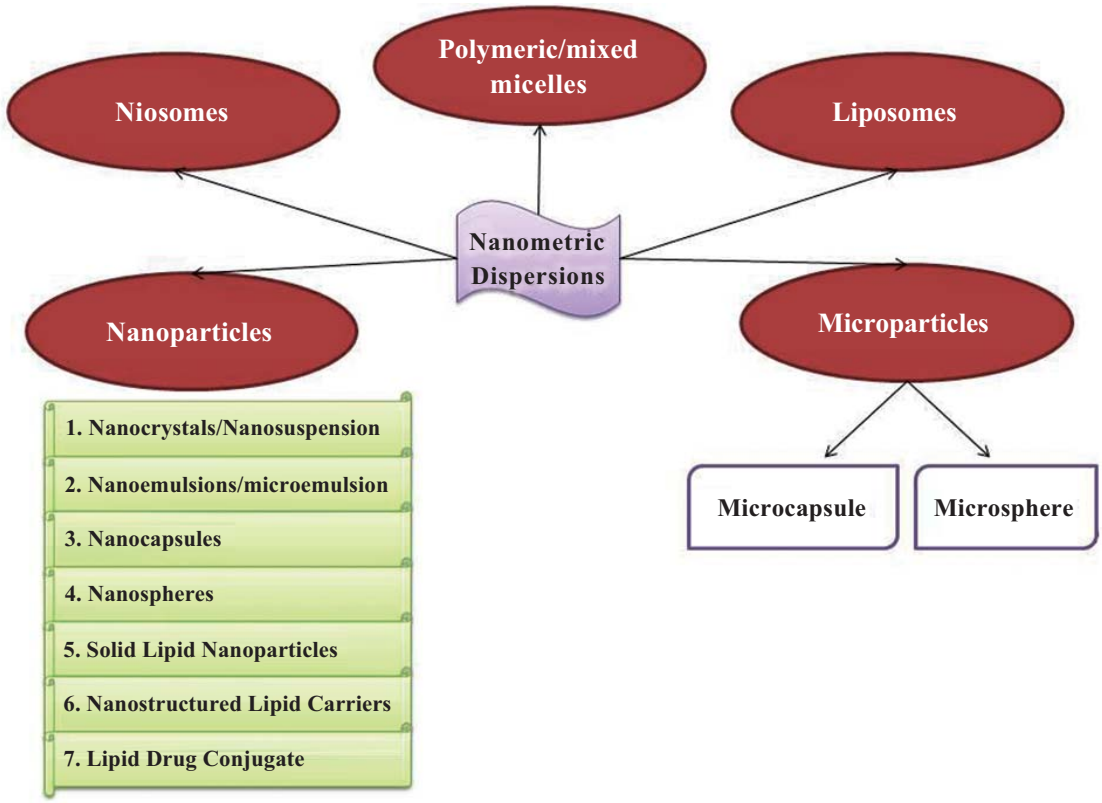


Fig. (3). Classification of nano drug delivery.

two classes *i.e.* BCS-1 and 2. Rest two; class-3 possesses less permeability and and class-4 has less solubility as well less permeability so their use in any formulation becomes quite challenging.

Notwithstanding, a drug is having high solubility and high permeability that is belonging to the BCS class 1, which might have a short biological span because of its rapid absorption. It needs to be taken by the patient in many intervals of time which ultimately results in the poor biological effects. To overcome this issue, the development of CPF has played a vital role, as the incorporation of a polymer or counter ion, has the potential decreasing the solubility followed by the effect of a drug.

Similarly, on the other hand, drugs possessing poor solubility and high permeability *i.e.* (BCS class 2) have also been utilized in a good manner, as low aqueous solubility results into ineffectual absorption of the drug. To deal with this situation, encapsulation of API along with the polymer helps in the appropriate delivery as well as sustaining the effect of the drug. A latest published paper has enlightened the significant outcomes of nano and elaborated that nano has increased the market of different BCS class drugs [47].

The following-listed table comprises the antipsychotic drugs belonging to the BCS class and their controlled formulations (Table **2**).

3. ANTIPSYCHOTIC DRUGS AS CONTROLLED PARENTERAL FORMULATIONS (CPF)

As discussed above, there are different ways to maintain the plasma drug concentration for an extended period of time (Fig. **4**). These formulations intensively have been developed by the researchers and each type has its own unique value and role for the management of psychosis. This review compiles the formulation development carried out using microspheres, esterification derived, and nanoformulation approaches by scientists.

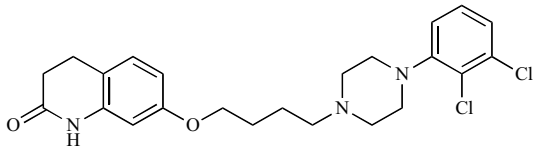
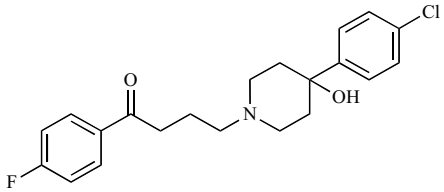
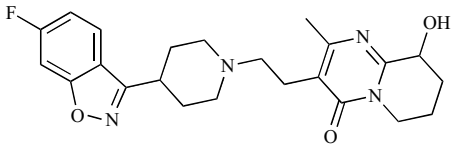
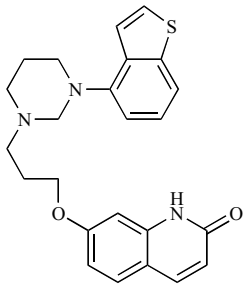
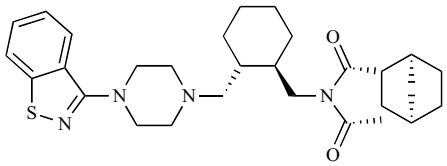
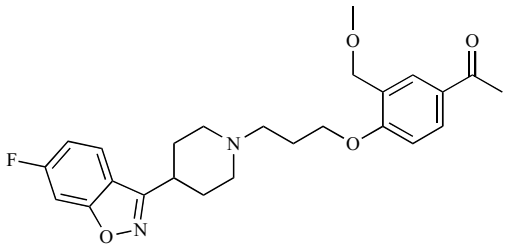
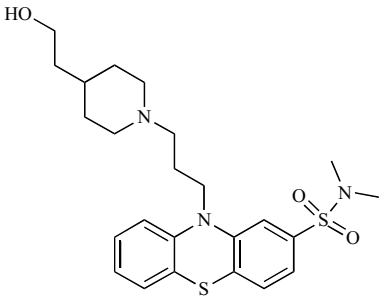
3.1. Microspheres

A phenomenon behind drug delivery through microspheres is wisely utilized for many chronic diseases, including the psychosis. microspheres have more surface area (small particle size) and provide a platform to both hydrophilic and hydrophobic drugs by controlling the rate release constantly for a predefined period. It belongs to the class of microparticles having a size of 1000 micron (spherical in shape) and has an excellent capability of encapsulating the drug. It consists of a drug surrounded by a polymer coating, which helps in the consistent release of drug by improving bioavailability [48]. Reports confirm that microspheres have enough potency to prolong the action of the drug in the biological system. Different techniques such as spray drying, solvent evaporation, wet inversion, and hot melt microencapsulation, *etc.* are widely employed to prepare the microspheres [49]. The following listed antipsychotic drugs have been prepared and evaluated as microspheres (Table **3**).

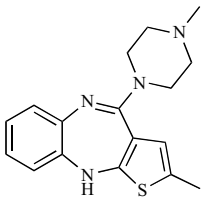
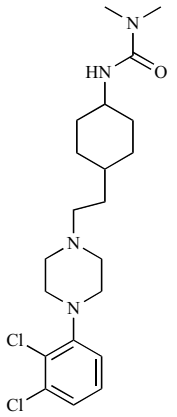
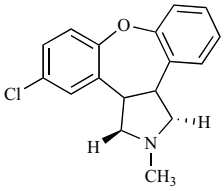
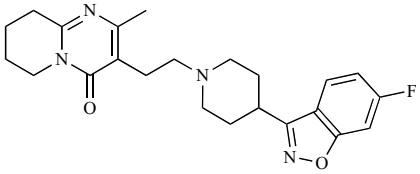
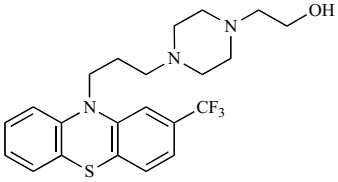
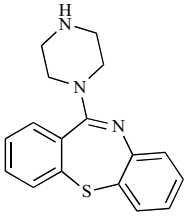
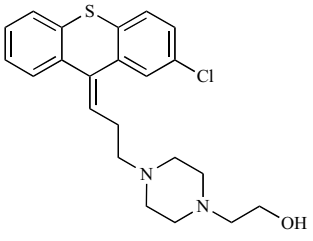
3.1.1. Haloperidol

It is one of the most prescribed antipsychotic drugs listed worldwide which is also explored for the management of Huntington's disease and Gilles de la Tourette's syndrome [50]. Haloperidol comes under the butyrophenone category

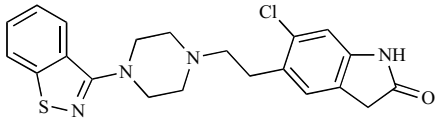
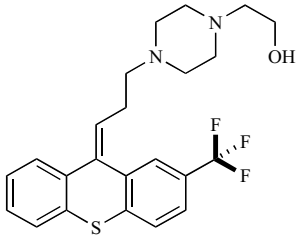
Table 2. Summary of controlled parenteral antipsychotic drugs along with their BCS class.

S. No.	Drug	BCS Class	CPF	Chemical Structure
1.	Aripiprazole	2	Microspheres, Salt	
2.	Haloperidol	2	Microspheres, Ester, Nano	
3.	Paliperidone	2	Microspheres, Ester, Nano	
4.	Brexpiprazole	2	Not reported	
5.	Lurasidone	2	Nano	
6.	Iloperidone	2	Salt	
7.	Pipotiazine	-	Ester	

(Table 2) contd….

S. No.	Drug	BCS Class	CPF	Chemical Structure
8.	Olanzapine	2	Microspheres, Salt, Nano	
9.	Cariprazine	2	Not reported	
10.	Asenapine	2	Not reported	
11.	Risperidone	1	Microspheres, Nano	
12.	Fluphenazine	-	Microspheres, Ester	
13.	Norquetiapine	-	Microspheres	
14.	Zuclopenthixol	-	Ester	

(Table 2) contd….

S. No.	Drug	BCS Class	CPF	Chemical Structure
15.	Ziprasidone	2	Nano, Ester, Microspheres	
16.	Flupenthixol	-	Ester	

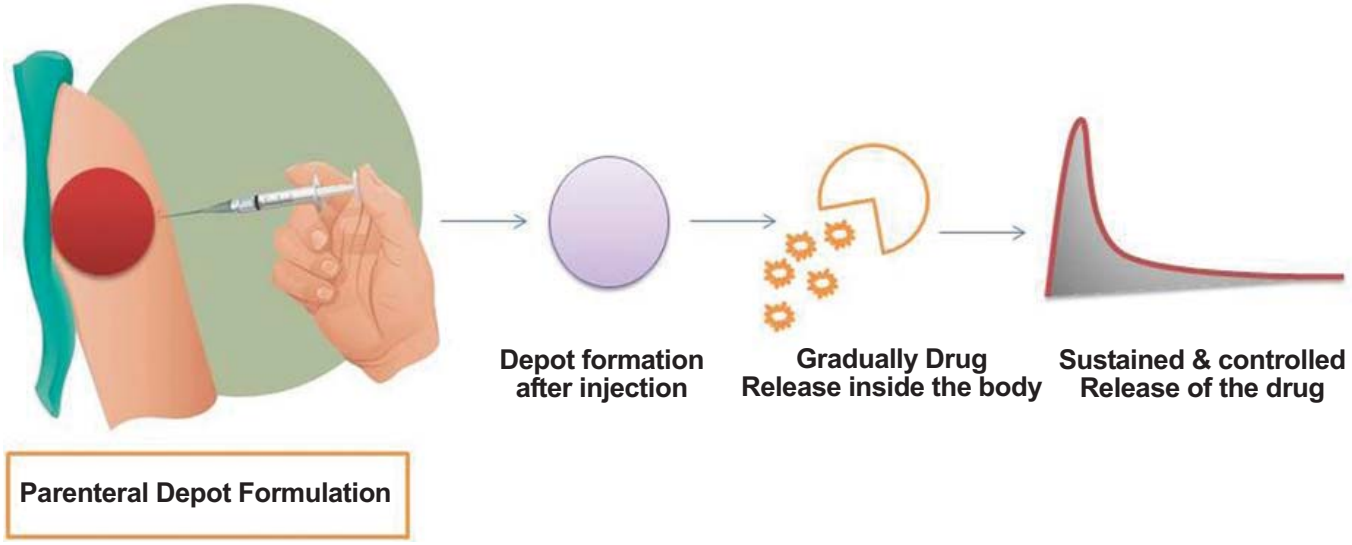


Fig. (4). Schematic representation of the sustained drug delivery.

Table 3. Summarized table of antipsychotic drugs and their extended time period.

S. No.	Drug	Microparticles	Esterification
1.	Haloperidol	Up to 2 months	-
2.	Aripiprazole	Up to 14 days Up to 2 months	-
3.	Risperidone	-	-
4.	Paliperidone	-	Up to 3 months
5.	Olanzapine	Up to 14 days In another study, up to 10 days	-
6.	Fluphenazine	30% of sustained release has been obtained	Up to 9 days
7.	Norquetiapine	Up to 20 days	-
8.	Flupenthixol	-	Up to 3 months
9.	Pipotiazine	-	Up to 15 days
10.	Zuclopenthixol	-	Up to 3 weeks

which is the FGA. It has low aqueous solubility (0.1 mg/ml) with 7.9 partition coefficient and 3.36 logP. This drug has an effective dose of 6-12 mg by oral and 1.5-3 mg by intramuscular (IM) route per day, which produces patient in-compliance that urges for the depot preparation. After administering from the oral route (2-3 times a day), it might undergo the first-pass metabolism that reduces its concentration in the plasma [51].

To improve the efficacy of haloperidol, microspheres has been prepared with biodegradable polymer poly (D, L-lactide-co-glycolide) (PLG) through emulsification-solvent evaporation method. Particle size (0.8, 2, and 8 microns), surface morphology and *in vitro* release study were performed to evaluate the drug-loaded PLG microspheres. Scientists concluded that prepared microspheres controls the release of Haloperidol up to 2 months through the intramuscular (IM) route [52].

3.1.2. Aripiprazole

It is the derivative of quinolinone, one of the most efficacious and frequently recommended drugs (Oral disintegrating tablet: 10 mg and 15 mg, Oral solution: 1 mg/ml, IM: 30 mg/day) which has an agonistic effect towards the dopamine receptor. In a comparison of oral and controlled formulations, CPA has shown significant improvement in the terms of tolerability along with efficacy. The drug is feasible in lyophilized powder form whereas sterile water acts as a vehicle to deliver it by IM route [53].

To achieve the long-term effect of aripiprazole, microspheres were prepared using PLGA (polylactic-co-glycolic acid) and cholesterol, both ingredients helped in retardation of the drug. Microspheres were prepared by a solvent evaporation method and characterized by following specifications *viz*. particle size, encapsulation efficiency, residual solvent analysis, surface morphology, and drug release behavior. The d-optimal design was used and the release pattern was studied. aripiprazole, microspheres were able to maintain the plasma concentration up to 14 days [54].

In a further aspect of the invention, polylactic acid (PLA) as a polymer along with methylene dichloride as a solvent was used to prepare microspheres by the solvent evaporation method. Common parameters for the estimation of microspheres; particle size, encapsulation efficiency, surface properties, and percentage yield of aripiprazole were observed. Further, by changing stirring speed between 2000-3000 rpm drug release was calculated as 88.41% and 94.65%, respectively [55].

In one of the laboratory investigations, three different grades of PLA (MW: 20,000, 95,000 and 110000) were used to prepare aripiprazole microspheres by a solvent evaporation method. This study was mainly directed towards drug-loading capability by varying temperature conditions. Authors have stated that prepared formulation containing 95000 MW of PLA has signified the desired morphological (smooth surface morphology) together with long-acting characteristics. Developed microspheres have been examined for release studies (*in vitro* and *in vivo*) and in the case of *in vivo*, the drug was injected subcutaneously to the rabbits that were detectable in the blood for the period of 2 months [56].

3.1.3. Risperidone

Risperidone (Tablet: 1mg twice dose), the first atypical antipsychotic drug has been formulated as CPA [57]. Till now, the number of research has been carried out to acquire more efficacious result in the depot form of Risperidone. Risperdal Consta, a depot formulation (Janssen) that is available in the market is approved by the Food and Drug Administration (FDA) in 2003 [58-60].

Risperidone Microspheres with the addition of biodegradable polymer; PLGA was prepared in one of the studies. The purpose of this study was to avoid the use of combination drugs. Here, two polymers in the ratio of 50:50 and 75:25 were selected, to provide controlled effects of Risperidone. During an *in vivo* study (Sprague-Dawley rats), the ratio of 75:25 has shown the desirable sustained release effects [61].

In one of the articles, the preparation of risperidone microspheres was done using oil/water emulsion and solvent evaporation studies. Biocompatible alkylene adipate polyester was used to prepare the microspheres. Various analytical methods have been used to characterize the formulation and particle size was found from 10-100 μm. The release rate of risperidone microspheres was found sustainable [62].

3.1.4. Fluphenazine

Fluphenazine brand name, prolixin (2.5-10mg/day) comes under the typical antipsychotic phenothiazines category. Nowadays, its use is replaced by atypical antipsychotics [63].

To prepare microspheres, lactide and lactide-co-glycolide were used as the polymer. *In vitro* release study showed up to 30% sustained release of fluphenazine in the form of microspheres [64].

In another study, PLGA loaded microspheres were prepared in comparison to fluphenazine Hcl and reported an increase in the degradation rate constant and a decrease in maximum time (T_{max}) parameters. Scientists concluded that fluphenazine PLGA loaded microspheres were having high polymer degradation rate, which helps in the acceleration of release rate of the drug in comparison to the loading [65].

3.1.5. Paliperidone

The therapeutic dose of paliperidone is 3-12 mg. In one of the trials, ethylcellulose was used as a polymer to prepare paliperidone microspheres. The emulsion solvent diffusion technique was used to prepare the microspheres and various parameters such as drug content, drug-polymer ratio, and particle size were studied. Drug release study was performed that showed a sustained effect of the drug. Different batches by varying concentrations were prepared out of which one formulation exhibited retardation in drug release (56.84%) amongst others which were optimized by the drug-polymer ratio [66].

3.1.6. Olanzapine

Olanzapine (Tablet: up to 20 mg, IM injection: 10 mg) is the most efficacious antipsychotic drug belonging to the class of thienobenzodiazepine which has a low partition coefficient of 2.2 [67, 68].

In order to prepare microspheres, PLGA was used as a polymer by the solvent evaporation method. The process was optimized through different parameters (drug loading, selection of surfactant, its quantity and solvent parameters) and evaluated by percent efficiencies, particle characteristics and many others chose criteria. Authors have mentioned that prepared Microspheres were able to sustain the effect of drug up to 14 days [69].

In another study to prepare olanzapine microspheres, different ratios (differs in molecular weight of PLGA) were taken into consideration. Total of 4 formulations was developed and optimized. An *in vivo* study was carried out in rats which signified the sustained effect of the drug up to 10-15 days that helped to reduce dosing frequency [70].

3.1.7. Norquetiapine

Norquetiapine is an active metabolite of quetiapine. Due to having less time period in a biological system (9-12 hrs), polymer (PLGA) loaded microspheres of norquetiapine free-base were prepared by an emulsion-solvent evaporation method. Prepared formulations were screened by the different analytical tools such as Powder X-ray Diffraction (PXRD), scanning electron microscopy (SEM), and Fourier Transform Infrared (FTIR). To determine release properties of the formulation, *in vitro* dissolution (rotary shaker) and *in vivo* (Sprague Dawley rats) study was performed. The prepared formulation had shown enhancement in half-life for a period of 20 days. For formulated Microspheres, maximum concentration (Cmax) =22.48±4.46ng/ml, t1/2=172.79±23.79 hrs and AUC=916.46±186.57ngh/ml were noted down that is found higher when compared with standard Norquetiapine [71].

3.2. Esterified Antipsychotics

Almost all the antipsychotic agents require dosing at regular intervals in a single day due to the potent concentration of the drug. Esterification is one of the preferable methods to sustain the drug for a durable period of time.

This depot system works on the basis of complex formation between the drug or active moiety and an ester (decanoate or palmitate). Due to the presence of hydroxyl group easily esterification can occur and drug forms depot when injected into the body. Various kinds of oils such as sesame or vegetable are used as a vehicle. An esterase enzyme present in the plasma hydrolyzed the esterified group of molecule and drug becomes available in the blood. But according to another report, the presence of esterase enzyme can be different among individuals and that could lead to variation in the concentration of the drug [72].

3.2.1. Haloperidol Decanoate

Decanoate form of haloperidol (Brand name Haldol Decanoate) got approval in 1967 for the management of psychosis [73-75].

In one report, haloperidol: Pamoate in a ratio of 1:1 or 2:1 has been prepared and characterized. The various method of preparation is described under the patent [76]. A number of clinical studies have been successfully performed at present and Haloperidol Decanoate (HD) found efficacious than its oral formulation [77-85].

3.2.2. Fluphenazine Decanoate (FZD)

Fluphenazine is insoluble in water, which has a partition coefficient of 9 [86]. Here, Sesame oil was selected as a vehicle to develop a depot form. Pharmacokinetic evaluation of the prepared formulation was done. Depot was administered by two different routes: intramuscular (IM) and intravenous (IV) in four Beagle dogs. The half-life of the Decanoate was found enhanced by the IM route (9.7±2.0 days) in comparison of both other formulations and routes (IM and IV route) [87]. Below listed Fig. (**5**) is a schematic picture of depot taking as an example of fluphenazine.

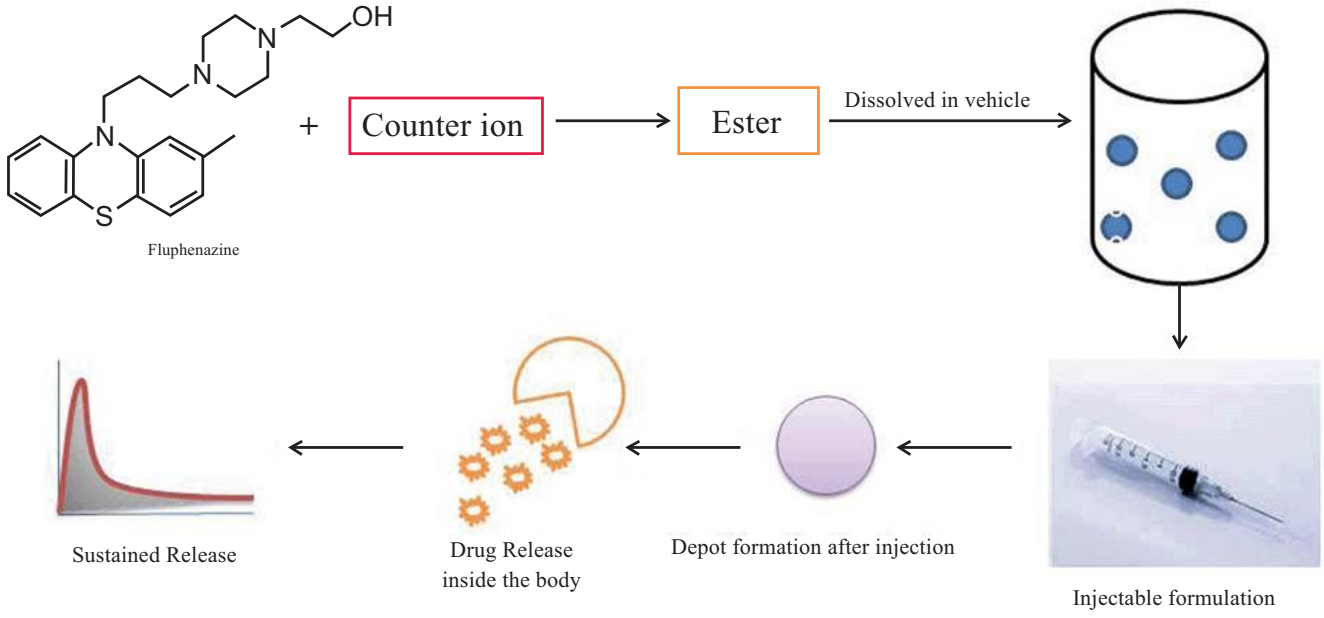


Fig. (5). Schematic representation on ester based depot formulation.

3.2.3. Paliperidone Palmitate (PP)

Paliperidone (Invega) an atypical, FDA approved (August 2009) active metabolite (9-hydroxy-risperidone) of Risperidone [88, 89]. It is insoluble in water and has a partition coefficient value 10.1 [90]. It is clinically available as long-acting IM form where palmitate was used as a counter ion [91]. Depot formulation of Paliperidone Palmitate (PP) is available in different dose strengths 39, 78, 117, 156, 234 mg. A report says that PP is able to give the effect up to 3 months with good tolerability [92].

3.2.4. Flupenthixol Decanoate

This drug belongs to the class of thioxanthenes. It is a potent neuroleptic compound (3 mg) with no or minimal sedative effects [93]. Decanoate formulation (fluanxol depot) has been introduced to maintain the plasma concentration for the longest time. Depot formulation was given by IM route within every 3 months to the psychotic patients. A trial was carried out after selecting the chronic female patients to evaluate the dose-response of Flupenthixol Decanoate (FTD) [94].

3.2.5. Pipotiazine Palmitate

Piportil, a brand name of Pipotiazine reported giving more antipsychotic results with less extrapyramidal side effects [17]. It stops the Psychosis condition by acting on dopamine receptors. Depot form of Pipotiazine using sesame oil as a vehicle (Pipotiazine Palmitate, an esterified form; 25 mg/ml, 50 mg/ml) was prepared. Pharmacokinetics have been carried out using both rats and dogs and reported half-life is about 15 days [95]. As per latest reports, due to a shortage of Pipotiazine API, it has withdrawn from the market near 2015-2016 worldwide.

3.2.6. Zuclopenthixol Decanoate

Zuclopenthixol (tablet: 10, 25 and 40 mg), is an FGA drug belongs to the thioxanthenes class. It acts by antagonizing the dopamine receptor [96, 97]. A decanoic solution of Zuclopenthixol (Clopixol) was prepared with the vegetable oil to make depot that is known as Zuclopenthixol Decanoate (200 and 500 mg). The dosage regimen of this depot formulation is every two-three weeks [98].

3.2.7. Iloperidone

It is a new atypical antipsychotic (Fanapat; tablet 1-12 mg, half life 18 hrs needs to administer twice daily) moiety in the market approved by the FDA in 2009 [99-101]. Iloperidone shows the action after binding with the serotonin receptor. A patent (8614232) was granted in 2013 on microcrystal injectable depot (1-200 microns) formulation by Novartis. This depot formulation is currently under development [102].

In one of the very recent trials *in situ* gel was prepared which was able to deliver the drug for a period of one month (*in vitro*). The novelty of formulation was that scientists have employed class 3 solvent; Dimethylsulfoxide (DMSO) in a very small quantity and Sucrose acetate isobutyrate (SAIB) was used that has given the sustained effect of the drug. The formulation was optimized by D-optimal design and it was able to retard the release up to 85.71% [103].

3.3. Nanoformulation

The current era of Pharma is centralized on the concept of 'nano', due to its size under 1000nm that ultimately results in good therapeutic responses. The focal point of Nanotechnology especially in the case of Psychosis is marked by decreasing the dose of drugs in the biological system that might cause fewer side effects. As we know, these drugs require a larger dose to show its curative effects but, on the other hand, it also induces adverse effects such as diabetes or blood-related disorders [104]. A drug or molecule in Nano size exists in any form *i.e*., Nanoemulsions, Solid Lipid Nanoparticles (SLNs), Nanocapsules, nanocrystals, *etc*. Moreover, the inclusion of the polymer provides a sheet to cover the drug from degradation by avoiding immediate release which helps to achieve controlled release of the drug. It provides a reliable, reproducible plasma concentration level of the administered moiety [47, 105, 106]. The below-listed antipsychotic drugs have been taken into consideration of Nanoformulation (Table **4**).

3.3.1. Haloperidol

3.3.1.1. Nanoparticles

Haloperidol Nanoparticles (200-2000nm) has been prepared using PLGA by an emulsion-solvent evaporation technique. The free drug was removed using a solid phase extraction method that has helped to attain the accurate efficacy of nanoparticles. It has been noticed that incorporation of PLGA helped to achieve longer drug release up to 13 days with minimum burst release [107-109].

3.3.1.2. Nanosuspension

Haloperidol was observed with the induction of oxidative stress as a side effect. Polysorbate loaded nanocapsules were prepared and suspended in the fish oil to make nanosuspension and several factors such as size, zeta potential, and polydispersity index were investigated. This formulation was administered to rats per day at the dose of 0.2 mg/kg. Authors have concluded that haloperidol nanosuspension was able to

Table 4. Antipsychotic nanoformulation with their extended time period.

Drug	Nanoparticles	SLN
Haloperidol	Up to 13 days	Extended-release
Risperidone	Up to 72 hrs	-
Olanzapine	-	Up to 48 hrs

reduce oxidative stress which was compared with the standard Haloperidol. This design was carried out up to 28 days [110].

3.3.1.3. Solid Lipid Nanoparticles

To deliver SLN Haloperidol intranasal route was explored in this protocol. An emulsification-diffusion method was employed to obtain SLN. The Box-Behnken design was applied to evaluate the variable formulation parameters. Following parameters such as *in vitro* drug release, particle size, zeta potential, stability and pharmacokinetic studies (on *Albino Wistar* rats) were carried out. Authors have reported that the concentration of SLN Haloperidol in the brain region found to be (C_{max}=329.17±20.89 ng/ml, T_{max}=2 h). Drug targeting efficiency (2362.43%) and drug transport percentage (95.77%) were studied which showed better results as a long-acting formulation [111].

3.3.2. Risperidone

In one of the recently published studies, soft lipid vesicles were prepared and employed as the transdermal delivery of Haloperidol. For increasing permeation and easily administration safranal and ethanol was chosen. The Box-Behnken design was employed to prepare the formulation. The absorption rate and bioavailability were found to be higher (177%). To test the irritant effect of prepared formulations, a test was performed and compared with the selected standard irritant. Histopathological data revealed that the formulation was not showing any irritant effect. Authors said that soft lipid vesicles have shown great characteristics as controlled drug delivery [112].

3.3.2.1. Nanoemulsions

To enhance the efficacy of a drug, intranasal is one of the preferred routes in the list of drug delivery. In the same context, nanoemulsions of Risperidone were prepared, characterized and further Swiss Albino rats were used to determine the drug blood concentration. Drug transport efficiency and percentage were calculated and results revealed that more significant outcomes have been attained using nanoemulsions [113].

3.3.2.2. Solid Lipid Nanoparticles

Authors have optimized two different techniques (high-pressure homogenization and ultrasound) to obtain efficacious SLN of Risperidone. After assessment of prepared SLN; *in vitro* toxicity (using Caco-2 cell line) study was performed. SLN has proven safe and efficacious results by both the methods [114].

In another study, Risperidone loaded SLNs were delivered through nasal route and SLNs were prepared by solvent emulsification evaporation method. The prepared formulation was characterized and pharmacokinetic parameters were studied. To detect the drug in brain Gamma scintigraphy was performed which assures the presence of a drug in the brain. The blood-brain ratio was reported 1.36±0.06 [115].

3.3.2.3. Nanoparticles

To control the release rate of risperidone, PLGA loaded Nanoparticles have been prepared by the nanoprecipitation method and characterized by particle size determination (85-219 nm). *In vivo* trial was done to assess the extended time period of formulation and drug level in blood was found up to 72 hrs [116].

In one very recent protocol, chitosan loaded nanoparticles of Risperidone were prepared and delivered by the nasal route. The final formulation showed the particle size of 132.7 nm, drug loading 7.6% and drug release 80.7% [117].

3.3.3. Olanzapine

3.3.3.1. Nanocapsules

As per literature, weight gain has been reported as one of the most noticeable side-effects of olanzapine. In order to overcome this issue, nanocapsules were prepared and its efficacy is determined by inducing the psychosis condition using D, L-amphetamine chemical, in the male Wistar rats. The prepared formulation was characterized by observing the several parameters and it was found that weight gain and level of cholesterol was found to be reduced by 63.4±19.6 g and 66.2±3.5 $g.dl^{-1}$ respectively [118].

3.3.3.2. Solid Lipid Nanoparticles

SLN of Olanzapine was prepared using different lipids by hot melt emulsification high-pressure homogenization technique. The highest partition coefficient and entrapment efficiency were found using glyceryl tristearate. The prepared formulation was found effective with the particle size of 190 nm with the release up to 48 hours [119].

3.3.3.3. Nanostructured Lipid Carrier

Nanosuspension of Olanzapine (Glyceryl tripalmitate, castor oil, and Pluronic F-68, Soyalecithin) was prepared using the solvent diffusion technique. *In vitro* release of Nanosuspension was found to be 83.54% at 45 minute and increment in the bioavailability was also reported [120].

3.3.3.4. Nanoparticles

PLGA loaded Nanoparticles (91.2±5.2nm) were prepared using the nanoprecipitation technique which gave 68.91±2.31% entrapment efficiency. To check the diffusivity of prepared Nanoparticles, sheep nasal mucosa was used and almost 13.21± 1.59% drug release was found in 210 minutes. Histopathology and the pharmacokinetic study were performed and found satisfactory [121].

3.3.4. Paliperidone

3.3.4.1. Solid Lipid Nanoparticles

To prepare SLNs of Paliperidone, Campul GMS 50K was used as a lipid matrix. The particle size of 200 nm was reported and entrapment efficiency was found to be 55% [122].

3.3.5. Lurasidone

It is one of the latest SGA molecules in the market which is a structural analog of ziprasidone. Lurasidone was discovered by the Dainippon Sumitomo Pharma in Japan and approved by the FDA in 2010. The prescribed dose of Lurasidone is in the range of (20-100mg/day) in humans. Its solubility is reported less in the water. Film-coated tablets are majorly used in clinical studies [123]. After the supervision of safety and efficacious data Lurasidone has been launched in the United Kingdom in 2014.

3.3.5.1. Nanocrystals

Lurasidone nanocrystals (228 nm) were prepared using the media milling technique. The process was optimized and characterized by different parameters, such as PXRD and prepared crystals had shown good saturation solubility, which enhances its efficacy.

4. SALT-BASED CPA

Addition of pamoic acid, palmitic acid or decanoic acid (Counter ions) declines the drug aqueous solubility, which helps in the retardation of a drug in the body. However, a pKa difference between the drug and counter ion is most noticeable criteria to develop salt of any drug. In recent past, reports published on anti-Alzheimer's nanocrystals formulations (Memantine hydrochloride and donepezil hydrochloride) justify that salt based nanocrystals were more efficacious than other available dosage forms [124, 125]. An involvement of nano-idea in the salt formation has doubled the profits of drugs, in terms of both sustaining & reducing the dose of the drug. These outcomes have pulled the attention of scientists working on long-acting parenteral.

4.1. Olanzapine Pamoate

Pamoate salt of Olanzapine is insoluble in the water which plays a key role in enhancing the half-life of this formulation for up to 4 weeks [126]. The complex (microcrystalline salt) was formed between Olanzapine and pamoic acid, which is further suspended in the aqueous phase [127]. This formulation has increased the effectiveness of the Olanzapine.

5. SUMMARY OF CPF IN PSYCHOSIS

From the different author's point of view, we can say that each type of formulations have shown great potential in extending the time period of a drug in the body. However, the latest demand for Pharma is gaining much attention in the area of Nano formulation due to cut-edge merits in all the manners that is already described above. The absence of polymer reduced the tasks of pre-formulation study as well use of nano dose helps to reduce the high dose which ultimately avoid the chances of any side effects. Not limited to this, investigation involving such as the development of nanocrystals formulation also helped to attain the controlled and prolonged drug delivery in a tremendous manner. In short, we can confidently say that the application of nanonization in the upcoming formulation will be much more advantageous for the treatment of Psychosis.

6. NEWLY INTRODUCED ANTIPSYCHOTIC MIGHT BE A GOOD OPTION AS DEPOTS IN THE FUTURE

6.1. Brexpiprazole

It's SGA'S developed by Ostuka brand name Rexulti (April 2015 by FDA), a potent antagonist molecule of the 5HT2A receptor (2-4mg/day). It is structurally similar to aripiprazole, but (An approved drug in the market) a neurochemical character distinguishes brexpiprazole from aripiprazole [128]. This drug has an affinity for dopamine as well as serotonin receptors to generate the antipsychotic effects. To date, various clinical and pre-clinical studies have been conducted which give the evidence of its efficacy [129]. As brexpiprazole has a potent dose, a long-acting or depot formulation might be a good option to avoid dosing schedule.

6.2. Cariprazine

Cariprazine (Vraylar) is a recent drug in the market (Forest Laboratories) for the schizophrenia treatment (D2 and D3 receptors). It requires daily dosing (once) as a capsule (1.5-6 mg) and mainly prescribed in the United States and Europe [130]. As it possesses good physicochemical properties, a long-acting formulation of cariprazine can be a good option to treat Psychosis.

6.3. Asenapine

Asenapine is available in the market as a Neutral Antipsychotic (Dose: 10 mg, Half-Life: 24 hr). It has antagonistic action on 5HT, serotonin and dopamine receptors. Currently, it is used for the cure of Acute Mania. It has been reported

Table 5. Patents on antipsychotic drugs.

S. No.	Drug	Formulation	Patent No.	Company	Refs.
1.	Olanzapine Pamoate Dihydrate	With the salt of Pamoic acid	US 7932249	Eli-Lilly and Co	[132]
2.	Paliperidone	Hydrogel	W02011018246A2	-	[133]
3.	Risperidone	Aqueous suspension	US 9320707	Janssen Pharma	[134]
4.	Iloperidone	Suspension	US 8293765	-	[135]
5.	Aripiprazole	Aqueous suspension	US 8952013	Ostuka Pharmaceuticals	[136]
6.	Haloperidol	Implant	US 8758795	University of Pennsylvania	[137]
7.	Iloperidone	Crystals	US 20050250813A1	Novartis	Wieckhusen, 2005

for causing various effects like sedation, akathisia, taste disturbance, low prolactin secretions, and weight gain [131]. Special advice is given to the patients that it must not be swallowed (avoidance of food or drink 10 min priorly before administration) as it involves first pass metabolism. This recommendation forces researchers to develop depot (injectable) that can help to reduce dose along with the avoidance of metabolic effects.

7. PATENTS ON ANTIPSYCHOTIC DRUGS

Table **5** shows a list of patents related to the antipsychotic drugs.

CONCLUSION

A condition with changes in behavior, cognitive problems, mood alterations, and difficulties while speaking or hearing are the primary symptoms that indicate a person might need anti-psychotic therapy. Notably, more than 1 million people (both pediatric and geriatric) suffer from impairment with the psychosis per year. It is believed that Psychosis is mainly associated with an increased level of dopamine and drugs available up until now, usually works by antagonizing the dopamine. Recent literature throws light on other involved neurotransmitters, neurotensin, glutamate, and Gamma-aminobutyric acid (GABA) which might be a promising target for future therapy. The market of antipsychotic has gained huge attention with the arrival of CPA and it is lucrative.

In 2008, Antipsychotic depot Risperdal Consta (J&J) has earned around $780 million in the sale. After seeing profit in terms of market and patient compliance, the importance of CPF has been sharpened gradually. Enrichment of the principal moiety on chemical structures, which is responsible for depot formations, gives a glorious way to work on CPAs.

The beauty of parenteral administration has noticeably been enhanced after the introduction of controlled parenteral drug delivery and reports show that it is intrinsically advantageous. With an idea to promptly attain the therapeutic concentration and to sustain the drug constantly for an extended period, controlled parenteral came into existence. Data gathered from many scientific databases (Google Scholar, Science Direct, Pubmed, *etc.*) reveal that globally, the dynamic contribution has been made till date, which encourages the formulator to prepare CPF in a remarkable manner. CPF has been accepted as an emerging tool for the diseases, which are associated with long or continuous treatment and recidivism. Almost all studies showed that CPA has significant potential to treat Psychosis condition. Currently, the market expressed that CPA is under commercial use but still much room is remaining for the translational outcomes. The need for the proper regulating body for *in vitro in vivo* correlation (IVIVC) will surely open a door for the thorough investigation of the CPF [138]. Furthermore, it is beneficial to know if any toxicity or adverse effects caused by long-term medicines, lacking in any data might be responsible for not listing under the Generally Regarded as Safe GRAS is for excipients list. With the expectation, this review will show the importance of the futuristic research to be carried out on CPA. Continuous efforts made towards the new anti-psychotic molecules probably will be able to decrease the morbidity and mortality caused by psychosis. The deep investigation says there are so many areas (anti-epilepsy, local anaesthetics) where researchers are taking an interest to deliver the drug as a depot formulation and hopefully near future will be boosted by upcoming controlled release formulation. As earlier, it was a barrier to deliver the drugs due to high or low solubility and permeability which were limiting their potency. This paper summarizes the strategies employed on controlled antipsychotics so far which will assist to the others.

CURRENT AND FUTURE DEVELOPMENTS

Development of the CPF is challenging than other drug delivery systems in the aspect of both cost and method of preparations. In relation to this, burst release, selection of proper dose and IVIVC guideline development are the bottleneck in the pipeline of CPF. To diminish these hurdles, amendment of proper rules and guidelines will be well appreciated. Tremendous applications of CPF in the cure for Human Immunodeficiency Virus (HIV), Parkinson's, Alzheimer's, hormone-related disease, epilepsy, tuberculosis, and diabetes has been clearly studied well. After seeing a worldwide contribution on CPF, it clearly indicates that depot formulations can be an excellent vehicle to drive patient care with efficacious data and fewer side effects.

LIST OF ABBREVIATIONS

API	=	Active Pharmaceutical Ingredient
AUC	=	Area under Curve
BCS	=	Biopharmaceutical Classification System
CATIE	=	Clinical Antipsychotic Trials of Intervention Effectiveness
Cmax	=	Maximum Concentration
CPA	=	Controlled Parenteral Antipsychotic
CPF	=	Controlled Parenteral Formulation
DMSO	=	Dimethylsulfoxide
ERT	=	Electroconvulsive Therapy
FDA	=	Food and Drug Administration
FGA	=	First-generation Antipsychotic
FTD	=	Flupenthixol Decanoate
FTIR	=	Fourier-transform Infrared
FZD	=	Fluphenazine Decanoate
GRAS	=	Generally Regarded as Safe
HD	=	Haloperidol Decanoate
IM	=	Intra-muscular
IV	=	Intravenous
IVIVC	=	*In Vitro In Vivo* Correlation
PLA	=	Polylactic Acid
PLG	=	Poly (D, L-lactide-co-glycolide)
PLGA	=	Polylactic-co-glycolic Acid

PP	=	Paliperidone Palmitate
PXRD	=	Powder X-ray Diffraction
SAIB	=	Sucrose Acetate Isobutyrate
SGA	=	Second-generation Antipsychotic
SLNs	=	Solid Lipid Nanoparticles
SEM	=	Scanning Electron Microscopy
Tmax	=	Maximum Time

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REFERENCES

[1] Gulati N, Gupta H. Parenteral drug delivery: a review. Recent Pat Drug Deliv Formul 2011; 5(2): 133-45. http://dx.doi.org/10.2174/187221111795471391 PMID: 21453250

[2] Shahiwala A, Mehta TA, Momin MM. Parenteral drug delivery systems. *In vitro* and *in vivo* tools in drug delivery research for optimum clinical outcomes, Ambikanandan M, Aliasgar S, Eds. CRC Press 2018; pp. 301-36.

[3] Chien Y. Novel drug delivery systems 1991.

[4] Bari H. A prolonged release parenteral drug delivery system-an overview. Int J Pharm Sci Rev Res 2010; 3(1): 1-11.

[5] Agrawal M, Limbachiya M, Sapariya A, Patel G. A review on parenteral controlled drug delivery system. Int J Pharm Sci Res 2012; 3(10): 3657.

[6] Sheikh AA. Injectable controlled release drug delivery systems. Asian J Pharm 2016; 10(4): S464-71.

[7] Park K. Controlled drug delivery systems: past forward and future back. J Control Release 2014; 190: 3-8. http://dx.doi.org/10.1016/j.jconrel.2014.03.054 PMID: 24794901

[8] Muralidhar P, Bhargav E. Controlled release injectable drug delivery: an over view. Asian J Biomater Res 2017; 3(1): 6-15.

[9] Jantzen GM, Robinson JR. Sustained-and controlled-release drug delivery systems. Drugs Pharm Sci 2002; 121: 501-28.

[10] Niraj VK, Srivastava N. Sustained and controlled drug delivery system-as a part of modified release dosage form. Int J Res Pharm Nano Sci 2015; 4(5): 347-64.

[11] Hoffman AS. The origins and evolution of "controlled" drug delivery systems. J Control Release 2008; 132(3): 153-63. http://dx.doi.org/10.1016/j.jconrel.2008.08.012 PMID: 18817820

[12] Kostanski JW, Matsuda T, Nerurkar M, Naringrekar VH, inventor; Otsuka Pharmaceutical Co Ltd Curr., assignee. Controlled release sterile injectable aripiprazole formulation and method 2017. United States patent US8030313B2. 2011.

[13] Burgess DJ, Wright JC. An introduction to long acting injections and implants. In: Long Acting Injections and Implants. Wright JC, Burgess DJ, Eds. New York: Springer Science & Business Media 2012; pp. 1-9. http://dx.doi.org/10.1007/978-1-4614-0554-2_1

[14] Kalyani M, Surendra P, Sirisha V. Parenteral controlled drug delivery system. Int J Res Pharm Nano Sci 2013; 2: 572-80.

[15] Altamura AC, Sassella F, Santini A, Montresor C, Fumagalli S, Mundo E. Intramuscular preparations of antipsychotics: uses and relevance in clinical practice. Drugs 2003; 63(5): 493-512. http://dx.doi.org/10.2165/00003495-200363050-00004 PMID: 12600227

[16] Ansel HC, Popovich NG, Allen LV. Pharmaceutical dosage forms and drug delivery systems. Baltimore: Williams & Wilkins; 1995.

[17] Lally J, MacCabe JH. Antipsychotic medication in schizophrenia: a review. Br Med Bull 2015; 114(1): 169-79. http://dx.doi.org/10.1093/bmb/ldv017 PMID: 25957394

[18] Mackin P, Thomas SHL. Atypical antipsychotic drugs. BMJ 2011; 342: d1126. http://dx.doi.org/10.1136/bmj.d1126 PMID: 21378070

[19] Tandon R, Jibson MD. Extrapyramidal side effects of antipsychotic treatment: scope of problem and impact on outcome. Ann Clin Psychiatry 2002; 14(2): 123-9. http://dx.doi.org/10.3109/10401230209149099 PMID: 12238737

[20] Nasrallah HA. Triple advantages of injectable long acting second generation antipsychotics: relapse prevention, neuroprotection, and lower mortality. Schizophr Res 2018; 197: 69-70. http://dx.doi.org/10.1016/j.schres.2018.02.004 PMID: 29506767

[21] Second-generation long-acting injectable antipsychotic agents: an overview. Drug Ther Bull 2012; 50(9): 102-5. http://dtb.bmj.com/content/50/9/102

[22] Chue P, Emsley R. Long-acting formulations of atypical antipsychotics: time to reconsider when to introduce depot antipsychotics. CNS Drugs 2007; 21(6): 441-8. http://dx.doi.org/10.2165/00023210-200721060-00001 PMID: 17521224

[23] Dixit N, Maurya SD, Sagar BPS. Sustained release drug delivery system. Ind J Res Pharm Biotechnol 2013; 1(3): 305.

[24] Shi Y, Li LC. Current advances in sustained-release systems for parenteral drug delivery. Expert Opin Drug Deliv 2005; 2(6): 1039-58. http://dx.doi.org/10.1517/17425247.2.6.1039 PMID: 16296808

[25] Sudhakar M, Kancharla R, Rao VU. A review on sustained release injectable depot drug delivery systems. Int J Adv Pharm Sci 2013; 4: 142-58.

[26] Moreno-Küstner B, Martín C, Pastor L. Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. PLoS One 2018; 13(4) e0195687. http://dx.doi.org/10.1371/journal.pone.0195687 PMID: 29649252

[27] Agid O, Foussias G, Remington G. Long-acting injectable antipsychotics in the treatment of schizophrenia: their role in relapse prevention. Expert Opin Pharmacother 2010; 11(14): 2301-17. http://dx.doi.org/10.1517/14656566.2010.499125 PMID: 20586707

[28] Kane JM, Aguglia E, Altamura AC, *et al.* Guidelines for depot antipsychotic treatment in schizophrenia. Eur Neuropsychopharmacol 1998; 8(1): 55-66. http://dx.doi.org/10.1016/S0924-977X(97)00045-X PMID: 9452941

[29] Dencker SJ, Axelsson R. Optimising the use of depot antipsychotics. CNS Drugs 1996; 6(5): 367-81. http://dx.doi.org/10.2165/00023210-199606050-00004

[30] Davis JM, Metalon L, Watanabe MD, Blake L. Depot antipsychotic drugs. Drugs 1994; 47(5): 741-73. http://dx.doi.org/10.2165/00003495-199447050-00004 PMID: 7520856

[31] Comaty JE, Janicak PG. Depot neuroleptics. Psychiatr Ann 1987; 17(7): 491-6. http://dx.doi.org/10.3928/0048-5713-19870701-14

[32] Gary JR, Martha EA. Depot neuroleptic therapy: clinical considerations. Canadian J Psy 1995; 40(3): 5-11. http://dx.doi.org/10.1177/070674379504003S02

[33] Sreeraj VS, Shivakumar V, Rao NP, Venkatasubramanian G. A critical appraisal of long acting injectable antipsychotics: translating research to clinics. Asian J Psychiatr 2017; 28: 57-64. http://dx.doi.org/10.1016/j.ajp.2017.03.018 PMID: 28784398

[34] Masand PS, Gupta S. Long-acting injectable antipsychotics in the elderly: guidelines for effective use. Drugs Aging 2003; 20(15): 1099-110. http://dx.doi.org/10.2165/00002512-200320150-00003 PMID: 14651433

[35] Lycett-Smith M, Azar M, Code M. Guidance on the administration to adults of oil-based depot and other long-acting intramuscular antipsychotic injections.

[36] Bosanac P, Castle DJ. Why are long-acting injectable antipsychotics still underused? BJPsych Adv 2015; 21(2): 98-105. http://dx.doi.org/10.1192/apt.bp.114.013565

[37] Kane JM. Utilization of long-acting antipsychotic medication in patient care. CNS Spectr 2006; 11(12)(Suppl. 14): 1-7. http://dx.doi.org/10.1017/S1092852900025852 PMID: 17146411

[38] Remenar JF. Making the leap from daily oral dosing to long-acting injectables: lessons from the antipsychotics. Mol Pharm 2014; 11(6): 1739-49. http://dx.doi.org/10.1021/mp500070m PMID: 24679167

[39] Baweja R, Sedky K, Lippmann S. Long-acting antipsychotic medications. Curr Drug Targets 2012; 13(4): 555-60. http://dx.doi.org/10.2174/138945012799499785 PMID: 22250654

[40] Kane JM, Garcia-Ribera C. Clinical guideline recommendations for antipsychotic long-acting injections. Br J Psychiatry Suppl 2009; 52(S52): S63-7. http://dx.doi.org/10.1192/bjp.195.52.s63 PMID: 19880920

[41] Brissos S, Veguilla MR, Taylor D, Balanzá-Martinez V. The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal. Ther Adv Psychopharmacol 2014; 4(5): 198-219. http://dx.doi.org/10.1177/2045125314540297 PMID: 25360245

[42] Naber D. Olanzapine pamoate for the treatment of schizophrenia. Expert Opin Pharmacother 2011; 12(4): 627-33. http://dx.doi.org/10.1517/14656566.2011.553193 PMID: 21254860

[43] Motiwala FB, Siscoe KS, El-Mallakh RS. Review of depot aripiprazole for schizophrenia. Patient Prefer Adherence 2013; 7: 1181-7. PMID: 24265550

[44] Martinez MN, Khan MA. Regulatory issues and challenges associated with the development of performance specifications for modified release parenteral products. In: Long Acting Injections and Implants, Wright. J. C, Burgess. D. J, Eds. Springer Science & Business Media 2012; pp. 505-35. http://dx.doi.org/10.1007/978-1-4614-0554-2_24

[45] Martinez M, Rathbone M, Burgess D, Huynh M. *In vitro* and *in vivo* considerations associated with parenteral sustained release products: a review based upon information presented and points expressed at the 2007 Controlled Re-lease Society Annual Meeting. J controlled release 2008; 129(2): 79-87.

[46] Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics: a treatise. Vallabh Prakashan 2005. https://books.google.co.in/books?id=PVCEMwEACAAJ

[47] Rizvi SAA, Saleh AM. Applications of nanoparticle systems in drug delivery technology. Saudi Pharm J 2018; 26(1): 64-70. http://dx.doi.org/10.1016/j.jsps.2017.10.012 PMID: 29379334

[48] Wang Y, Burgess DJ. Microsphere technologies. In: Long Acting Injections and Implants, Wright. J. C, Burgess. D. J, Eds. Springer Science & Business Media 2012; pp. 167-94.

[49] Sahil K, Akanksha M, Premjeet S, Bilandi A, Kapoor B. Microsphere: a review. Int J Res Pharm Chem 2011; 1(4): 1184-98.

[50] Dold M, Samara MT, Li C, Tardy M, Leucht S. Haloperidol versus first-generation antipsychotics for the treatment of schizophrenia and other psychotic disorders 2015. http://dx.doi.org/10.1002/14651858.CD009831.pub2

[51] U.S. Food and Drug Administration. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/015923s082,018701s057lbl.pdf"https://www.accessdata.fda.gov/drugsatfda_docs/ label/2008/015923s082,018701s057lbl.pdf

[52] Cheng Y-H, Illum L, Davis SS. A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol. J Control Release 1998; 55(2-3): 203-12. http://dx.doi.org/10.1016/S0168-3659(98)00056-X PMID: 9795060

[53] https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021436s038,021713s030,021729s022,021866s023lbl.pdf

[54] Nahata T, Saini TR. D-optimal designing and optimization of long acting microsphere-based injectable formulation of aripiprazole. Drug Dev Ind Pharm 2008; 34(7): 668-75. http://dx.doi.org/10.1080/03639040701836545 PMID: 18608461

[55] Talegaonkar S, Mittal A, Parmar S, Aqil M. Aripiprazole loaded polymeric biodegradable microspheres: formulation and *in vitro* characterization. J Dispers Sci Technol 2009; 30(8): 1198-202. http://dx.doi.org/10.1080/01932690802701788

[56] Hiraoka S, Uchida S, Namiki N. Preparation and characterization of high-content aripiprazole-loaded core-shell structure microsphere for long-release injectable formulation. Chem Pharm Bull (Tokyo) 2014; 62(7): 654-60. http://dx.doi.org/10.1248/cpb.c14-00110 PMID: 24990503

[57] Risperidone FDA [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020588s046lbl.pdf

[58] Möller H-J. Long-acting injectable risperidone for the treatment of schizophrenia: clinical perspectives. Drugs 2007; 67(11): 1541-66. http://dx.doi.org/10.2165/00003495-200767110-00003 PMID: 17661527

[59] Chue P. Risperidone long-acting injection. Expert Rev Neurother 2003; 3(4): 435-46. http://dx.doi.org/10.1586/14737175.3.4.435 PMID: 19810928

[60] Hosalli P, Davis JM. Depot risperidone for schizophrenia. Cochrane Database Syst Rev 2003; (4): CD004161. PMID: 14584007

[61] D'Souza S, Faraj JA, Giovagnoli S, Deluca PP. Development of risperidone PLGA microspheres. J Drug Deliv 2014; 2014620464. PMID: 24616812

[62] Nanaki S, Barmpalexis P, Papakonstantinou Z, Christodoulou E, Kostoglou M, Bikiaris DN. Preparation of new risperidone depot microspheres based on novel biocompatible poly (alkylene adipate) polyesters as long acting injectable formulations. J Pharm Sci 2018; 107(11): 2891-901. http://dx.doi.org/10.1016/j.xphs.2018.07.029 PMID: 30096352

[63] Fluphenazine FDA [Internet]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=089804

[64] Ramtoola Z, Corrigan OI, Barrett CJ. Release kinetics of fluphenazine from biodegradable microspheres. J Microencapsul 1992; 9(4): 415-23. http://dx.doi.org/10.3109/02652049209040480 PMID: 1403489

[65] Dunne MM, Ramtoola Z, Corrigan OI. Fluphenazine release from biodegradable microparticles: characterization and modelling of release. J Microencapsul 2009; 26(5): 403-10. http://dx.doi.org/10.1080/02652040802396575 PMID: 18785053

[66] Rupvate SR, Rokade MM, Sayyad SF, Chaudhari SR. formulation and evaluation of sustained release micro-spheres of paliperidone inventi rapid: Pharm Tech 2012.

[67] Owen RT. Olanzapine: a review of rapid and long-acting parenteral for-mulations. Drugs of today (Barcelona, Spain: 1998) 2010; 46(3): 173-81. http://dx.doi.org/10.1358/dot.2010.46.3.1476499

[68] Frampton JE. Olanzapine long-acting injection: a review of its use in the treatment of schizophrenia. Drugs 2010; 70(17): 2289-313. http://dx.doi.org/10.2165/11204930-000000000-00000 PMID: 21080745

[69] Nahata T, Saini TR. Optimization of formulation variables for the development of long acting microsphere based depot injection of olanzapine. J Microencapsul 2008; 25(6): 426-33. http://dx.doi.org/10.1080/02652040802033913 PMID: 18608793

[70] D'Souza S, Faraj JA, Giovagnoli S, Deluca PP. IVIVC from long acting olanzapine microspheres. Int J Biomater 2014; 2014. Article ID 407065. http://dx.doi.org/10.1155/2014/407065 PMID: 24578707

[71] Park C-W, Lee H-J, Oh D-W, Kang J-H, Han C-S, Kim D-W. Preparation and *in vitro*/*in vivo* evaluation of PLGA microspheres containing norquetiapine for long-acting injection. Drug Des Devel Ther 2018; 12: 711-9. http://dx.doi.org/10.2147/DDDT.S151437 PMID: 29670329

[72] Chaudhary K, Patel MM, Mehta PJ. Long-acting injectables: current perspectives and future promise. Crit Rev Ther Drug Carrier Syst 2019; 36(2): 137-181.

[73] Beresford R, Ward A. Haloperidol decanoate. A preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in psychosis. Drugs 1987; 33(1): 31-49. http://dx.doi.org/10.2165/00003495-198733010-00002 PMID: 3545764

[74] Hemstrom CA, Evans RL, Lobeck FG. Haloperidol decanoate: a depot antipsychotic. Drug Intell Clin Pharm 1988; 22(4): 290-5. http://dx.doi.org/10.1177/106002808802200402 PMID: 2897276

[75] Quraishi SN, David A, Brasil MA, Alheira FV. Depot haloperidol decanoate for schizophrenia. Cochrane Database Syst Rev 1999; (1). PMID: 10796438

[76] Greco K, Wright J. Aripiprazole, olanzapine and haloperidol pamoate salts 2006.

[77] Altamura CA, Colacurcio F, Mauri MC, Moro AR, De Novellis F. Haloperidol decanoate in chronic schizophrenia: a study of 12 months with plasma levels. Prog Neuropsychopharmacol Biol Psychiatry 1990; 14(1): 25-35. http://dx.doi.org/10.1016/0278-5846(90)90061-K PMID: 1967847

[78] Chouinard G, Annable L, Campbell W, Boisvert D, Bradwejn J. A Double–Blind Controlled Clinical Trial of Haloperidol Decanoate and Fluphenazine Decanoate in the Maintenance Treatment of Schizophrenia. In: Psychiatry the State of the Art, Pichot. P, Ed. Springer 1985; pp. 759-61. http://dx.doi.org/10.1007/978-1-4613-2363-1_118

[79] Eberhard G, Hellbom E. Haloperidol decanoate and flupenthixol decanoate in schizophrenia. A long-term double-blind cross-over comparison. Acta Psychiatr Scand 1986; 74(3): 255-62. http://dx.doi.org/10.1111/j.1600-0447.1986.tb06242.x PMID: 3788652

[80] McKane JP, Robinson ADT, Wiles DH, McCreadie RG, Stirling GS. Haloperidol decanoate v. fluphenazine decanoate as maintenance therapy in chronic schizophrenic in-patients. Br J Psychiatry 1987; 151(3): 333-6. http://dx.doi.org/10.1192/bjp.151.3.333 PMID: 3322467

[81] Zissis NP, Psaras M, Lyketsos G. Haloperidol decanoate, a new long-acting antipsychotic, in chronic schizophrenics: double-blind comparison with placebo. Curr Ther Res Clin Exp 1982; 31(4): 650-5.

[82] Deberdt R, Elens P, Berghmans W, *et al.* Intramuscular haloperidol decanoate for neuroleptic maintenance therapy. Efficacy, dosage schedule and plasma levels. An open multicenter study. Acta Psychiatr Scand 1980; 62(4): 356-63. http://dx.doi.org/10.1111/j.1600-0447.1980.tb00621.x PMID: 7468294

[83] Gelders YG, Reyntijens AJ, Ash CW, Aerts TJ. 12-month study of haloperidol decanoate in chronic schizophrenic patients. Int Pharmacopsychiatry 1982; 17(4): 247-54. http://dx.doi.org/10.1159/000468581 PMID: 7185769

[84] Vasavan Nair NP, Suranyi-Cadotte B, Schwartz G, *et al.* A clinical trial comparing intramuscular haloperidol decanoate and oral haloperidol in chronic schizophrenic patients: efficacy, safety, and dosage equivalence. J Clin Psychopharmacol 1986; 6(1)(Suppl.): 30S-7S. http://dx.doi.org/10.1097/00004714-198602001-00006 PMID: 3514689

[85] Mace S, Dzahini O, O'Hagan M, Taylor D. Haloperidol decanoate long-acting injection (HDLAI): results of a 1-year mirror-image study. Ther Adv Psychopharmacol 2018; 8(9): 241-9. http://dx.doi.org/10.1177/2045125318767587 PMID: 30181866

[86] Fluphenazine Decanoate FDA [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/071413s019lbl.pdf

[87] Luo J-P, Hubbard JW, Midha KK. Studies on the mechanism of absorption of depot neuroleptics: fluphenazine decanoate in sesame oil. Pharm Res 1997; 14(8): 1079-84. http://dx.doi.org/10.1023/A:1012165731390 PMID: 9279892

[88] Chue P, Chue J. A review of paliperidone palmitate. Expert Rev Neurother 2012; 12(12): 1383-97. http://dx.doi.org/10.1586/ern.12.137 PMID: 23237346

[89] Nussbaum AM, Stroup TS. Paliperidone palmitate for schizophrenia. Schizophr Bull 2012; 38(6): 1124-7. http://dx.doi.org/10.1093/schbul/sbs099 PMID: 22966147

[90] Paliperidone palmitate. U.S. Food and Drug Administration. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022264s023lbl.pdf"https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/ 022264s023lbl.pdf

[91] Greenberg WM, Citrome L. Paliperidone palmitate for schizoaffective disorder: a review of the clinical evidence. Neurol Ther 2015; 4(2): 81-91. http://dx.doi.org/10.1007/s40120-015-0030-4 PMID: 26662360

[92] Lamb YN, Keating GM. Paliperidone palmitate intramuscular 3-monthly formulation: a review in schizophrenia. Drugs 2016; 76(16): 1559-66. http://dx.doi.org/10.1007/s40265-016-0645-5 PMID: 27699643

[93] Flupenthixol Decanoate [Internet]. Available from:https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/071413s019lbl.pdf

[94] McCreadie RG, Flanagan WL, McKnight J, Jorgensen A. High dose flupenthixol decanoate in chronic schizophrenia. Br J Psychiatry 1979; 135(2): 175-9. http://dx.doi.org/10.1192/bjp.135.2.175 PMID: 387151

[95] Pipotiazine Palmitate [Internet]. Available from:http://products.sanofi.ca/en/piportil-l4.pdf

[96] Arango C, Bombín I, González-Salvador T, García-Cabeza I, Bobes J. Randomised clinical trial comparing oral versus depot formulations of zuclopenthixol in patients with schizophrenia and previous violence. Eur Psychiatry 2006; 21(1): 34-40. http://dx.doi.org/10.1016/j.eurpsy.2005.07.006 PMID: 16360311

[97] Wistedt B, Koskinen T, Thelander S, Nerdrum T, Pedersen V, Mølbjerg C. Zuclopenthixol decanoate and haloperidol decanoate in chronic schizophrenia: a double-blind multicentre study. Acta Psychiatr Scand 1991; 84(1): 14-21. http://dx.doi.org/10.1111/j.1600-0447.1991.tb01414.x PMID: 1681680

[98] Zuclopenthixol Decanoate [Internet]. Available from: https://www.lundbeck.com/upload/ca/en/files/pdf/pm/Clopixol.pdf

[99] Arif SA, Mitchell MM. Iloperidone: A new drug for the treatment of schizophrenia. Am J Health Syst Pharm 2011; 68(4): 301-8. http://dx.doi.org/10.2146/ajhp100079 PMID: 21289324

[100] Caccia S, Pasina L, Nobili A. New atypical antipsychotics for schizophrenia: iloperidone. Drug Des Devel Ther 2010; 4: 33-48. http://dx.doi.org/10.2147/DDDT.S6443 PMID: 20368905

[101] Ehret MJ, Sopko MA Jr, Levine A. Iloperidone: a novel atypical antipsychotic for the treatment of schizophrenia. Formulary 2008; 43(6): 190-8.

[102] https://patents.google.com/patent/US20090099232

[103] Dubey V, Saini TR. Development of long acting depot injection of Iloperidone by SABER technology. Indian J Pharm Sci 2018; 80(5): 813-9. http://dx.doi.org/10.4172/pharmaceutical-sciences.1000426

[104] Muthu MS, Agrawal P, Singh RP. Antipsychotic nanomedicine: a successful platform for clinical use. Nanomedicine 2014; 9(14): 2071-4. http://dx.doi.org/10.2217/nnm.14.164 PMID: 25405791

[105] Kittelson DB. Engines and nanoparticles: a review. J Aerosol Sci 1998; 29(5-6): 575-88. http://dx.doi.org/10.1016/S0021-8502(97)10037-4

[106] Mohanraj VJ, Chen Y. Nanoparticles-a review. Trop J Pharm Res 2006; 5(1): 561-73.

[107] Budhian A, Siegel SJ, Winey KI. Production of haloperidol-loaded PLGA nanoparticles for extended controlled drug release of haloperidol. J Microencapsul 2005; 22(7): 773-85. http://dx.doi.org/10.1080/02652040500273753 PMID: 16421087

[108] Budhian A, Siegel SJ, Winey KI. Haloperidol-loaded PLGA nanoparticles: systematic study of particle size and drug content. Int J Pharm 2007; 336(2): 367-75. http://dx.doi.org/10.1016/j.ijpharm.2006.11.061 PMID: 17207944

[109] Budhian A, Siegel SJ, Winey KI. Controlling the *in vitro* release profiles for a system of haloperidol-loaded PLGA nanoparticles. Int J Pharm 2008; 346(1-2): 151-9. http://dx.doi.org/10.1016/j.ijpharm.2007.06.011 PMID: 17681683

[110] Benvegnú DM, Barcelos RCS, Boufleur N, *et al.* Haloperidol-loaded polysorbate-coated polymeric nanocapsules increase its efficacy in the antipsychotic treatment in rats. Eur J Pharm Biopharm 2011; 77(2): 332-6. http://dx.doi.org/10.1016/j.ejpb.2010.12.016 PMID: 21168486

[111] Yasir M, Sara UVS, Som I. Haloperidol loaded solid lipid nanoparticles for nose to brain delivery: stability and vivo 2015.

[112] Imam SS, Ahad A, Aqil M, Akhtar M, Sultana Y, Ali A. Formulation by design based risperidone nano soft lipid vesicle as a new strategy for enhanced transdermal drug delivery: *in vitro* characterization, and *in vivo* appraisal. Mater Sci Eng C 2017; 75: 1198-205. http://dx.doi.org/10.1016/j.msec.2017.02.149 PMID: 28415407

[113] Kumar M, Misra A, Babbar AK, Mishra AK, Mishra P, Pathak K. Intranasal nanoemulsion based brain targeting drug delivery system of risperidone. Int J Pharm 2008; 358(1-2): 285-91. http://dx.doi.org/10.1016/j.ijpharm.2008.03.029 PMID: 18455333

[114] Silva AC, González-Mira E, García ML, *et al.* Preparation, characterization and biocompatibility studies on risperidone-loaded solid lipid nanoparticles (SLN): high pressure homogenization versus ultrasound. Colloids Surf B Biointerfaces 2011; 86(1): 158-65. http://dx.doi.org/10.1016/j.colsurfb.2011.03.035 PMID: 21530187

[115] Patel S, Chavhan S, Soni H, *et al.* Brain targeting of risperidone-loaded solid lipid nanoparticles by intranasal route. J Drug Target 2011; 19(6): 468-74. http://dx.doi.org/10.3109/1061186X.2010.523787 PMID: 20958095

[116] Muthu MS, Rawat MK, Mishra A, Singh S. PLGA nanoparticle formulations of risperidone: preparation and neuropharmacological evaluation. Nanomedicine 2009; 5(3): 323-33. http://dx.doi.org/10.1016/j.nano.2008.12.003 PMID: 19523427

[117] Qureshi M, Aqil M, Imam SS, Ahad A, Sultana Y. Formulation and evaluation of neuroactive drug loaded chitosan nanoparticle for nose to brain delivery: *in vitro* characterization and *in vivo* behavior study. Curr Drug Deliv 2019; 16(2): 123-35. http://dx.doi.org/10.2174/1567201815666181011121750 PMID: 30317997

[118] Dimer FA, Ortiz M, Pase CS, *et al.* Nanoencapsulation of olanzapine increases its efficacy in antipsychotic treatment and reduces adverse effects. J Biomed Nanotechnol 2014; 10(6): 1137-45. http://dx.doi.org/10.1166/jbn.2014.1817 PMID: 24749408

[119] Vivek K, Reddy H, Murthy RSR. Investigations of the effect of the lipid matrix on drug entrapment, *in vitro* release, and physical stability of olanzapine-loaded solid lipid nanoparticles. AAPS PharmSciTech 2007; 8(4) 16-24. http://dx.doi.org/10.1208/pt0804083 PMID: 18181544

[120] Sood S, Jawahar N, Jain K, Gowthamarajan K, Nainar Meyyanathan S. Olanzapine loaded cationic solid lipid nanoparticles for improved oral bioavailability. Curr Nanosci 2013; 9(1): 26-34.

[121] Seju U, Kumar A, Sawant KK. Development and evaluation of olanzapine-loaded PLGA nanoparticles for nose-to-brain delivery: *in vitro* and *in vivo* studies. Acta Biomater 2011; 7(12): 4169-76. http://dx.doi.org/10.1016/j.actbio.2011.07.025 PMID: 21839863

[122] Kumar S, Randhawa JK. Preparation and characterization of Paliperidone loaded solid lipid nanoparticles. Colloids Surf B Biointerfaces 2013; 102: 562-8. http://dx.doi.org/10.1016/j.colsurfb.2012.08.052 PMID: 23104026

[123] Meyer JM, Loebel AD, Schweizer E. Lurasidone: a new drug in development for schizophrenia. Expert Opin Investig Drugs 2009; 18(11): 1715-26. http://dx.doi.org/10.1517/13543780903286388 PMID: 19780705

[124] Mittapelly N, Rachumallu R, Pandey G, *et al.* Investigation of salt formation between memantine and pamoic acid: its exploitation in nanocrystalline form as long acting injection. Eur J Pharm Biopharm 2016; 101: 62-71. http://dx.doi.org/10.1016/j.ejpb.2016.01.003 PMID: 26850817

[125] Mittapelly N, Thalla M, Pandey G, *et al.* Long acting ionically paired embonate based nanocrystals of donepezil for the treatment of Alzheimer's disease: a proof of concept study. Pharm Res 2017; 34(11): 2322-35. http://dx.doi.org/10.1007/s11095-017-2240-1 PMID: 28808833

[126] Olanzapine Pamoate [Internet]. Available from: https://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM481944.pdf

[127] Chue P, Chue J. A review of olanzapine pamoate. Expert Opin Pharmacother 2012; 13(11): 1661-70. http://dx.doi.org/10.1517/14656566.2012.686169 PMID: 22746160

[128] Hope J, Castle D, Keks NA. Brexpiprazole: a new leaf on the partial dopamine agonist branch. Australas Psychiatry 2018; 26(1): 92-4. http://dx.doi.org/10.1177/1039856217732473 PMID: 29017334

[129] Das S, Barnwal P, Winston A B, Mondal S, Saha I. Brexpiprazole: so far so good. Ther Adv Psychopharmacol 2016; 6(1): 39-54. http://dx.doi.org/10.1177/2045125315614739 PMID: 26913177

[130] Campbell RH, Diduch M, Gardner KN, Thomas C. Review of cariprazine in management of psychiatric illness. Ment Health Clin 2018; 7(5): 221-9. http://dx.doi.org/10.9740/mhc.2017.09.221 PMID: 29955527

[131] Balaraman R, Gandhi H. Asenapine, a new sublingual atypical antipsychotic. J Pharmacol Pharmacother 2010; 1(1): 60-1. http://dx.doi.org/10.4103/0976-500X.64538 PMID: 21808592

[132] Julie KB, inventor; Eli Lilly and Co Inc., assignee. Olanzapine pamoate dihydrate. United States patent US7932249B2. 2011 April.

[133] Korinde AJ, inventor. Controlled release paliperidone composition. WO2011018246A2. 2011 Feb.

[134] Marc KJF, Willy MACD, Esther DGB, inventor; Janssen Pharmaceutica NV Inc., assignee. Aqueous suspensions of submicron 9-hydroxyrisperidone fatty acid esters. United States patent US9320707B2. 2016 April.

[135] Dierk W, Alexandra G, Markus A, inventor. Injectable depot formulation comprising crystals of iloperidone. United States patent US20090099232A1. 2009 April.

[136] Janusz WK, Takakuni M, Manoj N, Vijay HN, inventor; Otsuka Pharmaceutical Co Ltd Inc., assignee. Controlled release sterile injectable aripiprazole formulation and method. United States patent US8952013B2. 2015 Feb.

[137] Steven JS, Karen IW, Raquel EG, Robert HL, inventor; University of Pennsylvania Inc., assignee. Polymer-based surgically implantable haloperidol delivery systems and methods for their production and use. United States patent US8758795B2. 2014 June.

[138] Dadhaniya TM, Sharma OP, Gohel MC, Mehta PJ. Current approaches for *in vitro* drug release study of long acting parenteral formulations. Curr Drug Deliv 2015; 12(3): 256-70. http://dx.doi.org/10.2174/1567201812666150209143731 PMID: 25666683