WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 11, 471-481. Review Article ISSN 2277– 7105

GELUCIRE: A NOVEL TOOL IN FORMULATION OF POORLY SOLUBLE DRUGS

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Article Received on
12 April 2018,

Revised on 02 May2018,
Accepted on 23 May 2018

DOI: 10.20959/wjpr201811-12497

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ABSTRACT

The purpose of writing the review on novel lipidic carrier Gelucire was to accumulate the current literature with a special emphasis on its properties and applications that have recently become important in the field of fast as well as sustained/controlled release drug delivery. Efforts have been made in research and development of formulations using this novel tool, particularly in the formulation of solid dispersions of poorly soluble drugs. These nonionic, amphiphilic excipients are widely used in controlled-release matrices for improvement of the physicochemical properties of drug. The review concisely describes the properties and applications of Gelucire along with the relevant literature.

KEYWORDS: Gelucire, surfactant, solubility, solid dispersion.

INTRODUCTION[1-6]

Poorly water soluble drugs present significant challenges during the development of formulation of drugs due to their inadequate solubilization in digestive fluids and hence it is of paramount importance to enhance the solubility of poorly water soluble drug thereby improving the bioavailability. Different approaches to overcome this problem are currently being used. One way is to disperse the drug substance in a surface active carrier in order to enhance its bioavailability; this is commonly called solid dispersion. Over last few decade, surface active agents have been used in solid dispersion alone or in combination with polymeric material. The term surfactant includes suspending agents, wetting agents, emulsifiers, detergents, anti foam compounds etc.[1] The use of surfactants in solid dispersion not only improves the dissolution rate of poorly soluble drug but also improves the physical

stability. The surfactants aid in physical miscibility of hydrophobic drugs due to amphiphilic nature and reduce the drug recrystallization, also improves wettability and prevent drug precipitation in aqueous medium[1]. One of such interesting amphiphilic surfactant widely used for solid dispersions is Gelucire (Particularly, Gelucire 44/14). The incorporation of drugs into Gelucires has been reported to increase the dissolution rate of poorly soluble drugs, often leading to improved drug bioavailability. They have a wide variety of applications in oral and topical formulation. The applications of oral formulation include enhancement of solubility and bioavailability, sustain release, taste masking and protection of active pharmaceutical ingredient (API) from oxygen, light and humidity. The applications of gelucire in topical formulations include stabilization of creams, lotions and gels, thickener, superior penetration of drug through skin.[2,3] Gelucire containing only PEG esters are generally used in the preparation of fast/immediate/rapid release formulations. Gelucire containing only glycerides or mixture of glycerides and PEG esters are used in the preparation of sustained release formulations.[2,3]

Gelucires are inert, semisolid, waxy, nonionic, amphiphilic excipients that are widely used in controlled-release matrices for improvement of the physicochemical properties of drug. Gelucires are mixtures of mono-, di-, and triglycerides with polyethylene glycol esters of fatty acids.[1-4] Glycerides and PEG, these two components imparts hydrophobic and hydrophilic properties to the vehicle. It is listed in the European Pharmacopoeia as laurylmacrogolglycerides and in the United States Pharmacopoeia as laurylpolyoxyglycerides.[5] Gelucires are characterized by a wide range of melting points, from about 33°C to about 65°C, and by a variety of hydrophilic and lipophilic balance (HLB) values of approximately 1–18. Each Gelucire is characterized by two numbers, the first referring to the nominal melting point of the base and the second to the HLB value. For eg. in Gelucire 44/14, the suffixes, 44 and 14, in the excipient trade name refer to its melting point and hydrophilic-lipophilic balance (HLB), respectively.[2-4] In contact with aqueous fluids it forms a fine emulsion which solubilises the active substances and hence increases its oral bioavailability. Gelucires with low HLB can be employed to decrease the dissolution rate of drugs, and ones with high HLB for fast release.[6] Gelucire enhances the drug release process by forming hydrogen bonds with the active substance, leading to the formation of stable solids of amorphous drug in microparticles.

The advantages of Gelucires over the polymers in controlled drug delivery systems include[4,6]:

1. Low melt viscosity, obviating the need for solvents,
2. Absence of toxic impurities,
3. Potential for biocompatibility and biodegradability,
4. Prevention of gastric irritation by forming a coating around the drug.
5. Carrier for active pharmaceutical ingredient sensitive to oxidation, humidity or light

Method of preparation of Gelucire based solid dispersion

A solid dispersion can be prepared by using various methods like spray drying, freeze drying, hot melt extrusion, fusion method, solvent evaporation and supercritical fluid precipitation. A conventional manufacturing process consists in melting Gelucire at 60°C and then incorporating the drug substance. The mixture is then homogenized and poured into gelatin capsules. Only semi-solid oral dosage forms could be obtained. An interesting approach to improve handling of this excipient is to process Gelucire 44/14 into a powder to produce solid dosage forms as pellets, tablets and hard capsules.[4] Because of its unique balance of short, medium and long chain fatty acids, Gelucire 44/14 forms an exceptionally stable, fine dispersion when in contact with the G.I. fluids at body temperature.

Physicochemical properties[3,6]

Each component of Gelucire presents different affinity for water and act as surfactant and co-surfactant. Di- and triglycerides are lipophilic in nature. Certain Gelucires are produced by the reaction of hydrogenated palm kernel oil and polyethylene glycol, PEG 33 (Gelucire 44/14). It contains PEG 33 esters, glycerides, unreacted PEG 33 and a small amount of glycerol. The different kinds of Gelucires are characterized by a wide range of melting points from about 33°C to about 64°C, and most commonly from about 35°C to about 55°C and by a variety of HLB values from about 1 to about 14, most commonly from about 7 to about 14.[6]

The hydrophilic property of the polymer is quite useful in the dissolution enhancement as well as in controlled release formulations. The examples of hydrophilic grades of Gelucire are 50/13, 44/14, 48/16, 55/18, 35/10, 48/09 and among these, the most commonly used ones are 50/13 and 44/14.[2] The following are the examples of hydrophobic grades of Gelucire such as 43/01, 39/01, 33/01, 50/02, 54/02, 64/02, among which, Gelucire 43/01, 39/01 and 33/01 are commonly used.[2,3]

The main grades of Gelucire and their properties are described below:

Sr no.	Type	M.P	HLB	Properties	Applications
1	Gelucire 39/01 [Gattefosse] (semi-synthetic glycerides)	39	01	• Waxy solid. • Extremely hydrophobic due to the absence of PGE esters, which in turn provides release-retarding ability.	• Gelucire 39/01 is a carrier for oral formulations and specifically for hard or soft gelatin dosage forms. • Used in the formulations as excipient, carrier, vehicle, and consistency agent.
2	Gelucire 44/14 [Gattefosse France] Lauroyl polyoxyl-32 glycerides. (saturated polyglycolized glycerides)	44	14	• Semi-solid hydrophilic excipient with self emulsifying properties. • It is a non-ionic water dispersible surfactant. • It has excellent surfactive property that enhances the solubility and wettability of active pharmaceutical ingredients.	• Useful in dissolution enhancement as well as in controlled-release formulations. • It can also be used as meltable binder.[6] • In addition to filling into hard gelatin capsules, may also be used to make pellets, spheroids, coated fluid air-bed forms, matrix forms or be incorporated into soft gelatin capsules.
3	Gelucire 43/01 [Gattefosse]	43	01	• Highly hydrophobic lipid, • Provides release-retarding properties and floating behavior	• In preparation of sustained release formulations and drug release is primarily controlled by diffusion. • Also used as thickening agent in topical formulation.
4	Gelucire 50/13 [Gattefosse France] Stearoyl macrogol-32 glycerides (saturated polyglycolized glycerides)	50	13	• Hydrophobic non-ionic, water dispersible surfactant. • Good thermoplasticity.	• In preparation of sustained release formulations.
5	Gelucire 54/02 [Gattefosse]	54	02	• Hydrophobic	• In preparation of sustained release formulations and drug release is primarily controlled by diffusion.
6	Gelucire 33/01 [Gattefosse]	33	01	• Hydrophobic	• In preparation of sustained release formulations and drug release is primarily controlled by diffusion.

Other Gelucires, such as, 37/06, 43/01, 35/10, 37/02, 46/07, 48/09, 50/02, 53/10, 62/05 also have wide variety of applications in the development of lipid based formulation.

Grinding of the Gelucires must be performed at a temperature below the melting temperature. However, grinding induces disorder: mechanical activation and generation of energy can lead to physical and chemical changes in crystalline solid which can affect its efficacy.[4]

Characterization of Gelucire Containing Formulations

In order to characterize Gelucire containing formulations, several parameters can be studied including the physical stability of drug in the matrix systems. Moreover, crystallinity and polymorphic and/or pseudo-polymorphic form of drug in a matrix containing Gelucire can be assessed by differential scanning calorimetry (DSC) and powder X-ray diffractometry (PXRD). Diffuse reflectance infrared fourier transform spectroscopy (DRIFTS) can also be employed to identify the nature of interactions between drug and the constituents of the polymeric matrix. However, several other techniques such as hot stage microscopy (HSM), hot stage polarizing microscopy (HSPM), scanning electron microscopy (SEM), and saturation solubility of formulation are available by which Gelucire containing formulations can be analyzed.[6]

Hydration behavior of Gelucire

Svensson A. et al[9]: Studied the hydration behavior of gelucire. In pharmaceutical applications, it is important to know how the excipient interacts with the drug, and how the mixture behaves during manufacturing, storage as well as during administration. The uptake of water by an amphiphilic excipient, Gelucire 44/14, has been investigated in two ways: storage in humid air and addition of liquid water. During exposure to humid air, the uptake goes in stages that correspond to the dissolution of the components of the excipient, starting with the most hydrophilic ones: glycerol, then polyethylene glycol (PEG), PEG esters (PEG monolaurate and PEG dilaurate), and finally glycerides (trilaurin). In the pharmaceutical formulation, the active ingredient could dissolve in the liquid phase. At larger hydrations, obtained through addition of liquid water, the state of Gelucire 44/14 differs from those of its components. Gelucire 44/14 forms a lamellar phase and this phase melts at 30°C whereas the pure PEG esters form hexagonal and cubic mesophases. The cubic mesophases do not melt until the temperature exceeds 40°C. At body temperature, all crystals in Gelucire 44/14 melt to an isotropic fluid as soon as the total water content exceeds 5%. Therefore the formulation of amphiphilic excipients can be optimized to avoid the formation of mesophases that impede dissolution of the excipient at body temperature.

Hadri M. et al[11]: Studied the structural and vibrational properties of Gelucire 50/13 during the hydration with increasing water from 0% to 80%. The Gelucire 50/13 is used as sustained release matrix forming agent in pharmaceutical applications and and the hydration behavior of this amphiphilic excipient has been investigated in the spectral range 4000–0 cm^{-1} in Raman spectroscopy, and 4000–600 cm^{-1} in FTIR. At increasing water contents Gelucire 50/13 forms successive bicontinuous to micellar supramolecular structures, and the vibrational changes were directly correlated with this conformational changes of the Gelucire structure.

Rheological behavior of Gelucire mixtures

Ratsimbazafy V. et al[12]: Studied the rheological behaviors of Gelucire mixtures of Gelucires 50/02 and 50/13 with Proxyphylline. Pure Gelucire mixtures were very slightly shear thickening whereas Proxyphylline suspensions had a thixotropic shear thinning behavior and these rheological behaviors can be explained by the chemical composition and by the ratio of the two Gelucires used. Extended release of proxyphylline was obtained with all these mixtures. Drug release increased with Gelucire mixture HLB owing to higher erosion. A viscosity-release relationship was found and allowed, with these two Gelucires of extreme HLB and viscosities, to define the formulations which will give an optimal drug release, by the determination of their suspension viscosity. Modeling of dissolution kinetics has generally shown the predominance of surface erosion of the plugs relative to drug diffusion inside the matrix.

Applications and Research Endeavours

Over the last decade, an impressive number of gelucire based solid dispersions of poorly soluble drugs have been described in the literature.

- **Improvement in the dissolution rate of the drug**

Damian F. et al[13]: Prepared and characterized solid dispersions of the antiviral Thiocarboxanilide UC-781 with PEG 6000 and Gelucire 44/14 by the fusion method. The results obtained showed that the rate of dissolution of UC-781 was considerably improved when formulated in solid dispersions with PEG 6000 and Gelucire 44/14 as compared to pure UC-781. From the phase diagrams of PEG 6000 and Gelucire 44/14 it could be noted that up to approximately 25% w/w of the drug was dissolved in the liquid phase in the case of PEG 6000 and Gelucire 44/14 and the possibility of UC-781 to form solid solutions with the carriers under investigation was ruled out.

Karataş A. et al[14]: Designed a study to improve the dissolution rate of piroxicam at the physiological pH's through its increased solubility by preparing semi-solid dispersions of drug using Gelucires and Labrasol. Gelucire 44/14 and Labrasol at the concentration of 15% w/v in water provided 20- and 50-fold increase in the solubility of piroxicam, respectively. DSC analysis of this semi-solid dispersion indicated that there was no chemical reaction between the drug and excipients, and that a solid-state solution of piroxicam with excipient formed.

- **Study on mechanism of drug release**

Siepmann F. et al[15]: Elucidated the drug release mechanisms from lipidic matrix pellets, using Theophylline and Gelucire 50/02 as model drug and carrier material, respectively. The effects of different formulations and processing parameters on the resulting drug release kinetics in 0.1N HCl and phosphate buffer pH 7.4 were studied and the obtained results analyzed using adequate mathematical models in order to get further insight into the underlying mass transport mechanisms. The type of preparation technique was found to strongly affect the underlying drug release mechanisms. Drug release from pellets prepared by the melt-solidification method was primarily controlled by pure diffusion, whereas drug release from pellets prepared by the extrusion-spheronization method was purely diffusion-controlled only at early time points.

- **Effect of cosolvent in addition to Gelucire on the solubility of drug**

Kawakami K. et al[16]: Investigated solubilization behavior of drugs in Gelucire/cosolvent mixtures. Cosolvents used are Dimethylacetoamide (DMA) or Dimethylsulfoxide (DMSO), both of which are also expected to enhance drug solubility. Gelucire was confirmed to form micelles by surface tension and fluorescence measurements both in water and water/cosolvent mixtures. Two model drugs, Phenytoin and Indomethacin, were employed to observe the solubilization behavior of poorly soluble drugs in Gelucire/cosolvent mixtures. Addition of cosolvents to the Gelucire solution did not enhance the solubility very much, and thus the combined use of cosolvents with Gelucire offered only little advantage from the viewpoint of solubility.

Fini A. et al[17]: Prepared a number of systems at five compositions (5, 10, 20, 30 and 40% w/w) of Diclofenac/*N*-(2-hydroxyethyl) pyrrolidine salt and acidic Diclofenac in PEG6000 and Gelucire 50/13, as physical mixtures and as solid dispersions. The release percentage of

the drug from PEG6000/acidic Diclofenac reaches 50% after few minutes in the most favourable case and appears to be dependent on the composition of the samples: the more Diclofenac is present as dissolved in the pre-treated samples, the higher is the release. The optimum composition was found in the range of 5–10% w/w.

- **Controlled rate of drug delivery by using Gelucire**

Bidah D. et al[18]: Prepared spherical oral devices in order to obtain a controlled rate of delivery of Sodium salicylate, and studied by using synthetic gastric liquid and in vitro tests. These devices have been prepared by dispersing the drug into Gelucire. The kinetics of release of drug has been found to be controlled by the erosion of Gelucire. The rate of drug delivery is then proportional to the actual area of the device, and a relationship between the time and the remaining weight of the device to the power one-third has been obtained. The effect of the (liquid volume)/ (device weight) ratio on the rate of transfer was examined, and a decrease in this ratio provokes a decrease in the rate of transfer.

- **Rapid onset of action by using Gelucire dosage form (in vivo study)**

Yuksel N. et al[19]: investigated the in vitro and in vivo performance of the semi-solid dispersion prepared with Gelucire 44/14 and Labrasol into hard gelatin capsules (GL) for enhancing the dissolution rate of the drug. The results were evaluated by comparing with pure Piroxicam filled into hard gelatin capsules (PP) and a commercially available tablet dosage form containing a Piroxicam: β-Cyclodextrin complex (CD). Amongst the dosage forms, GL provided at least 85% Piroxicam dissolution within 30 min in each of the media, behaving like a fast-dissolving immediate release drug product. Oral bioavailability of 20 mg Piroxicam in GL, CD, and PP was compared after administration of a single dose to eight healthy volunteers. The apparent rate of absorption of Piroxicam from GL was significantly higher than that of the PP and similar to that of CD. The results of the in vivo study revealed that the GL dosage form would be advantageous with regards to rapid onset of action, especially in various painful conditions where an acute analgesic effect is desired.

- **In gastroretentive floating drug delivery system**

Gastroretentive systems are dosage forms having ability to retain itself in the stomach to increase absorption of released drug from acidic medium in a controlled manner. Gastroretention is achieved by four types of modifications such as High density systems, modified shape systems, mucoadhesive systems, and floating systems. Floating drug delivery

system is a gastroretentive drug delivery system, has bulk density less than gastric fluids and so remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.[10]

Single- and multi-unit dosage forms are two types of approaches available to formulate floating dosage forms. Large single-unit dosage forms undergo significant swelling after oral administration, and the swollen matrix inhibits gastric emptying even when the pyloric sphincter is in an uncontracted state and with swelling and expanding systems there is a risk of permanent retention and the use of bioadhesive systems may cause problems such as irritation of the mucous layer owing to high localized concentration of the drug. Single-unit systems such as tablets or capsules may exhibit the all-or-none emptying phenomenon, which may be overcome by the design of multiunit systems. Multiunit dosage forms such as pellets and granules may be more suitable because they claim to reduce the intersubject variability in absorption and lower the probability of dose dumping.[8,10]

The use of Gelucire produces matrices with a burst effect and a subsequent very low drug release rate. Addition of release enhancers (like HPMC, MCC, Aerosil, Tween 80 etc) to Gelucire matrices allow a more gradual drug release. The effect of the release enhancers seems to be related to the Gelucire matrix consistency.[8]

Adel et al[20]: extended Drotaverine Hcl residence in the stomach by forming calcium alginate floating beads using sodium alginate, isopropylmyristate (oil), and Gelucire 43/01 (lipid) adopting emulsion gelation technique. Incorporation of Gelucire 43/01 to oil-based beads enhanced the *in vitro* performance of the beads. Coated beads prepared using drug: Sodium alginate ratio of 1:3 w/w, 20% w/v, Isopropylmyristate 20% w/v, and Gelucire 43/01 showed promising *in vitro* performance. The beads floated for 12 hr in the dogs' stomach and produced three-fold increase of the total amount of Drotaverine Hcl absorbed within 24 hr compared to that of drotaverine HCl powder.

CONCLUSION

The drawbacks associated with conventional dosage forms of poorly water soluble drugs have been overcome by utilizing novel polymers or solubilizers like Gelucire (available in different grades). The use of this novel polymer offers different benefits like improves solubility, dissolution and stability of the dosage form. They have a wide variety of applications in oral and topical formulation including enhancement of solubility and

bioavailability, sustain release, taste masking and protection of active pharmaceutical ingredient (API) from oxygen, light and humidity. Fast/rapid release as well as controlled release drug delivery systems of poorly soluble drugs can be formulated using this novel formulation tool.

REFERENCES

1. Chaudhari S, Dugar R. (Application of Surfactants In Solid Dispersion Technology For Improving Solubility Of Poorly Water Soluble Drugs). Journal of Drug Delivery Science and Technology, 2017; 41: 68-77.
2. Panigrahi K C, Patra N, Jena G K, Ghose D, Jena J, Panda S K, Sahu M. (Gelucire: A Versatile Polymer For Modified Release Drug Delivery System). Future Journal of Pharmaceutical Sciences, 2018; 4: 102-8.
3. Showkat H S, Pahuja S. (Gelucire: A Versatile Formulation Excipient, International Journal Of Pharmacy and Pharmaceutical Research, Human), 2017; 10(3): 55-73.
4. Chambina O , Janninb V, Champion D, Chevaliera C, Rochat-Gonthiera, Pourcelota Y. (Influence Of Cryogenic Grinding On Properties Of A Self-Emulsifying Formulation). International Journal of Pharmaceutics, 2004; 278: 79–89.
5. Siripuram P K, Bandari S, Jukanti R, Reddy P, Reddy V. (Formulation and Characterization of Floating Gelucire Matrices of Metoprolol Succinate). Dissolution Technologies, 2010; 34-9.
6. Pahwa R, Kumar S, Saini N, Kumar V. (Gelucire Mediated Gastric Floating Drug Delivery Systems). Der Pharmacia Lettre, 2012; 4(4): 1038-43.
7. Tamayo P, Robles L V. (Gelucire 39/01 As A Matrix For Controlled Release Of Ranitidine Hydrochloride From Floating Granules). Rev Mex Cienc Farm, 2014; 45(3): 54-64.
8. Juarez-Soberanez D, Villafuerte-Robles L. (Gelucire 39/01 As Excipient For Gastroretentive Metronidazole Sustained Delivery). Int J Pharm Pharm Sci., 2011; 3(2): 86-91.
9. Svensson A, Neves C , Cabane B. (Hydration Of An Amphiphilic Excipient, Gelucire 44/14). International Journal of Pharmaceutics, 2004; 281(1–2): 107-18.
10. Kaushik A, Tiwari A, Gaur A. (Role of Excipients And Polymeric Advancements In Preparation Of Floating Drug Delivery Systems). Int J Pharm Investig, 2015; 5(1): 1–12.

11. Hadri M, Achahbara A, Khamkhami J, Khelifa B, Abbas O, Bresson S. (Lyotropic Behavior Of Gelucire 50/13 By XRD, Raman And IR Spectroscopies According To Hydration). Chemistry and Physics of Lipids, 2016; 200: 11–23.
12. Ratsimbazafy V, Bourret E, Duclos R, Brossard C. (Rheological Behavior of Drug Suspensions In Gelucire Mixtures And Proxyphylline Release From Matrix Hard Gelatin Capsules). European Journal of Pharmaceutics and Biopharmaceutics, 1999; 48(3): 247-52.
13. Damian F, Blaton N, Naesens I, Balzarini J, Kinget R, Augustijns P, Moote G.(Physicochemical Characterization Of Solid Dispersions Of The Antiviral Agent C-781 With Polyethylene Glycol 6000 And Gelucire 44/14). European Journal of Pharmaceutical Sciences, 2000; 10(4): 311-22.
14. Karata A, Ksel N, Baykara T. (Improved Solubility and Dissolution Rate Of Piroxicam Using Gelucire 44/14 and Labrasol). Farmaco, 2005; 60(9): 777-82.
15. Siepmann F, Muschert S, Flament M, Gayot A, Siepmann J.(Controlled Drug Release From Gelucire-Based Matrix Pellets: Experiment And Theory). International Journal of Pharmaceutics, 2006; 317(2): 136-143.
16. Kawakami K, Miyoshi K, Ida A. (Solubilization Behavior Of Poorly Soluble Drugs With Combined Use Of Gelucire 44/14 and Cosolvent). Journal of Pharmaceutical Sciences, 2004; 93(6): 1471-9.
17. Fini A, Moyano J, Gins J, Perez-Martinez, Rabasco A. (Diclofenac Salts Solid Dispersions In PEG 6000 and Gelucire 50/13). European Journal of Pharmaceutics and Biopharmaceutics, 2005; 60(1): 99-111.
18. Bidah D, Vergnaud J. (Kinetics Of In Vitro Release of Sodium Salicylate Dispersed In Gelucire). International Journal of Pharmaceutics, 1990; 58(3): 215-20.
19. Yuksel N, Karatas A, Ozkan Y, Savaser A, Ozkan S, Baykara T. (Enhanced bioavailability of piroxicam using Gelucire 44/14 and Labrasol: in vitro and in vivo evaluation). European Journal of Pharmaceutics and Biopharmaceutics, 2003; 56(3): 453-59.
20. Adel S, ElKasabgy. (Design Of Innovated Lipid-Based Floating Beads Loaded With An Antispasmodic Drug: In-Vitro And In-Vivo Evaluation). Taylor and Francis, 2013; 136-49.