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COMPRITOL 888 ATO HYDROGEL: A PROMISING TOPICAL DRUG DELIVERY SYSTEM FOR MYELOMALACIA

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Abstract: This Compritol® 888 ATO, a versatile lipid ingredient extensively employed in pharmaceuticals and cosmeceuticals, holds considerable promise for topical drug delivery systems targeting conditions such as myelomalacia. This review investigates the manifold applications of Compritol 888 ATO, ranging from its role as a lubricant and coating agent in oral solid medications to its integration into lipid-based colloidal drug delivery platforms like solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC). Myelomalacia, a condition where the softening of the spine poses an increased risk to nerves, particularly from bulging discs and similar ailments, can occur across any segment of the spine, although it is most prevalent in the neck and lower back areas. Effective therapy necessitates the efficient penetration or permeation of active molecules through the skin. Nano-sized drug carrier systems offer several key advantages crucial for this purpose. They enhance drug penetration into the skin, thereby reducing undesirable side effects. Additionally, these systems enable site-specific targeting of molecules within the skin, enhance formulation stability, and facilitate controlled release of drugs. By leveraging these advantages, nano-sized drug carrier systems hold significant promise for advancing therapies aimed at managing conditions like myelomalacia. Despite the proven effectiveness of Compritol® 888 ATO in prolonging drug release and enhancing formulation stability, gaps persist in understanding its chemical composition, long-term viability, and interactions with gastrointestinal enzymes. Addressing these knowledge deficiencies is crucial for developing reliable and safe drug delivery systems utilizing Compritol 888 ATO, thus advancing therapeutic interventions for conditions like myelomalacia. Utilizing NSAIDs hydrogel with Compritol 888 ATO for myelomalacia management offers localized drug delivery, enhanced penetration, sustained release, reduced side effects, improved compliance, minimized interactions, and potential synergistic effects.

Keywords: Compritol 888 ATO, Lipid excipient, Drug delivery, Myelomalacia, Solid lipid nanoparticles, Nanostructured lipid carriers, Sustained release, Emulsification

1. INTRODUCTION-

Compritol 888 ATO, commonly employed as a lipid excipient in the cosmetic industry, acts as a surfactant, emulsifier, and viscosity modifier in emulsions or creams. Its chemical composition comprises a combination of various esters derived from behenic acid and glycerol. This review aims to delineate its current and potential applications across diverse domains of drug delivery. Various lipid classes find common application in traditional dosage forms, primarily to prolong drug release from tablets and capsules. Furthermore, lipids are extensively incorporated into advanced nanopharmaceuticals owing to their distinctive physicochemical properties. Additionally, they are biodegradable and relatively cost-effective.

Studies show Compritol 888 ATO's potential as a lubricant or coating in oral solid dosage forms and as a matrix-forming agent for drug release regulation. Its primary use is in lipidbased colloidal drug delivery systems like solid lipid microparticles, nanoparticles, and nanostructured lipid carriers. Despite satisfactory regulatory and safety profiles, Compritol 888 ATO's utilization in pharmaceutical products remains limited, primarily to its role in sustaining release in extended-release tablets Aburahma MH, Badr-Eldin SM et al. [1].
Myelomalacia, which literally means "softening of the spinal cord," is the standard neuropathological term describing the visible appearance of focal spinal cord necrosis. Fingeroth, J. M., & de Lahunta, A. [2]. It is characterized by the absence of continuous cysts within the spinal cord. Histologically, myelomalacia displays microcysts, reactive astrocytosis, and thickening of the pia arachnoid. In the appropriate clinical context, a noncystic, non-enhancing signal abnormality, which appears hypointense compared to normal cord [2].
Myelomalacia softens the spinal cord due to factors like ischemia, trauma, or compression, leading to neurological deficits. Pathologies in vertebrae, discs, and blood vessels can compress or injure the spinal cord, worsening myelomalacia. Muscles, ligaments, and nerve roots also play roles in exacerbating spinal cord damage. Understanding these factors is crucial for effective diagnosis and treatment, which may involve relieving compression, improving blood flow, and managing symptoms to prevent further neurological deterioration and promote recovery.
Compritol 888 ATO, a solid lipid derived from glycerol esters of behenic acid (C22), comprises glycerol tribehenate (28–32%), glycerol dibehenate (52–54%), and glycerol monobehenate (12–18%). The primary fatty acid is behenic acid (>85%), with additional fatty acids (C16–C20) present. With partial acylglycerols, Compritol 888 ATO exhibits an amphiphilic nature and an HLB of approximately 2 (Jenning et al., 2000). Furthermore, its peroxide value remains below 6 meq O2 kg^−1, indicating relatively high chemical stability, a crucial attribute given the formulation's low chemical stability.
Unlike complex hard fats, a bulk material with a sufficiently high melting point was selected. Similar to many hard fats, Compritol is a blend of acylglycerols, exhibiting surface-active properties. Its utilization facilitates the emulsification process by expediting the formation of a rapid surfactant film, potentially enhancing the physical stability of lipid nanoparticles, Souto EB et al. [3].

2. Deciphering Myelomalacia: Unveiling Causes, Etiology, and Therapeutic Strategies in Anatomy

Focal cord atrophy commonly accompanies this condition, often stemming from spinal cord injury (SCI) caused by various factors like cord compression, ischemia, and hemorrhage. It stands as the most prevalent observation among individuals with prior spinal cord injury, with a prevalence of 55% among SCI patients. Many patients with myelomalacia display either no clinical symptoms or only mild myelopathic symptoms and signs Zhou Y et al. [5].

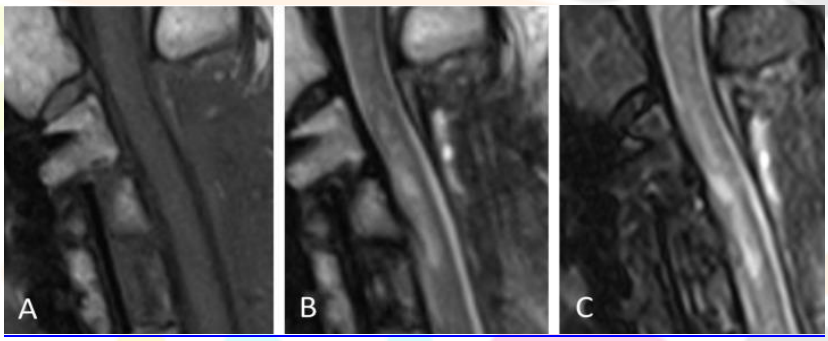

Fig. 1: Myelomalacia. (A) Sagittal T1-weighted image in a patient with cervical decompression and anterior/posterior spinal fusion. Based on a prior CT scan (not shown), the fusion is solid. (B) Sagittal T2 and (C) sagittal STIR images demonstrate noncystic T2 hyperintensity in the spinal cord between C3 and C5 with cord thinning, compatible with myelomalacia. There is no corresponding signal abnormality in the cord on the T1-weighted image, unlike in the previously seen case of posttraumatic cyst.

The overall consequence of such severe SCI may manifest as a focal zone of myelomalacia. In most instances, ascending/descending myelomalacia (ADM) is identified within 24–72 hours following an initial acute presentation of spinal cord injury Fingeroth, J. M., & de Lahunta, A. [2].

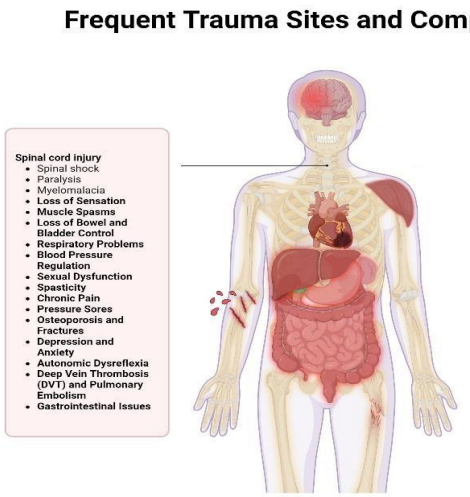

Fig. 2: Pathophysiology of Spinal Cord Injury: Understanding Myelomalacia and its Implications

Although the size of the spinal cord may seem normal, it frequently exhibits atrophy at the affected location due to myelomalacia. This condition typically manifests with spinal cord tethering, characterized by the loss of subarachnoid space predominantly in the dorsal compartment, alongside cord parenchymal expansion due to fibrous adhesions Zhou Y et al. [4]. The acute manifestation can endure from ten days to three months, usually initiating suddenly with flaccid paralysis and complete sensory deprivation. Occasionally, patients may also encounter pains and paresthesias. Sensory and motor deficits might progress over several days, though in certain instances, the degree of impairment remains static Jaffee, D., & Freeman, W. [5].

In 1926, Foix and Alajouanine introduced the concept of subacute necrotic myelitis through a report detailing two cases. These cases exhibited distinctive clinical characteristics:

- The onset of a progressive condition known as amyotrophic paraplegia begins with spasticity and later transitions to flaccidity. This progression typically moves from lower to upper segments, accompanied by muscle wasting in the lower segments as the spasticity extends to the upper segments.

- The initial presentation includes dissociated sensory impairment, which eventually progresses to complete sensory loss, typically occurring after the paralysis has advanced.

- Dissociation between the levels of albumin and cells in the spinal fluid

- A subacute progression leading to a fatal outcome within one to two years.

Symptoms commonly span across acute, subacute, and chronic forms. Intermittently, acute febrile episodes occur, yet fever commonly accompanies urinary tract or respiratory tract infections. Ordinarily, spinal fluid demonstrates elevated protein and cell levels, although sporadic dissociation and occurrences of normal fluid have been documented. Disease progression is relentless, devoid of remission periods, and inevitably culminates in fatality. Anatomically, spinal cord softening, accompanied by disruption of its typical structure, is the salient feature. Destruction typically involves both white and gray matter, although some studies have reported predominant involvement of white matter. Both myelin sheaths and axons are affected. Extensive demyelination in certain regions can lead to a spongy or lacunar appearance. Generally, the cellular response lacks inflammation. However, lymphocytic infiltrations were noted in some reviewed cases, with a few instances displaying polymorphonuclear involvement. Numerous compound granular corpuscles become evident. Intramedullary blood vessels typically exhibit hyperplasia, which sporadically leads to thrombosis, while hemorrhages are infrequently observed.

The subacute or chronic variant can persist for several months to over two years. In many instances, weakness in the lower limbs initially presents with heightened muscle tone and hyperactive or well-maintained reflexes, progressing to flaccidity, muscle wasting, and reflex loss. Sensory loss, coupled with motor impairment, often ascends, with initial sensory dissociation eventually culminating in complete loss. The most common spinal fluid alteration involves elevated protein levels, occasionally accompanied by pleocytosis or occurring in their absence. Pathological changes typically entail softening, predominantly observed in the cervical or thoracic regions. Degenerative processes affect both white and gray matter, although some researchers emphasize predominant gray matter involvement.

Fragmentation, vacuolation, or evident necrosis of the parenchyma, displaying a uniform appearance and resistance to staining, are commonly observed. Demyelination, characterized by a spongy appearance, may also occur. Vascular hypertrophy is frequently present, with involvement of large extramedullary vessels in some cases, but more pronounced affection of intramedullary vessels, often leading

to narrowing of the lumen. Necrosis or degenerative softening typically peaks near vessels demonstrating the most pronounced hyperplasia. Inflammation is typically absent, though occasionally lymphocytic infiltrations are reported. Compound granular corpuscles are prevalent in numerous areas, and reactive glial changes may also be present. The intention here is not to classify this overall picture as a distinct entity; instead, our aim is to highlight patterns and commonalities observed across a range of different cases. Some cases may potentially reflect the effects of a specific toxic or infectious agent.

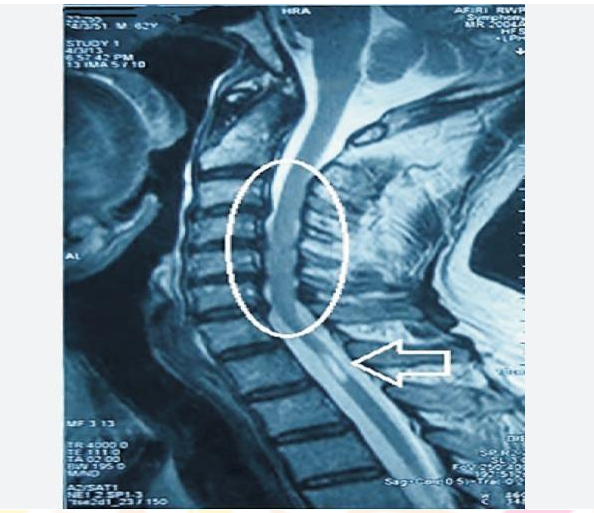

Fig. 3: Sagittal Film of MRI of th e Cervical Spine showing myelomalacia at DV1 level, and Intervertebral Disc protrusion at CV3/CV4, CV /CV and CV5/CV6 levels.

These cases have been classified under different labels, including acute or subacute necrotic myelitis, progressive necrosis of the spinal cord, myelomalacia, and myelodegeneration. Minimal consensus exists regarding the etiological factors or the nature of the pathological changes Jaffee, D., & Freeman, W. [5].

Ascending/descending myelomalacia (ADM) can occur not only as a focal myelomalacia but also as a progressive lesion that extends cranially and/or caudally from the initial site of intervertebral disc herniation (IVDH). Alternative terms used in literature to describe this phenomenon include the diffuse or progressive hemorrhagic myelomalacia, the ascending syndrome, hematomyelia, and progressive hemorrhagic necrosis of the spinal cord. ADM can impact larger segments, potentially involving the entire spinal cord. Unlike individuals with focal myelomalacia, those affected by ADM have no possibility of survival or enhancement in quality of life. Hence, it's vital for clinicians to grasp this occurrence and promptly identify it. This empowers them to support their patients and clients by minimizing unnecessary diagnostic procedures and recommending humane euthanasia when necessary. The consequences of acute spinal cord injury include both initial hemorrhage and a progressive pattern of ischemia and infarction, which seems to develop regardless of direct vessel rupture or ongoing compression.

The ascending type typically leads to a fatal outcome, while even the descending-only form can result in widespread lower motor neuron deficits affecting the pelvic limbs, bladder, and bowel, often requiring euthanasia as the most suitable course of action.

The main blood supply to the spinal cord originates from the ventral spinal artery, which receives blood from vessels entering the vertebral canal at each segment alongside the nerve roots. Significant diameter variation can occur in the thoracolumbar region. This artery, also known as the "artery of Adamkiewicz," is commonly referred to as the arteria radicularis magna. This artery plays a critical role by supplying multiple segments both cranially and caudally, which would otherwise have insufficient blood supply from the smaller radicular arteries at those levels. This pattern, known as a "desegmented pattern," is essential for adequate spinal cord perfusion. In humans, this condition is known as anterior spinal cord syndrome.

Three-dimensional biocompatible scaffolds, particularly hydrogels, are recommended for facilitating tissue bridging, effective exosome delivery, angiogenesis, and neurogenesis. Afsartala Z et al. [6]. Spinal cord injury (SCI) constitutes a considerable share of the worldwide injury burden, impacting around 27.04 million people globally, mainly resulting from traffic collisions and falls. These hydrogels promote axonal regeneration and aid in repairing spinal cord injuries (SCI). They have the capability to reversibly bind to different growth factors (GFs) like vascular endothelial GF (VEGF), fibroblast GF (FGF), plateletderived GF (PDGF), and neurotrophin-3 (NT-3), thus fostering SCI repair and improving motor function recovery. Moreover, hydrogels establish a supportive milieu for M2 macrophages to participate in injury regeneration. Recently, researchers have shifted their focus towards employing biomaterials, especially hydrogels, as carriers for encapsulating and delivering cells into damaged spinal cords.

The restricted ability of the central nervous system to regenerate is well acknowledged. In conditions such as spinal cord injury (SCI), a significant obstacle lies in the creation of an inhibitory environment after the injury, further complicated by the lack of a physical matrix for neurons and natural repair cells to attach to.

Biomaterials and tissue engineering play crucial roles in developing innovative SCI treatments. Hydrogels, especially, are adept at mimicking the soft tissue environment and CNS structure. Their adaptable chemistry allows for the integration of ECM molecules and adhesion proteins, facilitating efficient support and guidance for axonal regeneration. Furthermore, hybrid matrices combine the advantageous properties of different materials, enhancing SCI recovery efforts.

Hydrogels have distinctive physical traits allowing for their noninvasive injection into the body. Furthermore, they offer the advantage of local administration, efficiently filling injury-induced defects. As a result, they function as reservoirs for the controlled release of cells and molecules at the injury site. Serving as carriers for cells, hydrogels improve cell survival and integration. Structurally, they closely resemble macromolecular elements in the body and are deemed biocompatible, especially when sourced from natural polymers.

Special Features of Compritol 888 ATO:

Studies show Compritol 888 ATO's potential as a lubricant or coating in oral solid dosage forms and as a matrix-forming agent for drug release regulation. Its primary use is in lipidbased colloidal drug delivery systems like solid lipid microparticles, nanoparticles, and nanostructured lipid carriers. Despite satisfactory regulatory and safety profiles, Compritol 888 ATO's utilization in pharmaceutical products remains limited, primarily to its role in sustaining release in extended-release tablets Aburahma MH, Badr-Eldin SM et al. [1].

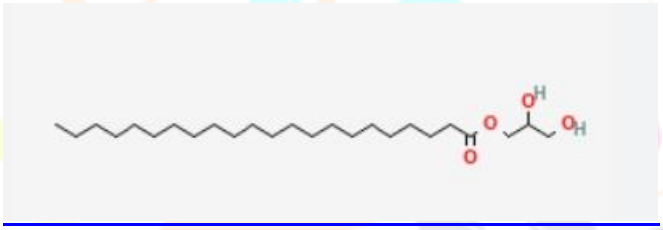

Fig. 4: Molecular structure of Glyceryl Behenate. Behenoylglycerol is a fatty acid ester formed by the formal joining of the hydroxyl group at position-1 of glycerol with the carboxyl group of docosanoic acid. Its functions include serving as a plant metabolite and an antineoplastic agent. It is classified as a 1-monoglyceride and a fatty acid ester, and it shares functional characteristics with glycerol and docosanoic acid.

Compritol 888 ATO, also known as glycerol behenate, serves extensively as a pharmaceutical excipient in solid dosage forms due to its lubricating properties. With its amphiphilic character and high melting point (approximately 70°C), it can be utilized for formulating aqueous colloidal dispersions. Research indicated that Compritol 888 ATO's crystalline structure contains minimal unstable polymorphic forms akin to triacylglycerols, which diminish under thermal stress. Numerous investigations have been undertaken to explore the thermal dynamics, crystalline characteristics, and potential interactions between Compritol 888 ATO and the drug, which could influence its release profile. Within these studies, the attributes of Compritol 888 ATO have predominantly been assessed through techniques such as differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), and Fourier transform infrared spectroscopy (FTIR).

Compritol 888 ATO: Characteristics and Properties for Hydrogel Preparation

Basic Knowledge:

The management of myelomalacia, characterized by focal spinal cord necrosis and neurological deficits, poses significant challenges due to its complex etiology and debilitating symptoms. One promising approach for alleviating the inflammation and pain associated with myelomalacia involves the utilization of NSAIDs (Non-Steroidal AntiInflammatory Drugs) formulated in a hydrogel matrix containing Compritol 888 ATO. This innovative therapeutic strategy offers several advantages, including targeted and sustained drug delivery directly to the affected spinal cord region, thereby providing localized relief while potentially minimizing systemic side effects commonly associated with oral NSAID administration. In this context, this introductory paragraph aims to delineate the various reasons why NSAIDs hydrogel formulated with Compritol 888 ATO represents a promising avenue for managing the symptoms of myelomalacia.

1. Localized drug delivery:

Hydrogels made of Compritol 888 ATO can provide a localized delivery of NSAIDs directly to the affected area of the spinal cord, offering targeted relief from inflammation and pain associated with myelomalacia

2. Enhanced drug penetration:
The formulation of NSAIDs in a hydrogel matrix containing Compritol 888 ATO can facilitate enhanced penetration of the drug through the skin and into the spinal cord tissue, allowing for deeper and more effective drug delivery.

3. Sustained release:
Compritol 888 ATO-based hydrogels can enable sustained release of NSAIDs over an extended period, ensuring a continuous therapeutic effect and minimizing the need for frequent dosing.

4. Reduced systemic side effects:
By delivering NSAIDs directly to the site of inflammation, the risk of systemic side effects associated with oral NSAID administration, such as gastrointestinal irritation and renal toxicity, may be reduced.

5. Improved patient compliance:
Topical application of NSAIDs via a hydrogel formulation may offer greater
convenience and improved patient compliance compared to oral medications, particularly for individuals with mobility issues or difficulty swallowing pills

6. Minimized drug interactions:
Localized delivery of NSAIDs through a hydrogel may minimize potential drug interactions with other medications taken orally, reducing the risk of adverse effects and drug-drug interactions.

7. Synergistic effects with compritol 888 ATO:
Compritol 888 ATO itself may possess properties that can enhance the therapeutic efficacy of NSAIDs, such as its ability to modulate drug release kinetics and improve drug solubility

Overall, utilizing NSAIDs hydrogel formulated with Compritol 888 ATO presents a promising approach for managing the symptoms of myelomalacia by providing targeted and sustained relief from inflammation and pain while potentially minimizing systemic side effects. However, further research and clinical trials are warranted to fully evaluate the efficacy and safety of this treatment approach.

Compritol, primarily made up of glyceryl dibehenate alongside varying quantities of glyceryl monobehenate and tribehenate, typically contains 15%–23% monoglycerides, 40%–60% diglycerides, and 21%–35% triglycerides, with a melting point between 69°C and 74°C. This solid lipid, glyceryl behenate, is commonly utilized in creating Solid Lipid Nanoparticles (SLNs). Despite having a small amount of the thermodynamically unstable αform, which disappears under thermal pressure, Compritol predominantly crystallizes in its β′-modification, which is highly sensitive to elevated temperatures. Research has shown its high loading capacity, offering an advantage in addressing re-crystallization challenges linked with other solid lipids. Additionally, Compritol exhibits amphiphilic properties and remarkable chemical stability, enabling it to effectively encapsulate both lipophilic and hydrophilic drugs.

As per Freitas and Müller [7], lipids can adopt various three-dimensional structures, including the unstable α, the metastable β', and the most stable β modification. An additional intermediate form, termed bi, exists between β' and β. The melting point of Compritol 888 ATO varies between 69 to 74°C, contingent upon the polymorphic form utilized, with the stable β polymorphic form exhibiting a higher melting point compared to the unstable α form or metastable β' forms. The specific polymorphic form of Compritol 888 ATO (α, β', or β) is determined by factors such as the rate of crystallization and temperature conditions during production and storage. In the process of nanoparticle formulation, the lipid initially crystallizes into the unstable and imperfect α polymorph, which subsequently transitions into the metastable β' form. However, during storage or destabilization of nanoparticles, the metastable β' form undergoes a transformation into the more stable (β'i or β) forms, characterized by a more perfected structure. This solid lipid (Compritol 888 ATO) transformation within nanoparticles could result in aggregation and an increase in the nanoparticle size, along with the expulsion of drug molecules that were incorporated within lipid imperfections.

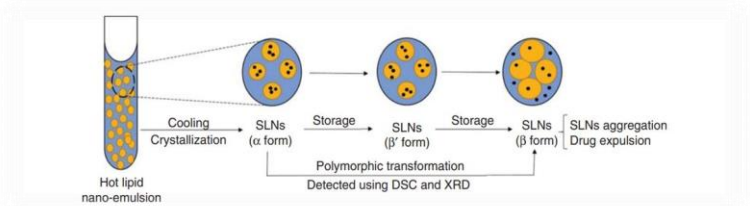

Fig. 5: Schematic representations of Compritol ATO 888 polymorphic transition in SLNs.
DSC: Differential scanning calorimetry; SLNs: Solid lipid nanoparticles; XRD: X-ray powder diffraction.

During the nanoparticle production process, the inclusion of surfactant molecules serves to impede the polymorphic transition of Compritol 888 ATO by engaging with the lipid, thereby preventing the reorientation of less-ordered configurations into a more organized structural lattice, ultimately leading to a reduction in melting enthalpy, Aburahma MH, Badr-Eldin SM et al. [1].

Passerini et al. [8] investigated the attributes of Compritol 888 ATO within microparticles loaded with theophylline. Their study revealed that the DSC analysis of Compritol 888 ATO displayed an endothermic peak at 72.88°C, affirming the existence of the stable β' form.

The drug-loaded microparticles exhibited a DSC peak at 72.98°C, attributed to the melting of Compritol 888 ATO, indicating that only the stable polymorph β' is formed throughout the solidification process. Additionally, the FTIR analysis of Compritol 888 ATO revealed a broad band between 3650 and 3100 cm-1 corresponding to --OH stretching, as well as a C-O stretching band at 1740 cm-1.

Rahman et al. investigated the physicochemical properties of Compritol 888 ATO. The DSC thermogram exhibited a characteristic melting endotherm at 71.2°C, indicating the crystalline nature of Compritol 888 ATO. The FTIR spectrum revealed absorption bands corresponding to C-H stretching at 2815 and 2849 cm-1, as well as C=O stretching at 1738 cm-1. XRD analysis demonstrated peaks at 20.8 and 22.8°, confirming the crystalline structure of Compritol 888 ATO.

Gel Characteristics:

The transformation of Compritol 888 ATO into lipid nanoparticles leads to the partial formation of lower-energy lipid modifications and a reduction in crystallinity, Negi, L. M., et al. [9]. Additionally, surfactants added during lipid nanoparticle preparation contribute to lowering the melting enthalpy of Compritol 888 ATO by dispersing the melted lipid phase and disrupting its crystallization, Negi, L. M., et al. [9]. It is hypothesized that surfactants
may immobilize lipid molecules through interfacial contact, thus preventing the reorientation of less-ordered configurations into a more organized structural lattice Rosenblatt, K. M., et al. [10]. Understanding the thermal behavior of Compritol 888 ATO is crucial, especially in applications like hot-melt coating processes, where it undergoes melting and exposure to high temperatures. Polymorphic transitions significantly impact drug release, with better sustained drug release associated with the metastable β' polymorph.

Other Features:

In a physical mix, the concentration of Compritol does not influence compressibility significantly. Similar compressibility results are achieved whether using lactose coated with 0.5% or 1% Compritol. However, higher compressibility is observed with concentrations of 2% and 3% Compritol. The cohesiveness of lactose varies depending on the process; hot melt coating leads to a reduction in tablet tensile strength. Regarding the transmission of forces during compression and axial ejection pressures, using Compritol via hot melt coating at a concentration of 0.5% provides lubricant performance equivalent to using 3% Compritol through blending.

Exploring the Therapeutic Horizon: Innovative Applications of Compritol 888 ATO in Advanced Pharmaceutical Delivery Systems

Modified-release dosage forms:

1. Lipid nanoparticles

They offer the advantage of high drug entrapment and are capable of delivering both lipophilic and hydrophilic drugs. Among lipid excipients, Compritol 888 ATO stands out as one of the most widely applied and cited in the preparation of solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Compritol 888 ATO-based nano-lipid carriers have demonstrated successful utilization across various delivery routes, including ocular, oral, pulmonary, topical, transdermal, and rectal administration. Authors often choose Compritol 888 ATO for its favorable characteristics, such as nonpolarity and lower cytotoxicity compared to other lipids Nastruzzi, C., (Ed.) [11]. Additionally, it boasts high drug entrapment efficiency percentage (EE%) owing to its abundance of mono-, di-, and triglycerides, facilitating drug solubilization.

Abdelbary and Fahmy Abdelbary, G., et al. [1]. employed modified high-shear homogenization and ultrasound techniques to formulate solid lipid nanoparticles (SLNs) containing different concentrations of either Compritol 888 ATO or Imwitor 900K as the lipid component. increasing the lipid concentration from 5 to 10% in the SLNs led to a reduction in the amount of entrapped diazepam [1].

Gokce et al. Gokce, E. H., et al. [30]. developed cyclosporine-loaded solid lipid nanoparticles (SLNs) for topical ophthalmic applications using Compritol 888 ATO through high-shear homogenization and ultrasound methods. The percentage of Compritol 888 ATO in the SLNs, ranging from 0.45 to 1%, had a direct impact on particle size. Specifically, an increase in the lipid percentage in SLN formulations resulted in larger particle sizes.

To enhance the treatment of fungal infections using terbinafine, solid lipid nanoparticles (SLNs) for topical application were prepared via the microemulsion technique. To effectively treat fungal infections using terbinafine, solid lipid nanoparticles (SLNs) for topical

application were prepared using the microemulsion technique. Irrespective of the lipid type, increasing the lipid concentration led to an increase in particle size and encapsulation efficiency (EE%), while it decreases the drug release rate. Among the three lipids studied, Compritol 888 ATO exhibited the most sustained drug release, attributed to its longer carbon chain length compared to the other lipids.

Cirri et al. Cirri, M., et al. [12] developed 'drug-in cyclodextrin-in NLCs' to enhance topical delivery of ketoprofen, merging cyclodextrins' solubilizing properties with NLCs' prolonged release and absorption enhancement abilities. Shah M et al. [13] aimed to improve the oral bioavailability of simvastatin by developing Compritol 888 ATO-based SLNs. Increasing
Compritol 888 ATO in SLN formulations led to larger particle sizes due to lipid

coalescence, but also increased drug entrapment efficiency by providing more space for drug molecules. In vivo studies showed a significant absorption improvement, with a relative bioavailability of 220% for simvastatin from optimized SLNs.

2. Microparticles/spheres

Rajkumar, M., & Bhise, S. B. [14] employed Compritol 888 ATO as a core-forming agent in lipid-based porous microspheres for carbamazepine delivery. Eudragit was used as a release retardant, and HPMC was added to inhibit recrystallization and sustain drug release. Increased concentrations of Eudragit and Compritol 888 ATO reduced drug release from the microspheres.

3. Pellets

Gavini, E., et al. [15] examined the suitability of Compritol 888 ATO and Precirol ATO 5 for preparing juniper oil-loaded SLMs for the topical treatment of acne vulgaris using the oilin-water emulsification method. Compritol 888 ATO-based preparations demonstrated higher percentage yield and encapsulation efficiency compared to Precirol ATO 5-based formulations. Additionally, Compritol 888 ATO-based SLM dispersions exhibited superior stability, with no increase in the mean dimensions of the microparticles.

4. Matrix tablets

Compritol 888 ATO has found successful application as a sustained-release matrix for tablets by various research groups. In a study by Gu, X., et al. [16], aimed at reducing the administration frequency of acrivastine and pseudoephedrine, controlled-release matrix tablets of both drugs were developed using five different excipients, including Compritol 888 ATO, Eudragit RS, Methocel K100M, Polyox WSR301, and Precirol ATO 5, either alone or in combinations. In vitro release studies revealed that using a single polymer as a matrix was insufficient to sustain drug release adequately. However, the combination of lipophilic Compritol 888 ATO with hydrophilic Methocel K100M demonstrated satisfactory controlled drug release for over 8 hours for both drugs.

5. Hot-melt extrudates

Vithani et al. [35] used Compritol 888 ATO for sustained-release diclofenac sodium matrices via cold and hot melt extrusion. Both methods produced similar dissolution profiles. Tablets from the extruded granules had good friability but faced challenges due to Compritol 888 ATO's hydrophobicity, mitigated by fillers.

6. Tablets' and capsules' lubricant

Compritol 888 ATO demonstrates superior lubrication properties compared to magnesium stearate, even at higher concentrations, without significantly affecting tablet hardness, disintegration, or dissolution. Jannin et al. [17] found that a 0.5% concentration of Compritol 888 ATO applied via hot-melt coating provided equivalent lubrication effectiveness to 3% via physical blending on Lactopress. This underscores the efficiency of hot-melt coating, attributed to its ability to uniformly distribute the lubricant on the lactose surface. N'Diaye et al. [17] demonstrated that Compritol HD5 ATO exhibits comparable granular characteristics and lubrication capacity to Compritol 888 ATO.

7. Cosmeceutical applications of Compritol 888 ATO

Studies demonstrate that incorporating sunscreen agents into solid lipid carriers enhances their ultraviolet (UV) protection properties. This enhancement is attributed to the reflection and scattering of UV radiation by the solid lipids, along with their high entrapment capacity for lipophilic UV filters.

Bose et al. [18] developed solvent-free solid lipid nanoparticles (SLNs) via probe ultrasonication to enhance the topical delivery of quercetin, leveraging its antiradical activity on the skin. SLNs based on Compritol 888 ATO outperformed those containing a mixture of Compritol 888 ATO and Precirol ATO 5.

Tursilli et al. [19] developed solid lipid microparticles (SLMs) loaded with the sunscreen agent octyl dimethylaminobenzoate using Compritol 888 ATO as the lipid and Poloxamer 188 as the emulsifier via melt-dispersion technique to improve sunscreen photostability.

7. Safety and regulatory status of Compritol 888 ATO

Compritol 888 ATO, a pharmaceutical excipient, is registered in both EP and USP, deemed relatively nonirritating and nontoxic. Its LD50 (mouse, oral) is reported as 5 g/kg, indicating moderate acute toxicity. It's recognized by the US FDA as GRAS, suitable for food additive use. Compritol 888 ATO comprises glycerin esterified with behenic acid, a long-chain saturated fatty acid (C22) found in dairy, fish, peanut, and canola oils.

8. Internationally marketed products containing Compritol 888 ATO

While extensively researched for various drug delivery systems, Compritol 888 ATO is sparsely utilized in pharmaceutical market products. Table 1 outlines internationally marketed products containing Compritol 888 ATO as an excipient. Primarily found in oral formulations, particularly extended-release tablets, its inclusion aims to leverage its sustained-release properties. This preference is due to the simplicity and reproducibility of manufacturing sustained-release matrix tablets.

Table 1. Internationally marketed products manufactured by different pharmaceutical companies that contain glyceryl behenate excipient.

Trade name	Active pharmaceutical ingredient	Dosage forms	re	Use
Zelnorm	Tegaserod maleate	Tablets	Novartis	Treatment of irritable bowel syndrome
Aplenzin	Bupropion hydrobromide	Tablets	Sanofi-Aventis US	Antidepressant
Effient	Prasugrel	Tablets	Eli Lilly and Co.	Reduce the risk of heart-related events
Glumetz a	Metformin Hcl	Extendedrelease tablets	Depomed	Oral antihyperglycem ic drug for management of type 2 diabetes
Horizant	Gabapentin enacarbil	Extendedrelease tablets	GlaxoSmithKline LLC	Treat moderateto-severe restless legs syndrome
Intuniv	Guanfacine	Extendedrelease tablets	Shire US Manufacturing, Inc.	Treatment of attention deficit hyperactivity disorder
Paxil-CR	Paroxetine hydrochloride	Extended release tablets	GlaxoSmithKline LLC	Management of depression
Requip XL	Ropinirole	Extendedrelease tablets	GlaxoSmithKline LLC	Treatment of Parkinson's disease

Toviaz	Fesoterodine fumarate	Extendedrelease tablets	Pfize, Inc.	Treatment of overactive bladder
Tracleer	Bosentan	Tablets	Actelion Pharms Ltd	Managing pulmonary arterial hypertension
Wellbutri n XL	Bupropion hydrochloride	Extendedrelease tablets	GlaxoSmithKline	Antidepressant used for smoking cessation
Zmax	Azithromycin	Sustained -release granules for oral	Pfizer, Inc.	Macrolide antibiotics for treatment of bacterial infections
Zyflo CR	Zileuton	Extendedrelease tablets	Cornerstone therapeutic, Inc.	Treatment of asthma
Cambia	Diclofenac potassium	Powder for oral solution	Nautilus Neurosciences, Inc.	Treatment of acute migraine attacks
Ibuprofen PM	diphenhydramine citrate, ibuprofen	Coated caplets	Dolgencorp LLC	Relief of occasional sleeplessness
Freelax	Magnesium hydroxide	Saline laxative Caplets	Wyeth	Relief of occasional constipation
Motrin PM	Diphenhydramine citrate Ibuprofen	Coated caplets	McNeil-PPC, Inc.	Relief of occasional sleeplessness

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

Compritol 888 ATO is absent from marketed nano-based pharmaceutical delivery systems primarily due to challenges in scaling up nanoparticulate formulations and navigating regulatory frameworks. Despite their popularity in research, lipid-based nano-delivery systems face hurdles in commercial adoption. Future utilization of Compritol 888 ATO is anticipated as pharmaceutical companies increasingly explore novel nano-formulation technology.

Conclusions and Perspectives

Compritol 888 ATO is a versatile excipient with applications across various industries, including food, cosmetics, and pharmaceuticals. It discusses its use in formulating controlled- release solid dosage forms and lipid-based colloidal systems such as SLMs, SLNs, and NLCs. Additionally, it highlights its utility as a lubricating agent in pharmaceutical formulations. Despite being a promising pharmaceutical ingredient, the number of marketed formulations containing Compritol 888 ATO remains limited.

Compritol 888 ATO, a glyceride excipient, is widely used in pharmaceuticals and cosmeceuticals for its versatility. It acts as a matrix former and hot-melt coating agent for controlled drug release, as well as a taste-masking agent. Recent research has focused on its role in lipid-based colloidal drug delivery systems across various administration routes. Marketed pharmaceutical products leverage its benefits for sustained release and lubrication. Maintaining excipient stability during formulation is crucial for market introduction. Topical drug targeting to specific epidermal sites presents challenges due to the drug's chemical properties and the formidable cutaneous barrier. A topical formulation's efficacy depends on the drug's release profile and pharmacokinetics during skin permeation. Examples include solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC).

Research has extensively explored how glyceryl behenate changes physically under various manufacturing conditions. However, there's a significant gap in understanding the chemical integrity and long-term stability of Compritol 888 ATO. Also, its performance in the body is complex due to interactions with different gastrointestinal enzymes. To develop safe and effective drug delivery systems, it's crucial to establish connections between laboratory experiments and real-life results. Understanding how Compritol 888 ATO reacts in the body and designing accurate laboratory models can help predict its behavior and guide formulation adjustments, reducing the risk of treatment failure.

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