Compritol 888 ATO: a multifunctional lipid excipient in drug delivery systems and nanopharmaceuticals

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Introduction: Compritol® 888 ATO is a lipid excipient that is generally used in cosmetic industry as a surfactant, emulsifying agent and viscosity-inducing agent in emulsions or creams. Based on its chemical composition, Compritol 888 ATO is a blend of different esters of behenic acid with glycerol.

Areas covered: Recently, there has been great interest in the multiple roles that Compritol 888 ATO plays in various pharmaceutical delivery systems. Accordingly, this review aimed at summarizing the current and potential applications of Compritol 888 ATO in various drug delivery areas.

Expert opinion: Different researches have highlighted the feasibility of using Compritol 888 ATO as a lubricant or coating agent for oral solid dosage formulations. It has also been explored as a matrix-forming agent for controlling drug release. At present, the most common pharmaceutical application of Compritol 888 ATO is in lipid-based colloidal drug delivery system such as solid lipid microparticles, solid lipid nanoparticles and nanostructured lipid carriers. Although, Compritol 888 ATO has acceptable regulatory and safety profiles and although the number of articles that emphasize on its applicability as an innovative excipient in pharmaceutical technology is continuously increasing, it is not widely used in the pharmaceutical market products and its use is limited to its sustain release ability in extended release tablets.

Keywords: Compritol® 888 ATO, glyceryl behenate, lipid excipients, pharmaceutical formulations, physicochemical characterization

1. Introduction

United States Pharmacopoeia (USP) defined pharmaceutical excipients as 'substances else than the active pharmaceutical ingredient (API) that have been assessed for safety and are deliberately incorporated in a delivery system'. Excipients are crucial components of a drug delivery system as they enable the delivery, manufacturability and stabilization of the API. Exploring new excipients is necessary to aid in formulating the newly discovered drug molecules [1]. According to the FDA, new excipients are “any inactive ingredients that are purposely added to diagnostic or therapeutic products, but: i) do not have therapeutic effects at the proposed dose, although they may improve drug delivery (e.g., increase drug absorption or sustain drug release); and ii) are not entirely qualified by present safety data with respect to the anticipated level of exposure, duration of exposure, or route of administration” [2].

Different lipid classes have been extensively used as pharmaceutical excipients due to their relative low cost, negligible toxicity and biodegradable properties [3]. Glycerides represent a family of lipid molecules that serve as multipurpose
Article highlights.

- The benefits of lipid-based formulations led to the exploration of new multifunctional lipid excipients.
- Compritol® 888 ATO is a unique lipid excipient with a wide range of potential applications in pharmaceuticals and cosmeceuticals.
- Although, solid lipid nanoparticles (SLNs) encompassing Compritol 888 ATO have been extensively explored in scientific literature, yet Compritol 888 ATO-based SLNs are not available commercially, owing to manufacturing impediments that prevent their industrial scaling up.
- During formulation, Compritol 888 ATO encounters different manufacturing processes that may impact its physical and chemical integrity.
- The polymorphic form of Compritol 888 ATO within the dosage form affects its stability, drug load and drug release profiles.
- There is still a lack of complete understanding of the in vivo behavior of Compritol 888 ATO after oral administration.

This box summarizes key points contained in the article.

Excipients in the pharmaceutics field. Among different glycerides, Compritol® 888 ATO has attracted particular interest as it has been successfully utilized in diverse pharmaceutical dosage forms (Figure 1). Compritol 888 ATO is used as a lubricating agent in the manufacturing of oral tablets and capsules [4,5]. It has been extensively employed as a matrix-forming agent in the preparation of different sustained-release tablets [6-10]. It has also been investigated as a hot-melt coating agent for powders or granules for controlled release purposes [11-13]. As a coating agent, Compritol 888 ATO provides several noteworthy advantages over polymers as it is generally recognized as safe [GRAS] and method of manufacturing of Compritol 888 ATO.

Compritol 888 ATO (glyceryl dibehenate European Pharmacopoeia [EP], glyceryl behenate National Formulary [NF]) is a hydrophobic mixture of mono—(12 – 18% w/w), di—(45 – 54% w/w) and tri—(28 – 32% w/w) behenate of glycerol with melting point in range of 69 – 74°C and with hydrophilic lipophilic balance (HLB) = 2. Compritol 888 ATO is prepared by the esterification of glycerin by behenic acid (C_{22} fatty acid) without the use of catalysts. The raw materials used in preparing are of vegetable origin and the esterified material is atomized by spray cooling [22]. It is worth mentioning that raw materials of vegetable origin are generally preferred over those of animal origin in pharmaceutical industry due to their abundance, variety and better safety profiles [25]. Compared to esters of glycerin with either palmitic (C_{16}) or stearic acid (C_{18}), Compritol 888 ATO has more pronounced hydrophobic property attributed to longer fatty acid chain length in behenic acid (C_{22}). Compritol 888 ATO is present in different forms: fine white powder, semisolid pellet or almost white unctuous flakes [26].

According to the EP, glyceryl dibehenate is a mixture of diacylglycerols (40 – 60%), together with monoacylglycerols (15 – 21%) and triacylglycerols (21 – 35%) [27]. However, the USP 32-NF 27 describes glyceryl behenate as a blend of glycerides of fatty acids, predominantly behenic acid and specifies that the content of 1-monoacylglycerides should range between 12 and 18% [28].

It is documented that the acid value of glyceryl behenate should be ≤ 4, the iodine value ≤ 3, the saponification value in range of 145 – 165, the residue on ignition ≤ 1%, the nickel ≤ 1 ppm, the water ≤ 1% and the free glycerin ≤ 1% [27,28]. Glyceryl behenate can be identified using thin-layer chromatography [26] and gas chromatography (GC). The Food Chemicals Codex specified that the lead content in glyceryl behenate should not exceed 1 mg/kg detected by graphite furnace atomic absorption spectrometry (GFAAS) [29].

Other member of the Compritol family manufactured by Gattefosse® [30] include Compritol HD5 ATO (behenoyl polyoxyll-8 glycerides NF) which contains > 50% mass fraction polyethylene glycol behenate together with tribehenin. The melting point of Compritol HD5 ATO ranges from 60 to 67°C. With an HLB of 5, Compritol HD5 ATO provides greater hydrophilicity than Compritol 888 ATO. In addition, Compritol E ATO (glyceryl behenate E471/ generally recognized as safe [GRAS]) is also manufactured by Gattefosse® [30]. Different grades of Compritol and their applications as reported by their main manufacturer [30] and systems that are administered through various routes in order to open new doors for its market application, and second, to identify the gap in the scientific published data that needs to be addressed by researchers.

2. Structure, pharmacopeial specifications and method of manufacturing of Compritol 888 ATO

Compritol 888 ATO is a unique lipid excipient with a wide range of potential applications in pharmaceuticals and cosmeceuticals. Among different glycerides, Compritol® 888 ATO has attracted particular interest as it has been successfully utilized in diverse pharmaceutical dosage forms (Figure 1). Compritol 888 ATO is used as a lubricating agent in the manufacturing of oral tablets and capsules [4,5]. It has been extensively employed as a matrix-forming agent in the preparation of different sustained-release tablets [6-10]. It has also been investigated as a hot-melt coating agent for powders or granules for controlled release purposes [11-13]. As a coating agent, Compritol 888 ATO provides several noteworthy advantages over polymers as it is generally recognized as safe [GRAS] and method of manufacturing of Compritol 888 ATO.
are presented in Table 1. The chemical structure of glyceryl behenate is illustrated in Figure 2 [31,32].

3. Properties of Compritol 888 ATO

Several studies have been conducted to examine the thermal behavior, crystallinity and possible interactions of the Compritol 888 ATO and the drug that may impact its release. In these studies, the properties of Compritol 888 ATO have been mainly characterized using differential scanning calorimetry (DSC), X-ray powder diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR) [33-36]. DSC thermogram, XRD diffractogram and FTIR spectrum of Compritol 888 ATO are presented in Figure 3.

Generally, lipid polymorphism occurs due to the difference in lateral packing possibilities of fatty acid chains in a particular organization of hydrocarbon chains [37]. According to Freitas and Müller [38], lipids exist in different three-dimensional structures: unstable α, metastable β' and the most stable β modification. Additional intermediate β, form exists between β' and β. The melting point of Compritol 888 ATO ranges from 69 to 74°C, according to the polymorphic form used [19], and stable β polymorphic form has higher melting point in comparison to the unstable α form or metastable β' forms. The polymorphic form of Compritol 888 ATO either (α, β' or β) depends on parameters such as crystallization rate and temperature during production and storage [31,32]. In slow crystallization rates, each glyceride crystallizes separately, producing a complex matrix containing different lamellar phases (crystallization rate of 0.4°C/min produces three dissimilar lamellar phases). On the contrary, a crystallization rate of 10°C/min or more produces single lamellar phase [35,36]. After crystallization, the transformation of lipid particles from less stable to more stable is referred to as polymorphic transition. During nanoparticle formulation, the lipid crystallizes into unstable imperfect α polymorph, which transforms into the metastable β' form. However, during storage or destabilization of nanoparticles, the metastable β' form changes into the more stable (β or β') forms with more perfect structure. The transformation of the solid lipid (Compritol 888 ATO)

![Figure 1. Schematic representations of versatile applications of Compritol ATO 888 lipid in the drug delivery field.](image-url)
in nanoparticles may lead to aggregation and increase in the in
particle size of nanoparticles along with the expulsion of drug
molecules incorporated in lipid imperfections (Figure 4) [19,39,40].

Table 1. Different Compritol grades, their chemical compositions, available forms and applications [22].

<table>
<thead>
<tr>
<th>Compritol grade</th>
<th>Chemical composition</th>
<th>Available form</th>
<th>Field of use</th>
<th>Administration route</th>
<th>Formulation techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compritol 888 ATO</td>
<td>Glyceryl dibehenate EP, Glyceryl behenate NF</td>
<td>Fine white powder (HLB = 2)</td>
<td>Human pharmaceutical products, Veterinary products, excluding food-producing animals</td>
<td>Oral</td>
<td>Lipid matrix for modified-release tablets, Lubricant for tablets, Suitable for use in melt-processing techniques, Lipid coat for protecting sensitive drugs, Lipid matrix to modify drug release, Consistency agent (thickener) for topical formulations, Suitable for different melt-processing techniques, Suitable for use in topical emulsions/microemulsions</td>
</tr>
<tr>
<td>Compritol 888 pellets</td>
<td>Glyceryl dibehenate EP, Glyceryl behenate NF</td>
<td>Semisolid pellets (HLB = 2)</td>
<td>Human pharmaceutical products, Veterinary products, excluding food-producing animals</td>
<td>Oral/Topical</td>
<td>Lipid matrix for modified-release tablets, Lubricant for in effervescent and fast-dissolving tablets, Suitable for use in melt-processing techniques</td>
</tr>
<tr>
<td>Compritol HD5 ATO</td>
<td>Behenoyl polyoxyl-8 glycerides NF</td>
<td>Fine white powder (HLB = 5)</td>
<td>Human pharmaceutical products, Veterinary products, excluding food-producing animals</td>
<td>Oral</td>
<td>Lipid matrix for modified-release tablets, Suitable for use in melt-processing techniques, Lipid coat for protecting sensitive drugs, Effective lubricant for tablets and capsules</td>
</tr>
<tr>
<td>Compritol E ATO</td>
<td>Glyceryl behenate E471/GRAS</td>
<td>Fine white powder (HLB = 2)</td>
<td>Nutraceutical</td>
<td>Oral</td>
<td>Lipid matrix for modified-release tablets, Lubricant for in effervescent and fast-dissolving tablets, Suitable for use in melt-processing techniques, Lipid coat for protecting sensitive drugs, Effective lubricant for tablets and capsules</td>
</tr>
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Figure 2. Schematic representations of the structure of monobehenate A. dibehenate B. and tribehenate C. of glycerol.

Surfactant molecules added during nanoparticle production process plays a role in prevention of Compritol 888 ATO polymorphic transition by interacting with the lipid and averting the reorientation of the less-ordered
configurations into more organized structural lattice resulting in a lower melting enthalpy [41,42].

Compritol 888 ATO polymorphism is an important factor that affects the dosage form stability, drug incorporation and release of the drug. Critical attention was paid by different research groups studying Compritol 888 ATO polymorphism as well as methods to control it when formulating lipid-based matrix particles. Passerini et al. [43] examined the characteristics of Compritol 888 ATO in theophylline-loaded microparticles. In their study, the DSC scan of Compritol 888 ATO exhibited an endothermic peak at 72.88°C confirming the presence of the stable \( \beta' \) form. The DSC of drug-loaded microparticles showed an endothermic peak at 72.98°C, due to the melting of Compritol 888 ATO, signifying that throughout the solidification process only the stable polymorph \( \beta' \) is formed. FTIR study of Compritol 888 ATO depicted a broad band between 3650 and 3100 cm\(^{-1}\) due to the \( \text{--OH} \) stretching, the C=O stretching at 1740 cm\(^{-1}\). Numerous vibrational bands appeared in FTIR spectra in the area between 700 and 1500 cm\(^{-1}\) and were related to the methylene groups. No shifts in the characteristic peaks of Compritol

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**Figure 3.** Differential scanning calorimetry thermogram A. X-ray powder diffraction diffractogram B. and Fourier transform infrared spectroscopy spectrum C. of Compritol® 888 ATO are shown. Reproduced with modifications from [21].

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**Figure 4.** Schematic representations of Compritol® ATO 888 polymorphic transition in SLNs. DSC: Differential scanning calorimetry; SLNs: Solid lipid nanoparticles; XRD: X-ray powder diffraction.
888 ATO were observed, which indicated the absence of interaction between theophylline and Compritol 888 ATO in the prepared microparticles. Studying the polymorphic behavior of Compritol 888 ATO alone and within the SLNs and NLCs, Souto et al. [32] found that the lattice arrangement of Compritol 888 ATO crystals generally comprises small amounts of the unstable α polymorphic form that disappears after thermal stress.

Fini et al. [34] had undergone a comparative study for the XRD diffractograms of different types of Compritols (Compritol 888 ATO, Compritol HD5 ATO and Compritol E ATO). Results showed great similarities between the diffractograms of the investigated Compritols as they all had a high-intensity peak at 21.2° 2θ and a smaller peak at 23.4° 2θ. Regarding their DSC thermograms, characteristic melting endotherms was evident at 76.40°C, 78.92°C and 60.72°C for Compritol 888 ATO, Compritol E ATO, and Compritol HD5 ATO, respectively. The three investigated Compritols showed comparable FTIR spectra that was related to the similarity in their qualitative composition.

Rahman et al. [21] studied the physicochemical properties of Compritol 888 ATO. The DSC thermogram showed a characteristic melting endotherm at 71.2°C indicating that Compritol 888 ATO is crystalline in nature. FTIR spectrum of Compritol 888 ATO showed absorption bands of C-H stretching at 2815 and 2849 cm⁻¹ and C=O stretching at 1738 cm⁻¹. XRD of Compritol 888 ATO showed peaks at 20.8 and 22.8°, which confirmed its crystallinity.

In their study for development of miconazole-loaded SLN using Compritol 888 ATO as a lipid matrix, Bhalekar et al. [35], also utilized DSC and FTIR for characterization of Compritol 888 ATO in the prepared SLNs. The DSC thermogram of Compritol 888 ATO revealed a maximum peak at 71.97°C where melting process took place. This peak was shifted to a slightly lower temperature side (70°C) in SLNs. This shift was attributed to the decrease in particle size associated with the increase in surface area that caused a decrease in melting enthalpy. In the IR spectrum of SLNs, miconazole peaks were buried in the peaks of Compritol 888 ATO, indicating drug entrapment in lipid matrix. Due to high-melting point of miconazole, it is suggested that it might have precipitated as core with Compritol 888 ATO coating it.

Owing to its physical and chemical complexity, Compritol 888 ATO generally shows a complex behavior and physical alterations on storage. Hamdani et al. [33] studied the physical and thermal properties of untreated, freshly solidified and aged samples of Compritol 888 ATO and Precirol® ATO 5. Both untreated and fresh solidified samples exhibited partially amorphous-layered structure that slowly crystallized on storage. The rate of crystallization was found to be more rapid in Precirol ATO 5 which contains shorter fatty acid chain than Compritol 888 ATO (palmito-stearate C₁₆-C₁₈ esters vs behenate C₂₃) and was highly dependent on the ageing conditions and storage temperature.

4. Effect of pharmaceutical processes on the physical and chemical properties of Compritol 888 ATO

Proper understanding of formulation and manufacturing variables that affect the excipient is necessary for rational design of lipid-based formulations. Excipient stability during formulation processes is a prerequisite for introducing a formulation into the pharmaceutical market. There are already extensively researched products that could not enter the market due to the lack of excipient stability (e.g., decomposition of lecithin in liposomes) [44]. The integrity of the excipients is affected by the processing variables (high temperature, pressure and other additives) they encounter during formulation production. Most of the published literature focuses on examining the drug state and stability within Compritol 888 ATO matrices [35,43]. Also, the physical changes in terms of lipid modification that occurs to Compritol 888 ATO during the formulation process are extensively investigated as they directly impact drug incorporation and release pattern [33,43].

In preparing SLNs, the stresses that might affect lipid stability are the initial melting procedure of the lipid to produce the hot pre-emulsion and the subsequent high temperature and high pressure during hot homogenization process. Partial formation of lower-energy lipid modifications and reduction in crystallinity take place due to the transformation of Compritol 888 ATO into lipid nanoparticles [45]. Also, the added surfactants during lipid nanoparticles preparation contributes to the lowering of the melting enthalpy of Compritol 888 ATO by distributing the melted lipid phase and distorting its crystallization [19,45]. It is postulated that the surfactant may immobilize lipid molecules by interfacial contact and, consequently, avoid reorientation of less-ordered configurations into more organized structural lattice [46].

It is important to understand the thermal behavior of Compritol 888 ATO when used for hot-melt coating process since it engages melting and exposure to high temperatures [3,13]. The thermal history, glycerides are exposed to, determines its crystal structure’s composition in terms of including hexagonal (α), orthorhombic (β‘) and/or triclinic (β), each with different polymorphic transition temperatures and melting points [13]. The polymorphic transitions affects drug release as better drug sustained release is related to the metastable β’ polymorph. Polymorphic transition from β’ form to β′ form often leads to drug expulsion by reducing amorphous regions in the carrier lattice. This transformation can be controlled using surfactant mixtures [13].

Published literature about Compritol 888 ATO chemical stability and integrity in pharmaceutical formulations is very limited. Radomska-Soukharev [47] investigated the chemical stability of Compritol 888 ATO in SLNs prepared by hot homogenization technique using a GC analysis in combination with a method for lipid extraction from aqueous SLNs dispersions. Results showed that the production process of
SLNs itself did not affect the chemical stability of Compritol 888 ATO.

The stability of Compritol 888 ATO-based matrix tablets was investigated by Patel et al. The lipid tablets were stored for 3 months at 40°C/75% relative humidity and then were reevaluated. Results indicated the absence of any major change in tablets properties and in vitro release profiles after the accelerated stability study [48]. On the other hand, Rao et al. examined the stability of directly compressed ketorolac tromethamine tablets exposed to sintering at 80°C for up to 3 h. Results showed that sintering caused retardation of drug release that was proportional to sintering time. Sintered tablets exhibited smoother surface compared to unsintered ones, which indicates that heat treatment caused melting and redistribution of wax. FTIR spectroscopy ruled out any chemical interaction between the drug and Compritol 888 ATO during sintering. The heat-treated tablets showed similar DSC thermogram and XRD diffractogram to that of their corresponding physical mixtures confirming the absence of any polymorphic changes as a result of sintering at high temperature [9].

5. Applications of Compritol 888 ATO in pharmaceutical drug delivery systems

5.1 Modified-release dosage forms

5.1.1 Lipid nanoparticles

Lipid nanoparticles have gained great interest during the past decade as they are more biocompatible and more stable compared to polymeric nanoparticles [18,49]. Also, they offer high drug entrapment along with the feasibility of delivering both lipophilic and hydrophilic drugs [50-52]. Compritol 888 ATO is considered one of the most applied and cited excipient in preparing SLNs and NLCs. Compritol 888 ATO-based nano-lipid carriers were successfully utilized for ocular, oral, pulmonary, topical, transdermal and rectal delivery routes. Authors have selected it because of its favorable characteristics exemplified by its nonpolarity and lower cytotoxicity than other lipids [16]. Moreover, it provides high drug entrapment efficiency percentage (EE%) due to the presence of large amount of mono-, di-, and tri-glycerides that helps in drug solubilization. Also, the less-defined mixture of acylglycerol provides additional space for entrapping drug molecules [53].

Abdelbary and Fahmy [54] utilized modified high-shear homogenization and ultrasound techniques to prepare SLNs that contained different concentrations of Compritol 888 ATO or Imwitor® 900K as the lipid component. Results showed that increasing the lipid concentration from 5 to 10% in the SLNs consequently resulted in a decrease in the amount of entrapped diazepam due to lipid phase crystallization that caused partial expulsion of the drug on the particle surface. Compared to Imwitor 900K, Compritol 888 ATO produced SLNs with larger particle size, higher drug entrapment and significantly more sustained diazepam release. Figure 5 illustrates the retardation of diazepam release from SLNs in comparison to drug solution.

Gokce et al. [55] formulated cyclosporine-loaded SLNs using Compritol 888 ATO for topical ophthalmic applications by the means of high-shear homogenization and ultrasound methods. The percentage of Compritol 888 ATO in the SLNs (ranged from 0.45 to 1%) showed a direct effect on particle size as increasing the percentage of lipid in SLN formulations caused an increase in the particle size. ex vivo experiments using excised pig cornea and confocal laser scanning microscopy analysis confirmed the penetration enhancement properties of Compritol 888 ATO-based SLNs.

Kuo and Chen [56] fabricated cationic SLNs to entrap saquinavir using a mixture of cationic stearylamine and dioctadecyl dimethyl ammonium bromide in the peripheral lipid phase along with nonionic Compritol 888 ATO and
cacao butter in the central lipid phase. Compritol 888 ATO was superior to cacao butter in terms of saquinavir efficient entrapment. Cationic SLNs containing lipid cores formed of a mixture of Compritol 888 ATO and cacao butter provided more spaces for saquinavir entrapment along with better-sustained drug release than those prepared using pure lipid.

NLCs composed of Compritol 888 ATO, Miglyol and sodium taurocholate, for increasing celecoxib pulmonary deposition, were formulated and characterized by Patolla et al. [57]. High-pressure homogenization technique was used for preparing the nanostructures. Results indicated that Compritol 888 ATO-based NLCs were deposited in the alveolar region of the mice lungs and were able to control the release of celecoxib. Also, they enhanced celecoxib lung residence time by delaying the systemic clearance of celecoxib.

For efficient treatment of fungal infections using terbinafine, SLNs for topical application were prepared by microemulsion technique where glyceryl monostearate, Compritol 888 ATO and cacao butter were employed as the lipid matrix. Compritol 888 ATO-based formulation showed lower terbinafine deposition within the skin layers compared to those prepared using Precirol ATO 5. This was attributed to the higher solubility of terbinafine in Compritol 888 ATO than that in Precirol ATO 5. Although, terbinafine has higher solubility in glycerol monostearate than Compritol 888 ATO, the concentration of terbinafine in the subcutaneous and dermis layers was low in glycerol monostearate-based formulations probably due to the larger particle sizes of glycerol monostearate-based SLNs that prevented efficacious penetration of the skin. The authors found out that the combination of glycerol monostearate and Compritol 888 ATO increases the ability of terbinafine to penetrate all skin layers [58].

Gonzalez-Mira et al. [59] developed flurbiprofen-loaded NLCs based on Compritol 888 ATO mixed with different amounts of Miglyol 812 and castor oil for treatment of different ocular inflammatory conditions. High-pressure homogenization technique was used for preparing the NLCs that showed nanoparticle size (<199 nm) and high EE% (<90%). Results showed that the NLCs depicted sustained release of flurbiprofen along with in vivo ocular tolerance. Improved drug permeation through the cornea from Compritol 888 ATO-based NLCs was revealed by ex vivo permeation analysis of flurbiprofen from isolated rabbit cornea.

Blasi et al. [18] optimized lipid nanoparticles intended for brain targeting. Results showed that Compritol 888 ATO, Softisan® 142 and cetyl palmitate wax could successfully produce nanoscale particles that were suitable for intravenous infusion using high-pressure homogenization technique. The morphology of the nanoparticles varied according to the type of lipid matrix employed, as Compritol 888 ATO and cetyl palmitate produced spherical nanoparticles, whereas Softisan 142 yielded wrinkled particles. Added to that, Softisan-based formulations is expected to behave as an emulsion in vivo as its melting temperature is <37°C, whereas the Compritol 888 ATO and cetyl palmitate-based NPs had melting temperature higher than that of the body, and thus would remain in a solidified form after injection.

Alex et al. [60] successfully encapsulated the poorly available lopinavir in Compritol 888 ATO-based SLNs to target intestinal lymphatic vessels in combined chemotherapy. SLNs were prepared using hot homogenization method followed by ultrasonication. The observed high-drug EE% (99%) in the SLNs was due to the lipophilic property of the drug. On the other hand, increasing Compritol 888 ATO concentration extended lopinavir release from SLNs due to the high solubility of lopinavir in Compritol 888 ATO and the uniform distribution of drug inside the SLN matrix. Compritol 888 ATO-based SLNs increased the cumulative percentage dose of lopinavir secreted in lymph and percentage bioavailability when compared with the pure drug dispersed in methylcellulose solution.

Rahman et al. [21] proposed different nondestructive methods to characterize risperidone SLNs prepared using Compritol 888 ATO and sodium lauryl sulfate as a surfactant. Near-infrared spectroscopy-chemical imaging revealed homogenous distribution of risperidone and Compritol 888 ATO within the SLNs. Also, there was no interaction between risperidone and Compritol 888 ATO as revealed by FTIR. The SLNs were spherical in shape with smooth surface. DSC and XRD showed that Compritol 888 ATO retained its crystalline nature within the investigated SLNs.

To overcome the poor oral bioavailability of montelukast sodium, Priyanka and Sathali [61] prepared montelukast sodium-loaded SLNs using stearic acid, glyceryl monostearate and Compritol 888 ATO as the lipid matrix and polyvinyl alcohol as the surfactant using hot homogenization followed by ultrasonication. Results revealed that, independent of the lipid type, increasing the lipid concentration simultaneously increased the particle size and EE%, while it decreased the drug release rate. Among the three lipids investigated, Compritol 888 ATO showed the most sustained drug release due to its longer carbon chain length than the other two lipids.

To prolong its drug release rate, Fang et al. [62] encapsulated tryptanthrin in different nanoparticles, namely SLNs, NLCs and lipid emulsions (LEs) in which lipid phase was either Compritol 888 ATO or Precirol ATO 5. The release rate of the nanoparticles decreased in the following order: NLCs > LEs > SLNs. Results proved that NLC preparation, formed by blending Compritol 888 ATO and squalene as the core materials, is a potential carrier with appropriate sustained release behavior and cytotoxicity effects that allowed tryptanthrin to be engulfed by breast cancer cells.

To enhance the bioavailability of several antiretroviral drugs, Kuo and Chung [63] fabricated SLNs with complex lipid core encompassing Compritol 888 ATO, tripalmitin and cacao butter for encapsulating stavudine, delavirdine and saquinavir. The lipids were stabilized by l-α-phosphatidylcholine, cholesteryl hemisuccinate and taurocholate. Spheroidal SLNs were formed with shallow surface pits that
resulted from the rapid cooling during the preparation process. Results showed that increasing the percentage of Compritol 888 ATO simultaneously increased the size of stavudine-entrapping SLNs and decreased the size of delavirdine- and saquinavir-entrapping SLNs.

In an attempt to improve topical delivery of ketoprofen, Giri et al. [64] developed ‘drug-in cyclodextrin- in NLCs’ to merge the solubilizing properties of cyclodextrins with the prolonged release and percutaneous absorption enhancer ability of NLCs that were prepared using a mixture of Compritol 888 ATO and Labrafac lipophile. The optimum (drug-in cyclodextrin)-loaded NLC system displayed superior in vitro drug permeation properties when compared to either drug-loaded NLC or drug suspension alone.

To enhance the oral bioavailability of simvastatin through minimizing its first-pass metabolism, Shah et al. [65] developed Compritol 888 ATO-based SLNs using solvent injection technique and 2³ full factorial experimental design. Results showed that increasing the amount of Compritol 888 ATO in the SLN formulations simultaneously caused an increase in particle size that was attributed to the tendency of lipid to coalesce at high concentration along with the fact that increasing lipid amount provides additional space for drug molecules to entrap. Also, the EE% was affected by the increase in Compritol 888 ATO amount because of the associated increase in the concentrations of mono-, di- and triglycerides that may act as solubilizers for highly lipophilic drug [53]. In vivo evaluation of simvastatin SLNs for its pharmacokinetic and biodistribution behaviors in mice demonstrated significant absorption improvement as the relative bioavailability of simvastatin from optimized SLNs was found to be 220%.

Compritol 888 ATO and propylene glycol were used by Bhalekar et al. [35] as lipid components to prepare topical miconazole nitrate-loaded SLNs using hot homogenization method. Tween 80 and glyceryl monostearate were used as the surfactants to stabilize SLN dispersions. All the prepared SLNs formulations showed high EE% (between 80 and 100%) and nano-range particle size (between 244 and 766 nm). The formulation containing 5% Compritol 888 ATO, 2.5% Tween 80, 1.5% glyceryl monostearate and 2% propylene glycol was selected for further investigations as it showed the smallest particle size and highest EE% as compared to the other prepared formulations. ex vivo penetration of miconazole nitrate from the Carbopol 940-based gel containing the selected SLN formulation using Franz diffusion cell into cadaver skins revealed significant increase in miconazole uptake in skin over the marketed gel.

In their study, González-Mira et al. [66] explored the feasibility of using NLCs composed of Compritol 888 ATO or stearic acid as solid lipids, and a blend of medium chain triglycerides and castor oil as liquid lipids, for skin delivery of flurbiprofen. According to the morphometrical properties and the EE%, two different NLC formulations, one based on Compritol 888 ATO and the other on stearic acid, were selected for ex vivo permeation study using human skin in comparison with conventional flurbiprofen solution. Results showed that the permeation parameters of flurbiprofen from investigated NLCs were higher than those from the drug solution. Flurbiprofen from Compritol 888 ATO-based NLC demonstrated the highest amount of drug permeation through skin which was related to the particle size and matrix crystallinity.

5.1.2 Microparticles/spheres

Rajkumar and Bhise [20] used Compritol 888 ATO as core forming agent in preparing lipid-based porous microspheres containing Eudragit as release retardant and hydroxypropyl methylcellulose (HPMC) to inhibit recrystallization and to sustain the release of carbamazepine. The drug release from microspheres was dependent on Eudragit concentration as well as Compritol 888 ATO and the increase in their concentration caused reduction of drug release from the microspheres.

Yehia et al. [67] developed an injectable depot liposphere delivery system using melt-dispersion technique for controlled delivery of donepezil. The effect of Compritol 888 ATO along with different lipids (cetyl alcohol and glyceryl tripalmitate) on different evaluation parameters was investigated using a 3² full factorial design. Results showed that high encapsulation was demonstrated for all the prepared liposphere batches; however, cetyl alcohol and glyceryl tripalmitate exhibited significantly higher mean percentage yield of lipospheres than Compritol 888 ATO. Significant decrease in the percentage of drug release was reported when Compritol 888 ATO ratio increased due to its high hydrophobic properties that hindered water influx that is followed by drug diffusion from the lipospheres.

Gan et al. [17] utilized Compritol 888 ATO combined with pH-sensitive polymer Eudragit S100 to prepare novel lipid-polymer composite microspheres that are capable of delivering and maintaining high level of 10-hydroxycamptothecin in the colon. The lipid-polymer microspheres were prepared via ultrasonic spray-freeze-drying technique. Results of the in vivo bioavailability study of lipid-polymer microspheres in comparison with conventional enteric microspheres revealed that the systemic absorption of 10-hydroxycamptothecin from the lipid-polymer microspheres was significantly less than that of enteric microspheres group. This indicated that more drugs are being delivered to the colon from the Compritol 888 ATO-polymer microspheres which improve the efficiency of treatment by diminishing the side effects of the drug.

Cavallari et al. [68] investigated the potential of using microspheres of Compritol 888 ATO with lidocaine embedded inside the mucoadhesive buccal patches to prolong and improve the buccal release of lidocaine. Lidocaine microspheres were prepared by spray-congealing process using a wide pneumatic nozzle, whereas the patches were formulated by solvent-casting method, using various bioadhesive and film-forming polymers. Results showed that the incorporation
of the drug within a lipophilic carrier, such as Compritol 888 ATO, prolongs drug release as it represents a second barrier to drug release, subsequent to that of the patch gel.

Sanna et al. [69] utilized Compritol 888 ATO to prepare SLMs and investigated their feasibility as a potential carrier for pulmonary administration. The SLMs were prepared by oil-in-water emulsification employing phase inversion technique. Results revealed that the particles were spherical with smooth surface. Also, sterilization did not substantially modify the morphology, the size, and the size distribution of microparticles. In vivo acute pulmonary toxicological assessment by analyzing bronchoalveolar lavage fluid after intratracheal instillation of SLMs dispersions in rats confirmed the short-term safety of the proposed SLMs.

Wolsk and Sznitowska [70] investigated the feasibility of utilizing different lipids (Precirol ATO 5, Compritol 888 ATO, Witepsol H15) with or without Miglyol 812 in preparing solid lipid microspheres for sustaining the release of cyclosporine A. The SLMs were produced using a hot-emulsification method followed by cooling for resolidification. Stable SLMs containing cyclosporine A were prepared using Compritol 888 ATO and Tween 80. Also, the drug did not precipitate in any of the Compritol 888 ATO-based formulations. On the contrary to that, precipitating drug crystals were present in Precirol ATO 5-based dispersions that were also unstable and formed semisolid gels on storage along with. All SLMs prepared using Compritol 888 ATO demonstrated an initial fast-release phase due to surface localized cyclosporine followed by a delayed-release phase due to the diffusion of the drug from the lipid matrix.

The release of diclofenac, sodium salt and pyrrolidine ethanol salt from solid dispersions prepared in the form of microspheres was investigated by Fini et al. [71]. Compritol 888 ATO and carnauba wax were investigated as lipid carriers to prepare microspheres via ultrasound-assisted atomization of the molten dispersions. Compared to Compritol 888 ATO microspheres, carnauba microspheres showed greater resistance to drug release due to its superior hydrophobic character.

5.1.3 Pellets
The possibility of utilizing Compritol 888 ATO and Precirol ATO 5 as lipophilic binders to prolong the release of phenylephrine hydrochloride from matrix pellets was evaluated by Hamdani et al. [14]. Results showed that phenylephrine hydrochloride release is significantly retarded with the increase in the amount of lipidic binder. Also, this study demonstrated that melt-pelletization technique could be applied to drugs presenting distinct physicochemical characteristics by using appropriate mixture of Compritol 888 ATO and Precirol ATO 5 from multiparticulate matrix systems.

Hamdani et al. [15] assessed the feasibility of utilizing a blend of Compritol 888 ATO and Precirol ATO 5 as lipid matrices and sodium bicarbonate as a gas-generating agent to prepare floating multiple-unit pellets by melt-pelletization process. Pellets exhibited excellent floating ability combined with sustained release property due to the lipophilic nature of Compritol 888 ATO and Precirol ATO 5.

Fini et al. [34] performed a comparative study regarding the efficiency of three different grades of Compritols (Compritol 888 ATO, HD5 ATO, E ATO) in controlling theophylline release from either solid dispersion or microspheres. Both melting and ultrasound-assisted atomization techniques were used for preparing solid dispersions of the same composition. The microspheres showed greater control on theophylline release when compared to the solid dispersions due to enhanced coating of theophylline particles. In the solid dispersions, the highest control of drug release was observed with Compritol 888 ATO in comparison to other grades. In the microspheres, the sequence of controlling theophylline release from the investigated Compritols was as follows: 888 ATO = HD5 ATO > E ATO. This sequence was in agreement with their HLB values.

Gavini et al. [72] investigated the suitability of Compritol 888 ATO and Precirol ATO 5 for preparing juniper oil-loaded SLMs for the topical treatment of acne vulgaris using oil-in-water emulsification method. Higher percentage yield of production and encapsulation efficiency were demonstrated by Compritol 888 ATO-based preparations compared to Precirol ATO 5. Likewise, Compritol 888 ATO-based SLM dispersions exhibited superior stability than Precirol ATO 5-based formulations that displayed increase in the mean dimensions of the microparticles.

5.1.4 Matrix tablets
Compritol 888 ATO has been successfully used by different research groups as a sustained-release matrix for tablets (Figure 6).

Aiming to reduce the frequency of administration of activatine and pseudoephedrine, Gu et al. [73] conducted a study for developing controlled-release matrix tablet of both drugs using five different excipients: Compritol 888 ATO, Eudragit RS, Methocel K100M, Polyox WSR301 and Precirol ATO 5 either alone or in combinations. In vitro release studies showed that using single polymer as a matrix could not sustain drug release sufficiently. However, the combination of lipophilic Compritol 888 ATO with hydrophilic Methocel K100M exhibited satisfactory controlled drug release for > 8 h for both drugs.

Li et al. [74] used Compritol 888 ATO for controlling the release of sodium ferulate from solid dispersions and physical mixtures prepared using either hot fusion or mechanical blending method. The prepared solid dispersions and physical mixtures were directly compressed into matrix tablets. Solid dispersion-based tablets were more effective in retarding drug release than the physical mixture-based tablets due to the efficient coating of drug particles by melted Compritol 888 ATO during the preparation process. In addition, the retardation of drug release from matrices was enhanced by increasing Compritol 888 ATO concentration. Scanning electron microscopy performed on the tablet surface and cross-section confirmed the multiplicity of porosity and the establishment of mini-channels that allowed diffusion of drug particles.
Ghimire et al. [75] developed chronopharmaceutical drug delivery in form of a press-coated tablets containing theophylline. Initially, a rapidly disintegrating drug core was prepared and was then press coated with Compritol 888 ATO and low-substituted hydroxypropylcellulose (L-HPC) barrier granules. Considerable delayed drug release from the press-coated tablet was achieved using appropriate weight ratio of Compritol 888 ATO to L-HPC in the outer coat.

The effect of combining lipophilic Compritol 888 ATO with hydrophilic cellulose polymers (combination of HPMC and Avicel) on the release of carbamazepine from granules and corresponding matrix tablet was studied by Barakat et al. [76]. Results showed that for compacted matrices, drug release exhibited more retardation by increasing Compritol 888 ATO:HPMC ratio. On the other hand, matrices with < 1 weight ratio of Compritol 888 ATO:HPMC showed significant increased erosion with increasing HPMC.

To avoid the systemic side effects caused by absorption of large amount of the drug from the upper gastrointestinal track on oral administration, Patel et al. [48] assessed the feasibility of combining Compritol 888 ATO, as a lipophilic retarding polymer, and pectin, as a microbially triggered polysaccharide, for developing controlled-release colon-targeted mesalamine matrix tablets. Results revealed that co-mixing of optimum amount of Compritol 888 ATO and a high amount of pectin favors the colon targeting and controlled release of mesalamine from the tablets.

Abd El-Halim et al. [77] developed a hydrophobic matrix tablet for prolonging the release of salbutamol using different waxy materials, including Precirol ATO 5, Compritol 888 ATO, beeswax, paraffin wax, carnauba wax and stearyl alcohol. Both direct compression and hot-fusion technique were used for the preparation of the tablets. Precirol ATO 5 exhibited the greatest retardation of salbutamol sulfate release on using the hot-fusion technique (31.3% at 6 h). On the contrary, Compritol 888 ATO significantly retarded the drug release compared to Precirol ATO 5 when the direct compression was used. This was attributed to the higher melting range of Compritol 888 ATO.

A study aiming at the development of an optimized zero-order release formulation containing venlafaxine hydrochloride based on three-layered tablet technology was performed by Basalious and Aboelwafa [78]. The layered tablet was formed by a wax-based middle matrix layer composed of a solid dispersion of venlafaxine hydrochloride/Compritol 888 ATO to which hydrophilic top and bottom barrier layers were applied. The release profile of the optimized layered tablet formulation was comparable to that of the target release model. In addition, in vivo pharmacokinetic study carried out in healthy human subjects demonstrated bioequivalence of the optimized three-layered tablet in comparison with the marketed extended-release capsule.

Kavitha et al. [79] used Compritol 888 ATO as a matrix former to sustain the release of water-soluble tramadol hydrochloride. Increasing Compritol 888 ATO concentration caused reduction in the drug release due to decreased permeation of dissolution medium into the tablets resulting from increased lipophilicity of the waxy substance. In addition, better retardation of drug release was reported when melt granulation was used for matrices preparation than direct compression. This

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**Figure 6. In vitro release profiles of lornoxicam from tablets containing different percentage of Compritol® ATO 888 performed in 0.1 N HCl of pH 1.2 for 2 h and in phosphate buffer of pH 6.8 for the subsequent 6 h at 37 ± 0.5°C (mean ± SD, n = 3).**

Reproduced after permission from [81].
finding was attributed to the more effective coating of drug particles by Compritol 888 ATO along with the superior integrity of the tablets prepared by melt granulation.

El Gamal et al. [80] investigated the feasibility of using a combination of HPMC 4000, Compritol 888 ATO and sodium bicarbonate as a gas-forming agent to prolong the gastric residence of acyclovir and thereby enhancing its bioavailability. The effects of HPMC 4000 and Compritol 888 ATO concentrations on the drug release were assessed. Results revealed that a promising gastroretentive controlled-release formulation of acyclovir can be obtained using high level of both polymers.

Compression-coated technology comprising an instantaneous release coat layer and a prolonged release tablet core was exploited by Hamza and Aburahma [81] to modify the release of lornoxicam. The coat layer contained freeze-dried lornoxicam/polyvinylpyrrolidone K-30 solid dispersion to enhance drug dissolution in acidic medium. On the other hand, the core tablet was composed of 3% of Compritol 888 ATO to sustain the drug release. The selected prepared compression-coated tablet formulation exhibited the desired release pattern characterized by initial burst release of lornoxicam in acidic conditions followed by its sustained release for 8 h.

The potentiality of Compritol 888 ATO for developing theophylline sustained-release lipophilic mini-tablets was assessed by Roberts et al. [82]. Different Compritol 888 ATO percentages (15–45%, w/w) were used to prepare 2, 3 and 4 mm mini-tablets that were compared to 12 mm matrix tablet containing 15% w/w Compritol 888 ATO. Drug release from mini-tablets was more rapid compared to 12 mm tablets due to the differences in physical dimensions that influence drug diffusion from the matrix. The rate of drug release from mini-tablets was decreased by increasing Compritol 888 ATO concentration and the tablets’ diameter. Thus, this study proved that changing the mini-tablet size or Compritol 888 ATO level could tailor drug release to produce pediatric formulation or multiparticulate dosage form with adequate sustained drug effect.

Ibrahim et al. [83] studied the capability of Compritol 888 ATO in retarding the release of chlorpheniramine maleate from HPMC-based matrix tablets. Direct compression technique was applied to prepare the tablets using different HPMC–Compritol 888 ATO blends. Results showed that the tablets’ hardness increased with increasing Compritol 888 ATO concentration. In vitro release studies revealed that matrix containing Compritol 888 ATO only released almost 100% of chlorpheniramine maleate after 8 h; however, matrix containing HPMC as a single matrix released < 75% over the same period. The prepared mixed matrices showed increase in drug release with relative increase in Compritol 888 ATO and concomitant decrease in HPMC concentrations. This finding was explained based on the disruptions in the gel structure of HPMC by the large hydrophobic molecules of Compritol 888 ATO that leads to reduced barrier strength than in matrix containing HPMC only.

Abd-Elbary et al. [7] performed a study aiming at the development a controlled-release etodolac lipid matrix tablets with reduced frequency of administration. The influence of different lipid types (stearic acid, cetyl alcohol, cetostearyl alcohol, Imwitor 900K, Precirol ATO 5 and Compritol ATO 888) on drug release has been studied. Results revealed an inverse correlation between the drug:lipid ratio and the drug release rate. Among the different lipids used, Precirol ATO 5- and Compritol 888 ATO-based formulae exhibited the highest retardation in the drug release rate.

A study by Obaidat and Obaidat [10] investigated the use of Compritol 888 ATO as a matrix former to prolong the release of tramadol hydrochloride, aiming to extend its therapeutic effect and minimize its side effects. The tablets were prepared either by direct compression of the drug with Compritol 888 ATO or compression of granules prepared by hot-fusion technique. Results revealed that Compritol 888 ATO can be efficiently used for controlling tramadol hydrochloride release, whereas, increasing its ratio causes further drug release retardation. The hot-fusion technique showed more effective drug release retardation compared with the direct compression owing to more efficient coating of drug particles by the hot melt.

Aiming to compare the effect of different preparation techniques on sustained theophylline and phenylpropanolamine hydrochloride release from matrix tablets, Zhang and Schwartz [84] utilized Compritol 888 ATO as the wax matrix former. Two techniques were investigated, namely melt granulation and dry blending either with or without heat treatment at 80°C for 30 min. Results revealed that heat treatment of the tablets above the melting point of Compritol 888 ATO caused retardation of release for both preparation techniques due to melting and redistribution of the wax, forming a matrix system with higher tortuosity after cooling.

Gohel and Nagori [8] conducted a study for the fabrication of captopril modified-release oral formulation utilizing Compritol 888 ATO and ethyl cellulose as rate-limiting polymers. Preliminary trials using various drugs to Compritol 888 ATO ratios showed more efficient drug release retardation when Compritol 888 ATO concentration is increased.

Şengel-Türk et al. [85], investigated the use of Compritol 888 ATO, Ludipress® and Cellactose® 80 for the development of once-daily tablet formulation containing microspheres of diltiazem hydrochloride. Diltiazem-loaded Eudragit® RS 100 microspheres were directly compressed into tablets using the previously mentioned excipients. Results revealed the suitability of Compritol 888 ATO for sustaining the drug release due to its hydrophobic nature. Also, Compritol 888 ATO showed good compression properties up to 40% wax level. However, at higher levels, the compression was not successful due to punch sticking and capping of tablets.

Patere et al. [6] investigated the feasibility of using Compritol 888 ATO as a release retardant for prolonging the release of metoprolol succinate. Different ratios of Compritol 888 ATO versus metoprolol succinate were exploited and the effect of the preparation methods on drug release was
studied. Drug:Compritol 888 ATO in 1:2 ratio successfully retarded the release of metoprolol succinate. Moreover, melt-granulation method was more effective in reducing drug release rate compared to both direct-compression and wet-granulation methods.

Most of the aforementioned papers have selected the optimized tablet formulation based on in vitro dissolution testing. However, the in vitro dissolution testing does not adequately mimic the physiological conditions. The absorption mechanism for lipid-based oral formulations is so complicated and there is a great chance for hydrolysis of the lipid excipients by the lipolytic enzymes present in the gastrointestinal tract [86,87]. Accordingly, lipolysis of Compritol 888 ATO should, therefore, be taken into account during in vitro drug release studies. This can be achieved using physiologically relevant in vitro digestion models to better predict the dynamic changes the lipid formulation would encounter in vivo [88,89].

5.1.5 Hot-melt extrudates
In hot-melt extrusion (HME) process, Compritol 888 ATO was utilized for preparing extrudates with immediate or sustained release.

In their study, Vithani et al. [90] developed sustained release diclofenac sodium solid lipid matrices comprising Compritol 888 ATO via cold melt extrusion and HME. A reported unique advantage of Compritol 888 ATO is its ability to be extruded in form of coherent matrix at temperatures below its melting temperature. In cold extrusion, diclofenac sodium and Compritol 888 ATO blends were processed up to 60°C, whereas during hot extrusion, temperatures were elevated to 75°C. Results revealed that the dissolution profiles of both cold and hot extrusions were similar. The tablets formed after compression of the extruded granules showed good friability. However, the poor tablets attributed to Compritol 888 ATO hydrophobicity was prevented by incorporation of fillers.

In another study, Chi et al. [91] used a combination of Compritol 888 ATO and ethyl cellulose to prepare sustained-release ambroxol hydrochloride matrix pellets by extrusion spherization at 40°C for 12 h followed by heat treatment at 80°C for 30 min. Results showed that drug release was lower after heat treatment at 80°C due to the melting and redistribution of Compritol 888 ATO. On the other hand, Michalk et al. [92] investigated the influence of varying solid lipid extrusion process parameters on the properties of milled enrofloxacin extrudates containing Compritol 888 ATO. Opposing to Chi et al. [91], results showed that employing a lower or higher temperature than the melting temperature of Compritol 888 ATO within the extrusion process did not have any impact on the drug-release profiles.

5.2 Tablets’ and capsules’ lubricant
A wide range of fatty acid esters have been applied as lubricants for tablet compression [93]. Among them, Compritol 888 ATO was first introduced on the pharmaceutical market as a solid-phase lubricant for tablet formulations [4,5]. As a lubricant, Compritol 888 ATO is more advantageous than magnesium stearate as it has less influence on tablet hardness, disintegration and dissolution even when used in a greater concentration than magnesium stearate [94].

Comparing the lubricating effectiveness of Compritol 888 ATO by physical blending or hot-melt coating onto Lactopress, Jannin et al. [4] found that a concentration of 0.5% Compritol 888 ATO used in hot-melt coating technique gave the same lubricant performance of 3% Compritol 888 ATO used in blending technique. This finding highlighted the efficiency of lubrication by hot-melt coating compared to that of blending technique. This efficiency was explained based on the imparting of a more uniform distribution of the lubricant on the lactose surface.

A study performed by N'Diaye et al. [5] revealed that Compritol HD5 ATO, a glyceryl and polyethylene glycol dibehenate, showed similar granular characteristics and lubrication capacity as Compritol 888 ATO.

6. Cosmeceutical applications of Compritol 888 ATO

Different studies showed that ultraviolet (UV) protection properties of sunscreen agents were enhanced when they were incorporated in solid lipid carriers [95-97]. This was accredited to the reflection and scattering of the UV radiation by the solid lipids [95-97]. Also, the solid lipid matrix usually exhibit sufficient entrapment capacity for lipophilic UV filter [97]. Further advantages include the good affinity of the lipid for the stratum corneum along with the high occlusive effect which improves the topical delivery of sunscreen agents [19,97]. The use of Compritol 888 ATO was not limited to preparing lipid-based carriers for pharmaceutical purposes alone, but it effectiveness in preparing lipid-based cosmeceuticals for dermal applications was also investigated.

Bose et al. [19] prepared solvent-free SLNs using a probe ultrasonication method for topical delivery to benefit from the antiradical activity of quercetin on the skin. Compritol 888 ATO-based SLNs were superior to those composed of Compritol 888 ATO mixture with Precirol ATO 5. In vitro permeation studies revealed higher amounts of quercetin accumulated within the skin when compared to the control formulation with micrometer drug particles. Such accumulation of quercetin in the skin is extremely necessary for delaying UV radiation-mediated cell damage that principally occurs in the epidermis.

To achieve enhanced sunscreen photostability, Tursilli et al. [95] developed SLMs loaded with sunscreen agent octyldimethylaminobenzoate using Compritol 888 ATO as a lipid and Poloxamer 188 as the emulsifier employing melt-dispersion technique. The produced microparticles exhibited satisfactory loading efficiency, morphological structure and particle size uniformity (1.67 – 15.81 µm). Encapsulating the sunscreen agent within Compritol 888 ATO lipid microparticles caused marked decrease in the drug photo-induced
decomposition. This finding was attributed to the ability of the lipid matrix of the particles to reflect and scatter the UV radiation [95-97].

7. Safety and regulatory status of Compritol 888 ATO

The applicability of any pharmaceutical excipient greatly relies on its regulatory and toxicological status. Compritol 888 ATO is registered in both EP and USP [27,28]. It is generally regarded as a relatively nonirritant and nontoxic material. It is reported that acute dose is lethal to half of the exposed animals: LD50 (mouse, oral): 5 g/kg. According to US FDA, Compritol 888 ATO is accepted for use as a food additive and is listed as GRAS [98]. As mentioned, Compritol 888 ATO is the ester of glycerin with behenic acid. The latter is a long-chain saturated fatty acid (C22) that is found in small quantities in normal dietary component like dairy fats, fish oil, peanut oil and canola oil. It is reported that behenic acid is not well absorbed because of its long chain length yet it is claimed to have a cholesterol-elevating effect [99].

According to the US Code of Federal Regulations, Compritol 888 ATO can be used in food with no limit other than current good manufacturing practice. Also, Compritol 888 ATO can be used as a formulation aid and an excipient in tablets at a level not to exceed good manufacturing practice [100]. The US Cosmetic Ingredients Review Expert Panel evaluated glyceryl behenate as safe cosmetic ingredient regarding use and concentration [101].

8. Internationally marketed products containing Compritol 888 ATO

Although Compritol 888 ATO is extensively utilized in different drug delivery systems in researches, it is included in a rather limited number of pharmaceutical market products. Table 2 collectively list the internationally marketed products manufactured by different pharmaceutical companies in which Compritol 888 ATO is present as an excipient. As

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Active pharmaceutical ingredient</th>
<th>Dosage forms</th>
<th>Manufacture</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zelnorm</td>
<td>Tegaserod maleate</td>
<td>Tablets</td>
<td>Novartis</td>
<td>Treatment of irritable bowel syndrome</td>
</tr>
<tr>
<td>Aplenzin</td>
<td>Bupropion hydrobromide</td>
<td>Tablets</td>
<td>Sanofi-Aventis US</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Effient</td>
<td>Prasugrel</td>
<td>Tablets</td>
<td>Eli Lilly and Co.</td>
<td>Reduce the risk of heart-related events</td>
</tr>
<tr>
<td>Glumetza</td>
<td>Metformin Hcl</td>
<td>Extended-release tablets</td>
<td>Depomed</td>
<td>Oral antihyperglycemic drug for management of type 2 diabetes</td>
</tr>
<tr>
<td>Horizant</td>
<td>Gabapentin enacarbil</td>
<td>Extended-release tablets</td>
<td>GlaxoSmithKline LLC</td>
<td>Treat moderate-to-severe restless legs syndrome</td>
</tr>
<tr>
<td>Intuniv</td>
<td>Guanfacine</td>
<td>Extended-release tablets</td>
<td>Shire US Manufacturing, Inc.</td>
<td>Treatment of attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td>Paxil-CR</td>
<td>Paroxetine hydrochloride</td>
<td>Extended-release tablets</td>
<td>GlaxoSmithKline LLC</td>
<td>Management of depression</td>
</tr>
<tr>
<td>Requip XL</td>
<td>Ropinirole</td>
<td>Extended-release tablets</td>
<td>GlaxoSmithKline LLC</td>
<td>Treatment of Parkinson’s disease</td>
</tr>
<tr>
<td>Toviaz</td>
<td>Fesoterodine fumarate</td>
<td>Extended-release tablets</td>
<td>Pfize, Inc.</td>
<td>Treatment of overactive bladder</td>
</tr>
<tr>
<td>Tracleer</td>
<td>Bosantan</td>
<td>Tablets</td>
<td>Actelion Pharms Ltd</td>
<td>Managing pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Wellbutrin XL</td>
<td>Bupropion hydrochloride</td>
<td>Extended-release tablets</td>
<td>GlaxoSmithKline</td>
<td>Antidepressant used for smoking cessation</td>
</tr>
<tr>
<td>Zmax</td>
<td>Azithromycin</td>
<td>Sustained-release granules for oral suspension</td>
<td>Pfizer, Inc.</td>
<td>Macrolide antibiotics for treatment of bacterial infections</td>
</tr>
<tr>
<td>Zyflo CR</td>
<td>Zileuton</td>
<td>Extended-release tablets</td>
<td>Cornerstone therapeutic, Inc.</td>
<td>Treatment of asthma</td>
</tr>
<tr>
<td>Cambia</td>
<td>Diclofenac potassium</td>
<td>Powder for oral solution</td>
<td>Nautilus Neurosciences, Inc.</td>
<td>Treatment of acute migraine attacks</td>
</tr>
<tr>
<td>Ibufprofen PM</td>
<td>diphenhydramine citrate, ibuprofen</td>
<td>Coated caplets</td>
<td>Dologencorp LLC</td>
<td>Relief of occasional sleeplessness</td>
</tr>
<tr>
<td>Freelex</td>
<td>Magnesium hydroxide saliie laxative</td>
<td>Caplets</td>
<td>Wyeth</td>
<td>Relief of occasional constipation</td>
</tr>
<tr>
<td>Motrin PM</td>
<td>Diphenhydramine citrate ibuprofen</td>
<td>Coated caplets</td>
<td>McNeil-PPC, Inc.</td>
<td>Relief of occasional sleeplessness</td>
</tr>
</tbody>
</table>
evident, Compritol 888 ATO is mainly incorporated in marketed oral formulation, mostly extended-release tablets, to benefit from its sustained-release properties. This is attributed to the popularity of the sustained-release matrix tablets due to the simplicity in their design and easiness and reproducibility of their manufacturing process.

9. Potential uses of Compritol 888 ATO in the pharmaceutical marketed products

Compritol 888 ATO is not yet present in any marketed nano-based pharmaceutical delivery system. This is basically due to the difficulties that impede the adoption of nanoparticulate formulations commercially owing to their complicated scaling up requirements and difficulties in their regulatory framework. There is still a large gap between the popularity of lipid-based nano-delivery systems in the research field and their presence in the pharmaceutical market. It is expected that the near future would open doors for further utilization of Compritol 888 ATO once the pharmaceutical companies become more engaged in novel nano-formulation technology.

10. Conclusion

Compritol 888 ATO is a multifunctional excipient that has wide range of applications in food, cosmetics and pharmaceutical industries. This article gives an extensive review of the thermal properties and use of Compritol 888 ATO as an excipient in pharmaceutical drug delivery for the formulation of controlled-release solid dosage forms, lipid-based colloidal system exemplified by SLNs, SLNs and NLCs, and also its use as a lubricating agent.

Although Compritol 888 ATO is a potential pharmaceutical ingredient, yet, the number of marketed formulation that contains it is limited. This number is expected to increase further as a direct result of the increase in researchers attention toward Compritol 888 ATO as an innovative excipient. Studies that facilitate better understanding of Compritol 888 ATO performance in vivo and the complex interaction between Compritol 888 ATO and physiological environment are encouraged. Also, additional investigations that tackle Compritol 888 ATO shelf-life stability and long-term safety are required to increase its applications in pharmaceutical formulations.

11. Expert opinion

Drug delivery using formulations based on lipid excipients is considered one of the promising strategies for designing pharmaceutical dosage forms that address different drug delivery challenges in order to improve therapeutic benefits. Different lipid classes are commonly used in traditional dosage forms basically to sustain drug release from tablets and capsules. Also, lipids are widely included in advanced nanoporpharmaceuticals due to their unique physicochemical properties. Regarding their safety, lipid excipients have an appropriate safety profile as they resemble the body components. In addition, they are biodegradable and have relatively low cost.

Glycerides represent a family of multifunctional lipid excipients that are widely used in pharmaceuticals and cosmetics. Among different glycerides available, Compritol 888 ATO, which is a mixture of behenic acid esters with glycerol, has gained particular interest. Compritol 888 ATO is used as a matrix-forming agent to modulate/prolong drug release in addition to its unique performance as a hot-melt coating agent for controlled-release purposes. Further, it is used as a taste-masking agent to improve drugs palatability. Recently, glyceryl behenate have been extensively researched in lipid-based colloidal drug delivery system such as SLMs, SLNs and NLCs for ocular, oral, pulmonary, topical, transdermal and rectal delivery routes. On industrial level, there are a number of marketed pharmaceutical products containing Compritol 888 ATO. These products utilize Compritol 888 ATO to advantage for its sustained release and lubricating abilities. A prerequisite for introducing a pharmaceutical formulation into the market is ensuring the excipient stability during formulation processes. Although some studies have investigated the physical modifications and polymorphic transformations that glyceryl behenate undergo when it is exposed to different processing variables during manufacturing, yet, there is a clear lack in sound researches regarding Compritol 888 ATO chemical integrity and long-term stability. Further, the in vivo performance of Compritol 888 ATO is complicated as it may be subjected to different lipolytic enzymes in the gastrointestinal tract, and a critical aspect for developing safe and effective delivery systems is establishing reliable in vitro–in vivo correlations. In view of that, a clear understanding of the lipolysis profile and in vivo performance of Compritol 888 ATO is essential to guide formulation design strategies. There is a need for in vitro digestion models that adequately mimic the physiological conditions to be able to predict the dynamic changes that Compritol 888 ATO would encounter in vivo. This would play a role in adequately modifying the formulation design in early stage of development and minimize the risk of in vivo therapeutic failure.

To summarize, Compritol 888 ATO is a promising multifunctional excipient. Nevertheless, its physical and chemical integrity during different processing conditions along with its in vivo performance needs to be addressed more efficiently before utilization in pharmaceutical formulations. Also, the research advances attempted so far in employing Compritol 888 ATO for formulating nanoporpharmaceuticals should be complimented with successful utilization on an industrial scale. The processing difficulties and scaling-up techniques that embed industrialization of nanoporpharmaceuticals need to be addressed and optimized. It is expected that the growing shift toward nano drug delivery platforms will open additional functional roles for Compritol 888 ATO in drug delivery systems.
Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents, received or pending, or royalties.

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**Confirmed the ability of Compritol 888 ATO lipid microparticles to increase sunscreen photostability.**


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