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Gelucire: A versatile polymer for modified release drug delivery system

Kahnu Charan Panigrahi [a, *], Ch. Niranjan Patra [a], Goutam Kumar Jena [a], Debashish Ghose [a], Jayashree Jena [a], Santosh Kumar Panda [b], Manoranjan Sahu [b]

[a] Roland Institute of Pharmaceutical Sciences, Berhampur, India
[b] School of Pharmaceutical Education and Research, Berhampur University, India

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ABSTRACT

Poly ethylene glycol (PEG) ester surfactants are synthesized by reacting polyethylene glycol with fatty acid. The polyethylene glycol comprises the hydrophilic part of the surfactant and the fatty acid is the lipophilic part. By varying the molecular weight of the PEG and the fatty acid, surfactants covering wide range of hydrophilic lipophilic balance (HLB) values can be produced. Gelucire is the family of vehicle derived from mixtures of mono, di and triglycerides with PEG esters of fatty acids. These are available with range of properties depending on their HLB and melting point range (33–65 °C). They have a wide variety of application in oral and topical formulations. The applications of oral formulation include solubility and bioavailability enhancement, sustain drug release, taste masking and active pharmaceutical ingredient (API) protection from oxygen, light and humidity. The applications of topical formulations include stabilization of creams, lotions and gels, thickener, superior penetration of drug through skin. Gelucire containing only PEG esters are generally used in the preparation of fast release formulations. Gelucire containing only glycerides or a mixture of glycerides and PEG esters are used in the preparation of sustained release formulations. Owing to their extreme hydrophobicity and low density, are considered as appropriate carriers for designing sustained release drug delivery systems. In this review manuscript, applications of various grades of gelucire are compiled in the form of tables and discussed critically. A current literature on patents on gelucire based formulations was also discussed.

1. Introduction

The use of surfactants in pharmaceutical formulations has been an incredible growth in last five decades. The term surfactants include solubilizers, emulsifiers, wetting agents, suspending agents, detergents, anti-foam compounds and many others [1]. Therefore, their classification is pivotal to select suitable surfactant to maximize effect. There has been division according to their ionization, chemical type, by popular (often ambiguous) nomenclature and their behaviour and solubility in water. Among all these classification, the solubility based classification is more widely acceptable throughout the globe i. e. hydrophilic lipophilic balance (HLB) system (Table 1). HLB is the relative efficiency of the hydrophilic portion of surfactant molecule to the lipophilic portion of same molecule. Griffin's scale [2] is an arbitrary scale between 0 and 20 which expresses numerically the size and strength of polar portion to the non-polar portion of the molecule. Although originally applied to non-ionic surfactants, its use has now been extended to ionic surfactants. HLB for ionic surfactants are much higher, up to 50, based on their ionization properties [3].

Polyethylene glycol (PEG) ester surfactants are prepared by reacting polyethylene glycol with a fatty acid [4]. The polyethylene glycol and fatty acid comprises the hydrophilic and lipophilic part of the surfactant respectively. By varying the molecular weight of the PEG and the fatty acid, surfactants with wide range of hydrophilic lipophilic balance (HLB) values can be obtained. Recently, much attention has been focused on the use of fats and fatty acids as carrier in drug delivery systems [5]. Gelucire is derived from mixtures of mono, di and triglycerides with PEG esters of fatty acids [6]. These are available with range of properties depending on their HLB and melting point range of 33 to 65 °C [7]. They have a wide variety of applications in oral and topical formulation. The

* Corresponding author.
E-mail address: kanhu.pharma@gmail.com (K.C. Panigrahi).
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Table 1
Application of surfactant based on HLB range.

HLB range	Water solubility	Application
1–3	No dispersibility in water	Release retardants
3–6	Poor dispersibility in water	w/o emulsifier
6–8	Milky dispersion	Wetting agent
8–10	Stable milky dispersion	o/w emulsifier
10–13	Translucent to clear solution	detergents
>13	Clear solution	solubilizers

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. Gelucire containing only PEG esters are generally used in the preparation of fast/immediate/rapid release formulations [8]. Gelucire containing only glycerides or a mixture of glycerides and PEG esters are used in the preparation of sustained release formulations [9]. Owing to their extreme hydrophobicity, are considered as appropriate carriers for designing sustained release drug delivery systems. Basing on HLB value gelucire can be classified into hydrophilic and hydrophoibic grades. Gelucireexhibiting HLB value less than 6 can be called as hydrophobic; 6 to 9 are water dispersible and above 9 can be recognized as hydrophilic grade. The examples of hydrophilic grades of gelucire are gelucire 50/13, 44/14, 48/16, 55/18, 35/10, 48/09 and hydrophobic grade are 43/01, 39/01, 33/01, 50/02, 54/02, 64/02. All the above grades of gelucire have got extensive applications in formulation development. However in the current review we have attempted to review critically on the applications following grade of gelucirevis-a-vis hydrophilic (50/13, 44/14) and hydrophobic (43/01, 39/01 and 33/01). The grades of gelucire on which extensive research has been published were selected for review. Hence the objective of the present manuscript is to make a compilation review on research publications and patents on various applications of some selected grades of gelucire.

1.1. Hydrophilic gelucire

The following are theexamples of hydrophilic grades of gelucire such as 50/13, 44/14, 48/16, 55/18, 35/10, 48/09. Among the above grades, gelucire 50/13 and 44/14 were selected for review as a lot of research works are published using these two grades.

1.2. Gelucire®50/13

It is a non-ionic, water dispersible surfactant composed of well-characterized PEG-esters, a small glyceride fraction and free PEG. Its chemical name is Stearoyl macrogol-32 glycerides. It is able to self-emulsify on contact with aqueous media forming a fine dispersion i.e. microemulsion [10]. It has excellent surfactive power to enhance the solubility and wettability of active pharmaceutical ingredients both *In-vitro* and *In-vivo*. It enhances the *In-vivo* drug solubilization and facilitates absorption. It has good thermoplasticity for use as binder in melt/fusion processes. It has HLB value 11 and melting point 50 °C. It is used in melt granulation or agglomeration techniques. It is also suitable for hard gelatin capsule molding and adsorption onto neutral carrier powders for use in tabletting, capsule filling and sachets.

A current literature review on gelucire 50/13 revealed that it has got widespread application in formulation of solid dispersions and self emulsifying drug delivery systems to improve solubility, dissolution and bioavailability of drugs. A summarized table on gelucire 50/13 based research publications are presented in Table 2. Khobragade et al. [11] prepared solid dispersion of meloxicam (ME) with various ratios of (Gelucire 50/13), PEG 4000, PEG 6000, PEG 20000, PVP K-30 and Poloxamer (Lutrol F68) by fusion method. The *In-vitro* dissolution showed significant improvement in drug dissolution especially with gelucire 50/13. Jang SW et al. [12] formulated solid dispersions of everolimus (EVR) with gelucire 50/13 using melt granulation method to improve its physicochemical properties and dissolution rate. The dissolution rate of EVR from the optimized solid dispersion (SD) composed of the drug, gelucire 50/13 and microcrystalline cellulose in a weight ratio of 1:5:10, was markedly rapid and higher than that from the drug powder and the market product (Afinitor®, Novartis Pharmaceuticals) in all dissolution mediums tested from pH 3.0 to pH 6.8. Jammula S et al. [13]studied the effect of Gelucire 50/13 on dissolution and tableting properties of cefuroxime axetil (CA) by melt-granulated dispersion and surface adsorption techniques. Gelucire 50/13 was used as the melt-dispersion carrier and Sylysia 350 was used to adsorb the melt dispersion. Solubility studies showed an eight-fold increase in solubility at a ratio of 1:1.5 for CA: gelucire 50/13. Chowdary et al. [14] studied the dissolution rate enhancement of acelofenac using modified starch, starchphospahate & gelucire 50/13 alone and in combination. The dissolution rate of aceclofenac could be significantly enhanced by solid dispersion in starch phosphate and gelucire 50/13. The combination of starch phosphate and gelucire 50/13 gave a significantly higher enhancement in the dissolution rate of aceclofenac. Devireddy S. R. et al. [15] prepared solid dispersions (SD) of gliclazide; and vitamin

Table 2
Reported literature on Gelucire 50/13.

Name of the drug	Method	Dosage form/product	Result	References
Meloxicam	Hot melt coating of non peril seeds	Pellet	Enhancement of bioavailability of drugs with low water solubility	[11]
Everolimus	Melt granulation	Powder	Improving dissolution rate and oral absorption	[12]
Cefuroxime axetil	Melt granulation	Hard gelatin capsule	Improvement of solubility by eight fold	[13]
Aceclofenac	Solid dispersion (kneading method)	Powder	Enhancement of dissolution rate and dissolution efficacy	[14]
Gliclazide	Solid dispersion (fusion method)	Tablet	Improvement of solubility and in vivo bioavailability of gliclazide	[15]
Glibenclamide	Hot melt granulation	Solid dispersion amorphous	Production of high potential of hot melt granulation technique for the production of solid dispersion	[16]
Tinidazole	Solid dispersion (physical mixture, kneading method)	Powder	Enhancement of solubility and dissolution as compared to pure drug	[17]
Probucol	solid selfemulsified lipid based drug delivery system	Hard gelatin capsule	Improvement in dissolution rate	[18]
Tacrolimus	Lipid based solid dispersion	Liquid SMEDDS	Enhancement of dissolution rate, intestinal permeability	[19]

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E using gelucire 44/14 and gelucire 50/13 by fusion process. Solid dispersions were subjected for solubility studies in various buffers. *In-vivo* study in albino rabbits has justified the improvement of solubility and bioavailability. Upadhyay et al. [16] prepared fast-release gastroretentive solid dispersions of glibenclamide using gelucire 50/13 by hot melt granulation technique. Powder X-ray diffraction (PXRD) study showed that glibenclamide was present in SD in an amorphous form while fourier transform infra red (FT-IR) spectroscopy revealed the presence of hydrogen bonding in the SDs. There was improvement in solubility and dissolution rate for all formulations. Hence gelucire 50/13 can be used primarily for enhancement of solubility, dissolution and bioavailability. Sahoo A. et al. [17] enhanced the solubility of tinidazole using the technique of solid dispersion which is reported to be one of the simple technique for solubility enhancement using Gelucire 50/13 and PEG 6000. Patel N. et al. [18] enhanced the dissolution rate of Probucol by formulating solid selfemulsified lipid based drug delivery system using gelucire 50/13. Patel P. et al. [19] prepared liquid SMEDDS of tacrolimus which showed significantly higher dissolution rate, intestinal permeability and lower rate of drug metabolism.

1.3. Gelucire® 44/14

It is composed of PEG-esters, a small glyceride fraction and free PEG. Its chemical name is Lauroyl polyoxyl-32 glycerides. It is able to form microemulsion i.e. emulsify on contact with aqueous media forming a fine dispersion. It is a non-ionic water dispersible surfactant. It has excellent surfactive property that enhances the solubility and wettability of active pharmaceutical ingredients *In-vitro* and *In-vivo*. Its bioavailability enhancement can be attributed to improved *In-vivo* drug solubilization which facilitates absorption. It can be used as binder in melt processes, associated with rapid formation of stable crystalline phase because of its thermo plasticity behaviour. It can be formulated by melt granulation or melt extrusion techniques for capsule filling, tabletting, sachets etc. It has HLB value 11 and melting point 44 °C. It is available in the form of semi solid blocks. I can be used in the field of human pharmaceutical products, veterinary products excluding food producing animals.

A recent literature review on research publications based on gelucire 44/14 revealed that it has been widely used for improvement in solubility, dissolution rate and stability. A summarized table on gelucire 44/14 based research publications are presented in Table 3. Jatwani S et al. [20] attempted to improve solubility of simvastatin by using hydrophilic carriers Polyethylene glycol 6000 (PEG 6000), Sorbitol, Gelucire 44/14. The solid dispersions were prepared by two methods vis-a -vis fusion and solvent evaporation method. From the results it was clear that solid dispersion showed improved dissolution rate than pure drug and physical mixtures. Combination of carriers showed better dissolution as compared to single carrier. Anupama S et al. [21] prepared the dispersion granules of albendazole using a hot melt technique using gelucire 44/14 and PEG 8000. DSC and XRD data indicated the amorphous nature of albendazole in solid dispersion. SEM revealed partial loss of drug crystallinity which can bring about significant changes in the drug dissolution rate. Cavallari C et al. [22] prepared solid dispersions of olanzapine, with carriers like (Lutrol® F68, Lutrol® F127, Gelucire® 44/14). Differences in the release profiles between Lutrol- and Gelucire-containing systems were interpreted in terms of the formation of polymer micelles by the Lutrols when in aqueous solution. Karatas et al. [23] investigated the physical stability of the semi-solid dispersions into the hard gelatin capsules prepared with Gelucire 44/14, Labrasol and different additives such as microcrystalline cellulose (MCC), mannitol and lactose (α-monohydrate) used for enhancing the stability of the formulations. FT-IR and DSC results both confirmed the amorphous state of piroxicam in all semi-solid dispersions under storage condition for 12 months. Antunes et al. [24] prepared immediate release formulations for Carbamazipine using gelucire 44/14. Monolithic Gelucire 44/14 structures are prone to prolonged erosion times, thereby slowing down drug dissolution. They combine either granulation or spray-drying, followed by compression into tablets, with an optimized composition of disintegration promoting agents. This formulation strategy allows obtaining nearly 100% drug release within 10 min of dissolution study. Patil AM et al. [25] formulated solid dispersion of Lornoxicam using hydrophilic polymers like gelucire 44/14 and crospovidone by spray drying technique. Physical mixture and solid dispersion were prepared at three molar ratios of drug: polymer (1:2, 1: 4, and 1:6) for both the polymers. Solid dispersion batches prepared using gelucire 44/14 had shown rapid and better extent of drug release. Aparna K. et al. [26] formulated solid dispersions of nifedipine with four different polymers as hydroxypropylcellulose (HPC), polyvinylpyrrolidone K 29/32 (PVP K 29/32), polyethyleneglycol 6000 and Gelucire 44/14 to enhance the solubility. Borhade V. et al. [27] formulated nanoemulsion of clotrimazole. The nanoemulsion composed of Capryol 90, Solutol HS 15 and Gelucire44/14 enhanced solubility of clotrimazole up to 25 mg/ml. Dissolution profile of clotrimazole nanoemulsion in various media showed 100% drug release within 15 min irrespective of pH of the medium. Kawakami K. et al. [28] enhanced the solubility of phenytoin and indomethacin using gelucire 44/14 in combination with dimethylacetamide (DMA) or dimethylsulfoxide (DMSO).

1.4. Hydrophobic gelucire

The following are theexamples of hydrophobic grades of gelucire such as 43/01, 39/01, 33/01, 50/02, 54/02, 64/02. Among the above grades, gelucire43/01, 39/01 and 33/01 were selected for

Table 3
Reported literature on Gelucire 44/14.

Name of the drug	Method	Dosage form/product	Result	References
Simvastatin	Solid dispersion	Powder	Better release profile	[20]
Albendazole	Hot melting technique	Amorphous powder	Enhancement in dissolution rate	[21]
Olanzapine	Physical mixture of solid dispersion	Crystalline form	Improve stability and performance	[22]
Piroxicam	Solid dispersion	Hard gelatin capsule	Enhancement of physical stability	[23]
Carbamazipine	Melt granulation and spray drying	Tablet	100% drug release within 10 min	[24]
Lornoxicam	Spray drying	Powder	Improvement dissolution profile	[25]
Nifedipine	Solid dispersion	Capsule	Enhancement of dissolution rate and solubility	[26]
Clotrimazole	Spontaneous nano emulsification method	Nano-emulsion	100% drug release within 15 min	[27]
Phenytoin	cosolvency	Solution	Enhancement of solubility and dissolution as compared to pure drug	[28]
Ibuprofen	Fusion method	Granule	Immediate release of loading dose of drug	[29]

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review as a lot of research works are published using these three grades.

1.5. Gelucire®43/01

It is a hard fat as per European pharmacopoeia (EP) and National formulary (NF). It can be used as a protective carrier for API sensitive to oxidation, humidity or light. It is a lipid for use in modified release dosage forms (lipid matrix in capsules, floating granules). It is used as a lipid binder in melt techniques where the physicochemical properties and plasticity of the lipid agglomerates provides high resistance to fracture. It is useful for flash melt and chewable tablets. It is used as consistency agent (thickener) for topical formulations. It has HLB value 1 and melting point of 43 °C. It is available in the form of semi solid block. It can be formulated by melt granulation or melt extrusion techniques for capsule filling, tabletting, sachets etc. It is suitable for hard gelatin capsule molding. It can be used in the preparation of topical emulsions and microemulsions.

A current literature review on gelucire 43/01 based research publications showed that it has been used extensively in the formulation of floating and sustain release drug delivery system (Table 4). Upadhyay P [07] prepared and characterized beads of metformin hydrochloride (MH) using gelucire 43/01. The beads demonstrated favourable in vitro floating ability which was attributed to gelucire 43/01. Incorporation of sodium alginate further synergized the extended release. Patel R et al. [29] prepared sustained release floating granules of Ibuprofen using gelucire 43/01and 44/14. Gelucire 44/14 enhanced solubility of ibuprofen whereas gelucire 43/01 enhanced the retention time of ibuprofen in stomach where it is more permeable. Shimpi et al. [30] prepared floating granules of diltiazem hydrochloride by melt granulation technique. The basic objective of this study was to explore the application of gelucire 43/01 for the design of multi-unit floating systems of a highly water-soluble drug diltiazem hydrochloride. Granules were retained in stomach for 6 h. Approximately 65%–80% of drug was released over 6 h with initial fast release from the surface. It was reported that hydrophobic lipid gelucire 43/01 can be considered as an effective carrier for design of a multi-unit floating drug delivery system. Siripuram et al. [31] formulated floating sustained-release matrices of metoprolol succinate using gelucire 43/01 and gelucire 44/14 by melt-solidification technique. The *In-vitro* floating characteristics of gelucire matrices were greater than 12 h with good *In-vivo* gastric retention. The results indicated that gelucire 43/01 is an appropriate carrier for the development of sustained-release gastro retentive drug delivery systems. Jammula S et al. [32] developed biphasic floating mini-tablets of cefuroxime axetilby melt granulation technique using two different grades of gelucire namely 50/13 and 43/01 to maintain constant plasma drug concentration. The optimized batch of minitablets was filled into 0 size hard gelatin capsule. In vitro dissolution study for capsule showed an immediate burst release followed by sustain release up to 12 h. The sustain release with floating was attributed gelucire 43/01 because of its extreme hydrophobicity and low density. Patel et al. [33] prepared gastro-retentive tablets of famotidine by a solvent free melt granulation technique using gelucire 43/01 as hydrophobic meltable carrier. All formulations showed floating within 3 min and had total floating duration for more than 12 h. It was observed that a type of filler and the ratio of gelucire 43/01 to HPMC K4Mhad significant influence on buoyancy lag time. Adel S. et al. [34] formulated beads drotaverine hydrochloride by emulsion gelation technique. The optimized formulation showed extended residence of drotaverine hydrochloride in the stomach with increased bioavailability.

1.6. Gelucire®39/01

It is a protective carrier for API sensitive to oxidation, humidity or light. It is a lipid for use in modified release dosage forms (lipid matrix in capsules, floating granules). It is used as a lipid binder in melt techniques where the physicochemical properties and plasticity of the lipid agglomerate provides high resistance to fracture. It is useful for flash melt and chewable tablets. It is used as consistency agent (thickener) for topical formulations. It has HLB value 1 and melting point of 39 °C. It can be formulated by melt granulation or melt extrusion techniques for capsule filling, tabletting, sachets etc.

An updated literature review on gelucire 39/01 based formulations revealed thatit can be used in sustain release, floating, bioavailability enhancement of drugs (Table 5). Upadhaya et al., [35] developed multiparticulate drug delivery system of metformin using combination of Gelucire 39/01 and 43/01 by melt granulation technique. Combination of ethylcellulose, methylcellulose and microcrystalline cellulose with gelucire were explored for release of drug and consistency for optimized formulation. IVIVC studies confirmed increased bioavailability of drugs in combination form and followed level A correlation. Saxena et al. [36] developed in situ gelling emulsion of piroxicam by mixing different concentrations of molten gelucire 39/01 with low viscosity sodium alginate solution. Pharmacodynamic studies in albino rats revealed significantly increased analgesic/anti-inflammatory response from in situ emulgels compared to conventional in situ gelling formulations. Madgulkar AR et al. [37] developed novel taste masked mouth-dissolving tablets of tramadol using gelucire 39/01 as mouth melt binder. The crucial aspect in the formulation of mouth-dissolving tablets is to mask the bitter taste lower disintegration time with proper mechanical strength of tablet. Gelucire 39/01 was successfully used to prepare optimized taste masked mouth-dissolving tablets of Tramadol HCl with adequate mechanical strength and rapid disintegration. Chauhan et al. [38] prepared risedronate

Table 4
Reported literature on Gelucire 43/01.

Name of the drug	Method	Dosage form/product	Result	References
Diltiazem hydrochloride	Melt granulation	Floating granules	Hydrophobic lipid Gelucire 43/01 can be considered as an effective carrier for the design of a multi unit floating drug delivery system of highly water soluble drug	[30]
Metoprolol succinate	Melt solidification tech	Capsule	Gelucire 43/01 is an appropriate carrier for the development of sustained-release floating drug delivery systems	[31]
Cefuroxime axetile	Melt granulation technique	Capsule	3 times improvement in oral bioavailability	[32]
Famotidine	Solvent free melt granulation technique	Tablet	Showed floating within 3 min and had total floating time of more than 12 h	[33]
Drotaverinehydrocloride	Emulsion gelation technique	beads	Extended residence of drotaverine hydrochloride in the stomach increased bioavailability	[34]

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Table 5
Reported literature on Gelucire 39/01.

Name of the drug	Method	Dosage form/product	Result	References
Metformin hydrochloride	Melt granulation	Multiparticulate drug delivery system	IVIVC studies confirm increased bioavailability of drugs in combination	[35]
Piroxicam	Mixing	Emulgels	*In vitro* toxicity studies carried out in albino rats revealed no sign of gastric ulceration upon prolong dosing	[36]
Tramadol Hcl	Formulation of mouth dissolving tablet	Mouth dissolving tablet	Taste is masked in mouth dissolving tablets of Tramadol Hcl with adequate mechanical strength and rapid disintegration	[37]
Resedronate sodium	Melt solidification	Matrices	Increase in drug release on ageing	[38]

sodium and gelucire 39/01floating matrices using melt solidification technique. The sustained release floating matrices were evaluated for *In-vitro and In-vivo* floating ability and in vitro drug release. Ageing causes changes in the crystal structure of gelucire, which is responsible for an increase in drug release.

1.7. GELUCIRE ®33/01

It is a protective carrier for API sensitive to oxidation, humidity or light. It has less melting point lipid for use in modified release dosage forms (Table 6). It is used as a lipid binder in melt techniques for preparation of semisolid matrix. It is useful for flash melt and chewable tablets. It is used as consistency increasing agent (thickener) for topical formulations. It has HLB value 1 and melting point of 33 °C. It can be formulated by melt granulation or melt extrusion techniques for capsule filling, tableting, sachets etc. It is suitable for adsorption onto neutral carrier. It is also used for preparation of pH dependent release formulations.

An updated literature review on gelucire 33/01 based formulations revealed thatit can be used in formulation of capsules, semisolid dosage forms. Barakat et al. [39]prepared a pressure-controlled colon delivery capsule (PCDC) containing theophylline (TPH) dispersion in a lipid matrix as a chronotherapeutic drug delivery system for the treatment of nocturnal asthma. The system was made by film coating using Eudragit S100 based formula over the sealed-hard gelatin capsules containing the drug-lipid dispersion. The lipid formula was composed mainly of gelucire 33/01 with different ratios of surfactants (1–10%). The film-coated capsules showed complete resistance to both the acidic environment (pH 1.2) for 2 h and phosphate buffer pH 6.8 for 3 h at 37 °C. The optimized formulation exhibited a significantly higher C_{max}, T_{max} and a nonsignificantly different AUC compared with marketed product Avolen(®) SR. Higher TPH blood levels from 1 to 8 h post-administration was detected. Massik MA et al. [40] developed semisolid matrix filled capsule for improving dissolution and stability of phenytoin sodium. The fill matrices included lipophilic bases (castor oil, soya oil, and Gelucire 33/01), amphiphilic bases (Gelucire 44/14 and Suppocire BP), and water-soluble bases (PEG 4000 and PEG 6000). The dissolution rate study indicated that formulations containing lipophilic and amphiphilic bases showed the best release profiles. Sistla R. et al. [41] formulated sustained release capsule of aceclofenac by liquid filming technique using gelucire 33/01.

1.8. Recent patents on gelucire based formulations

Patents on gleucire based formulations are presented in Table 7. Patents were filed on the applications of various grades of gelucirevis-a-vis 48/16, 44/14, 50/13, 35/10, 37/02, 53/10, 43/01, 50/02, 54/02, 62/05 and 64/02. These grades were used in formulation of drugs with diverse applications such as improvement in solubility, bioavailability, enhanced absorption, lipid based nanocarrier for cancer treatment, biphasic formulation, semi solid formulation, solid state solution, dispersions etc. Farah N et al. [42] patented a pharmaceutical composition comprising solid dispersion of BCS class II drug in Gelucires with pH modifiers using a novel process. Gelucires are polyethylene glycol (PEG) glycerides composed of mono- and di esters of polyethylene glycol. Gelucire® 48/16, a novel carrier available in powder and pellet forms, is PEG-32 stearate, while, conventional gelucires, Gelucire® 44/14 and Gelucire® 50/13 are lauroyl polyoxyl-32glycerides NF and stearoyl polyoxyl-32 glycerides NF respectively. Telmisartan is selected as model BCS class II drug. The patented composition can be used in formulation of granules, capsules and tablets. Roussin P et al. [43] patented sustained release theophylline formulations, excipient systems and methods of production. A stable sustained release theophylline formulation is prepared by incorporating theophylline into a semi-solid matrix comprising polyglycolized glycerides (GELUCIRE® excipient) and a mixture of nucleation enhancers. Theophylline is admixed with molten GELUCIRE to make the sustained release formulation. The nucleation enhancer composition is then incorporated in the admixture to make the sustained release formulation resistant to changes in dissolution upon aging. Orally administrable compositions are prepared by filling gelatin capsules with the formulation. The polyglycolized glycerides (GELUCIRE) and the nucleation enhancer composition can also be used as an excipient system for preparing sustained release pharmaceutical compositions. Grsoy RN [44] patented lipid-based nanocarrier systems for cancer treatment. A nanocarrier system, mixture of Labrasol and Gelucire 44/14 as the surfactant, Maisine or Peceol as the oil phase and polyethylene glycol 300 as the cosolvent. Martini A [45] patented semi-solid formulations for immediate release

Table 6
Reported literature on Gelucire 33/01.

Name of the drug	Method	Dosage form/product	Result	References
Theophylline	Pressure controlled capsule formulation	Capsule	Higher theophylline in blood levels from 1 to 8 h post administration was detected.	[39]
Phenytoin sodium	Formulation of capsule	Hard gelatin capsule	Pharmaceutical quality of phenytoin sodium capsule can be improved by using semisolid lipophilic matrix filled in hard gelatin capsule	[40]
Aceclofenac	Liquid filming technique in hard gelatin capsule	Hard gelatin capsule	sustained release with gelucire 33/01	[41]

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Table 7
Recent patents on Gelucire based formulations.

Title	Patent no	Date	Grades of Gelucire	Inventors
Pharmaceutical composition comprising solid dispersion of BCS class II drugs with Gelucires.	WIPO patent application WO/2016/005994	01/14/2016	48/16, 44/14, 50/13	[42]
Sustained release theophylline formulations, excipient systems and methods of production	United states patent 6171615	01/09/2001	50/13, 53/10	[43]
Lipid-based nanocarrier systems for using cancer treatment	European patent EP2790683	06/29/2016	50/13, 44/14, 43/01	[44]
Semi-solid formulations for immediate release intended for the oral administration of drugs	United States Patent Application 20070141140	06/21/2007	44/14	[45]
Pharmaceutical formulations for 1,4-dihyrdropyridine compounds having improved solubility	WIPO patent application WO/2008/058234	05/15/2008	44/14	[46]
Formulations of finasteride	United states patent application 20060099251	05/11/2006	44/14	[47]
Formulations with improved bioavailability, comprising a steroid derivative and a polyglycolysed glyceride	United states patent application 20090149434	06/11/2009	44/14, 35/10, 37/02, 50/13	[48]
Composition for enhanced absorption of NSAIDS	WIPO patent application WO/2002/083105	10/24/2002	44/14	[49]
Drug delivery system	WIPO patent application WO/2002/045696	06/13/2002	44/14	[50]
Biphasic capsule formulation	European patent EP0734253	02/20/2002	44/14, 50/02,50/13, 54/02,62/05, 64/02	[51]
Semi-solid formulations for the oral administration of taxoids	WIPO patent application WO/2005/013968	02/17/2005	44/14	[52]
Solid state solutions and dispersions of poorly water soluble drugs	WIPO patent Application WO/1999/021534	05/06/1999	53/10	[53]

intended for the oral administration of drugs The present invention relates to a pharmaceutical composition suitable for oral administration, in the form of semisolid matrix, comprising an active ingredient poorly soluble in water and present in a quantity of 15–45% by weight of the percent composition of the pharmaceutical composition; a surfactant agent constituted by a polyglycolised glyceride; and a pharmaceutically acceptable hydrophilic carrier. Tehim A [46] patented Pharmaceutical formulations for 1,4-dihyrdropyridine compounds having improved solubility. A pharmaceutical composition comprising a mixture of glycerol and PEG1500 esters of long fatty acids having a melting point of approximately 44 °C and a hydrophilic/lipophilic balance of approximately 14 (Gelucire 44/14) and d-alpha-tocopheryl polyethylene glycol 1000 succinate (Vitamin E TPGS). Johannsson F [47] patented a pharmaceutical tablet of finasteride, a wetting agent selected from the group consisting of Gelucire, sodium lauryl sulfate and polysorbate, a binding agent selected from the group consisting of gelatin, dextrin, povidone starch and microcrystalline cellulose, optionally in combination with other excipients.

Podolski J. et al. [48] patented a formulation with improved bioavailability, comprising a steroid derivative and a polyglycolysed glyceride. Jamali F. et al. [49] patented a pharmaceutical composition of non-steroidal anti-inflammatory active agent, disintegration agent and anti-precipitation agent. The disintegrating agent is sodium bicarbonate whereas the anti-precipitation agent is gelucire. Ibuprofen granules 'prepared under this conditions have significantly improved absorption rate in propantheline-treated rats as compared with a crushed commercially available ibuprofen tablet. Craig D. et al. [50] patented a composition comprising at least one active pharmaceutical or nutraceutical agent and a lipophillic phase in which the lipophilic phase enables the enhanced absorption of at least one active pharmaceutical or nutraceutical active agent. The lipophillic phase is preferably a mixture of polyethylene glycol fatty acid ester and glycerides. Barnwell SG et al. [51] patented a capsule formulations containing at least two different fill compositions which are prevented from mixing either by providing both of the fill compositions as solids or by providing a physical barrier which separates the fill compositions so that they are prevented from mixing. The invention has the advantage that two different formulations can be provided in a single capsule without one of the formulations having an adverse effect on the other. Borovac T et al. [52] patented a semi-solid formulation comprising one taxoid and one polymeric material that is chosen among Vitamin E TPGS and Gelucire 44/14. The comparison of the drug release profiles of semi-solid formulations shows that Vitamin E TPGS exhibited the highest solubilization properties, with a release of 80% for the 100 mg/g dosage and up to 100% for the 50 mg/g dosage. Tallavajhala SV et al. [53] patented a composition useful to increase the solubility of poorly soluble therapeutically active compounds, by means of an excipient comprising a mixture of saturated polyglycolyzed glycerides (GELUCIRE) andpolyoxypropylene-polyoxyethylene block copolymers.

2. Conclusion

Gelucire is the family of vehicle derived from mixtures of mono, di and triglycerides with PEG esters of fatty acids. It is available in wide range of HLB values starting with 01–16. It can be used as a carrier in wide variety of formulations such as immediate release, sustain release, biphasic release, semisolid dosage form, nano-formulations, stabilizer etc. Hence the review presented in this review manuscript can be used as a ready reference for researchers using gelucire as a carrier.

Conflicts of interest

Authors declare no conflict of interest.

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