ISSUE 1

NEW TRIO FORMULATION FOR ACNE MANAGEMENT

MOVE TOWARDS ENHANCED SYNERGISTIC THERAPEUTIC BENEFITS

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ACNE VULGARIS

Acne vulgaris is common and affects nearly all adolescents and adults at some time in their lives. Various clinical presentations of acne include seborrhoea, comedones, erythematous papules and pustules, less frequently nodules, deep pustules or pseudocysts, and ultimate scarring in few of them. When assessing the severity of the acne, one needs to consider the distribution, type and number of lesions (comedones, papules, pustules, nodules) and the presence or absence of scarring, which can be a major treatment determinant. Successful management of acne needs careful selection of anti-acne agents according to clinical presentation and individual patient needs. Reduction of comedones and *Propionibacterium acnes* is the main aim of treatment. Most effective acne regimens treat inflammatory and comedonal acne lesions with a combination of drugs having complementary mechanisms.[1,2]

MANAGEMENT OF ACNE

Topical therapies are recommended for first-line treatment of acne, namely retinoids, benzoyl peroxide (BPO) and fixed-dose combinations of retinoids with benzoyl peroxide or clindamycin. BPO has multiple mechanisms of action, and is not associated with any bacterial resistance; it is also

inexpensive. Topical retinoids are considered useful for comedonal lesions and long-term acne control; and they are the mainstay of therapy for acne. Topical antibiotics are a potential step-up therapy in papulopustular (inflammatory) acne. Convenience and treatment adherence may be enhanced with combination therapy or once-daily application instead of separate therapies or routines requiring multiple applications.[3]

INCREASING THERAPEUTIC EFFECTS OF ACTIVE AGENTS THROUGH INNOVATIVE DRUG DELIVERY FORMS

Drug delivery system with controlled release technology has emerged as a powerful tool for the treatment of various diseases. The therapeutic index of the active agent can be enhanced by increasing its stability, solubility and bioavailability, along with specific site delivery. Polymers have been playing an integral role as carrier in formulating an efficient drug delivery system by their stability, drug loading capacity and tunable properties.[4]

Chitosan is the natural cationic polymer which is derived from chitin. It has received growing attention mainly due to its biodegradable, biocompatible, non-toxic, mucoadhesive and ability to target specific delivery properties. This novel drug delivery system may display a strong ground for topical treatment of acne in order to enhance the therapeutic performance of the topical anti-acne agents, and may further improve patient's compliance and a concomitant reduction in the side effects.[4]

> "Chitosan demonstrates high biocompatibility, low toxicity, and ability to biodegrade, making it a promising candidate for drug delivery"

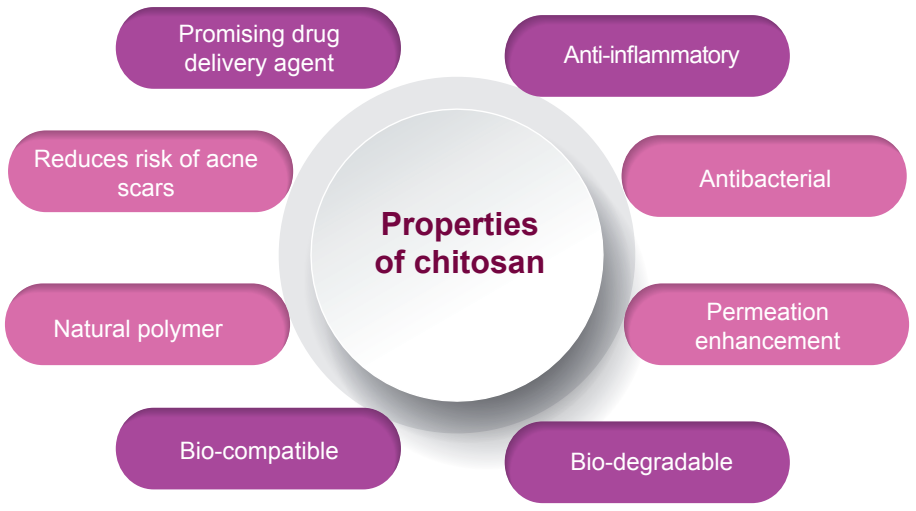
CHITOSAN- A PLEIOTROPIC MOLECULE FOR ENHANCED DELIVERY AND APPLICATION

Chitosan is derived from the partial deacetylation of chitin, a natural polysaccharide composed of β1 → 4 linked N-acetylglucosamine. It has a potential role as a vehicle for drug and DNA delivery via nanoparticles. It demonstrates high biocompatibility, low toxicity, and ability to biodegrade, making it a promising candidate for drug delivery.[4] Chitosan is considered the most important polysaccharide for various drug delivery purposes because of its cationic character and primary amino groups, which are responsible for its many properties such as mucoadhesion, controlled drug release, transfection, in situ gelation, and efflux pump inhibitory properties and permeation enhancement (Figure 1).[5]

ANTIMICROBIAL ACTIVITY OF CHITOSAN

The polycationic character of chitosan confers antimicrobial properties, which favors interaction with negatively-charged microbial cell walls and cytoplasmic membranes. These interactions result in decreased osmotic stability, membrane disruption, and eventual leakage of intracellular elements. In addition, chitosan may enter the nuclei

Figure 1: Various properties of chitosan



Adapted from: **1.** Ahmed S, Ikram S. Chitosan & its derivatives: A review in recent innovations. *IJPSR*. 2015;6(1):14-30. **2.** Elgadir MA, Uddin MS, Ferdosh S, Adam A, Chowdhury AJK, Sarker MZI. Impact of chitosan composites and chitosan nanoparticle composites on various drug delivery systems: A review. *J Food Drug Anal.* 2015;23(4):619-29.

of bacteria and fungi and inhibit mRNA and protein synthesis by binding to microbial DNA. When nano-scaled, chitosan has a higher surface to volume ratio, translating into higher surface charge density, increased affinity to bacteria, and greater antimicrobial activity.[6] Furthermore, in relation to acne, chitosan perturbs the surface integrity of *P. acnes*, which could account for its antimicrobial activity.[7]

> “Chitosan perturbs the surface integrity of *P. acnes*, which could account for its antimicrobial activity”

ANTI-INFLAMMATORY EFFECTS OF CHITOSAN

Chitosan possesses immunological functions which includes inhibition of pro-inflammatory cytokines.[6]

A study[6] showed that chitosan nanoparticles demonstrated reduction in IL-12 protein, a cytokine involved in inflammatory response in pathogenesis of acne, in a dose-dependent manner. Similarly, induction of IL-6 by *P. acnes* in keratinocytes was inhibited in the presence of chitosan nanoparticles almost completely, even at a low dose concentration. In addition, chitosan nanoparticles did not have a toxic effect on human monocytes.

Thus, it can be inferred that the chitosan nanoparticles can inhibit *P. acnes* induced cytokine production in human monocytes and keratinocyte and this is not simply due to the release of cytokines at cell death.[6]

CHITOSAN AS A DELIVERY VEHICLE FOR TOPICAL THERAPEUTICS

Nanoparticulate systems can be used as vehicles for the modified liberation of a wide variety of active substances. The active substance liberation system for topical application aims to (1) facilitate labile substance transport, increasing compound efficacy, and improving final product appearance; (2) maximize the length of time compounds remain in the skin, minimizing transdermal absorption; and (3) liberate products in specific areas.[8] Evidence suggests that chitosan as a vehicle for BPO may provide superior antimicrobial effect against *P. acnes*, each providing a different mechanism of action.[6]

> Chitosan encapsulation of the anti-acne agents could be one approach to improve the efficacy by reducing the side effects associated with topical application

CHITOSAN, ADAPALENE AND BENZOYL PEROXIDE: USE OF COMBINATION THERAPY IN ACNE MANAGEMENT

In clinical practice, use of combined therapy has shown to be more effective than monotherapies. Combination therapy of adapalene with BPO reduces the complexity of acne treatment.[9] Adapalene is anticomedogenic, reduces comedones and has anti-inflammatory properties, while BPO is a unique antimicrobial agent not shown to induce microbial resistance.[10] Mounting evidence suggests that the efficacy of this combination is higher than that of both molecules used separately. However, tolerability and safety were comparable to those of adapalene and BPO monotherapy.[9] However, skin irritation is the adverse effect of both adapalene and benzoyl peroxide.

Chitosan encapsulation of these anti-acne agents could be one approach to improve the efficacy by reducing the side effects associated with topical application. Owing to these properties of chitosan, a study[11] showed that chitosan microparticles prepared with incorporating all-trans retinoic acid (ATRA) enhances dermal localization and sustaining the release of ATRA into the skin. Thus, the microparticles developed in this work can be a good candidate to improve the topical therapy with retinoid.

The benefits of using chitosan encaspsulated anti-acne topical agents are as following:

THERAPEUTIC BACTERICIDAL ACTION

- Nanoparticles synthesized with chitosan demonstrate a direct antimicrobial activity in vitro against *P. acnes*, the bacterium linked to the pathogenesis of acne.[6]
- Chitosan has been shown to induce bacterial cell wall membrane disruption as demonstrated by electron microscopy, suggesting a mechanism for antimicrobial activity.[7]

- Chitosan binds to negatively charged bacterial surface of *P. acnes*, facilitating its antibacterial activity.[7]
- BPO is a bactericidal agent which kills *P. acnes* by releasing oxygen within the follicle.
- BPO, a commonly used anti-acne drug, effectively encapsulated in the chitosan-nanoparticles, demonstrates superior antimicrobial activity against *P. acnes* compared to BPO alone. In addition, this combination demonstrates less toxicity to eukaryotic cells.[6]
- Amine groups of chitosan, particular tertiary amines, are thought to catalyze the antimicrobial mechanism of benzoyl peroxide; together, BPO and chitosan has additive antimicrobial activity against *P. acnes.*[7]

REDUCES RISK OF ATROPHIC ACNE SCARS

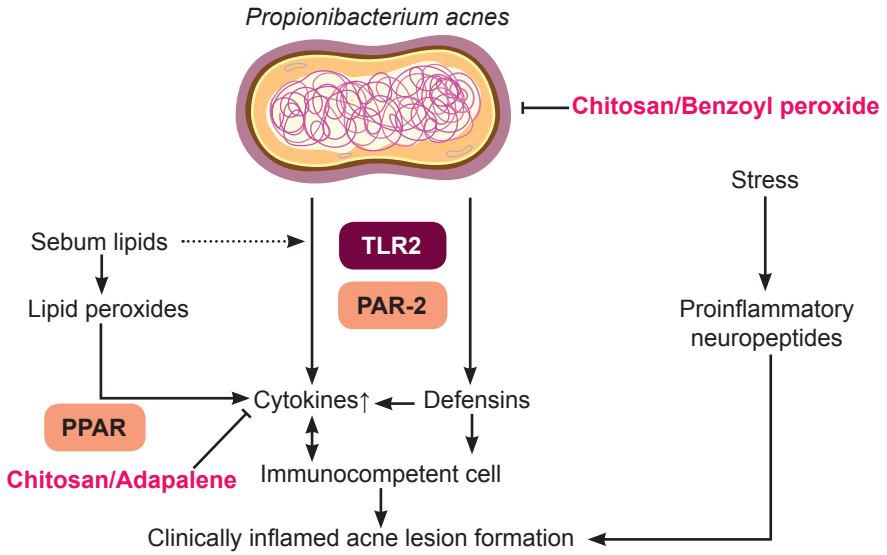
- Atrophic scars are frequent in patients with acne, especially if acne is not treated early and effectively.
- Chitosan nanoparticles activate keratinocyte and fibroblast proliferation, and regulate collagen synthesis and cytokine and macrophage secretion, thereby, reducing scars.[8]
- Adapalene has also been shown to act on secondary lesions including scarring and pigmentation.[12]
- A recent study[13] showed that adapalene and BPO prevented the formation of scars and reduced the number of existing scars after 24 weeks of treatment.
- The encapsulation of chitosan nanoparticles minimized the irritation and toxicity of retinol, and the retinol-loaded chitosan nanoparticles can be potentially used for acne and acne scar management.[14]

INFLAMMATORY CONTROL

- There is mounting evidence suggesting the role of inflammation in acne formation. Sebaceous lipids play a pro-inflammatory role; there is upregulation of pro-inflammatory mediators, early involvement of toll-like receptors (TLRs) and peroxisome proliferator-activated receptors (PPARs), and a potential neurogenic component driven by neuropeptide upregulation. All these factors lead to clinically inflamed acne lesion formation (Figure 2).[15]
- The chitosan nanoparticles exhibit anti-inflammatory properties as they inhibit *P. acnes* induced inflammatory cytokine IL-12 production in human monocytes and IL-6 production in human keratinocytes.[6]
- Topical retinoids also block several important inflammatory pathways that are activated in acne: Toll-like receptors, leukocyte migration, and the AP-1 pathway.[12]
- A recent study[9] evaluated the efficacy, tolerability and safety of a topical, fixed-dose combination of adapalene 0.1% and benzoyl peroxide 2.5% gel for the treatment

> Chitosan nanoparticles activate keratinocyte and fibroblast proliferation, and regulate collagen synthesis and cytokine and macrophage secretion, thereby, promoting wound healing and reducing scars

Figure 2: Pathogenic targets of chitosan, adapalene and benzoyl peroxide in acne



Abbreviations: TLR2 - Toll-like receptor 2; PAR-2 - Protease activated receptor 2; PPAR - Peroxisome proliferator-activated receptors

Adapted from: Tanghetti EA. The Role of Inflammation in the Pathology of Acne. *J Clin Aesthet Dermatol.* 2013;6(9):27-35.

> A combined treatment with chitosan plus benzoyl peroxide can destroy drug-resistant bacteria without any side effect of dermal irritation

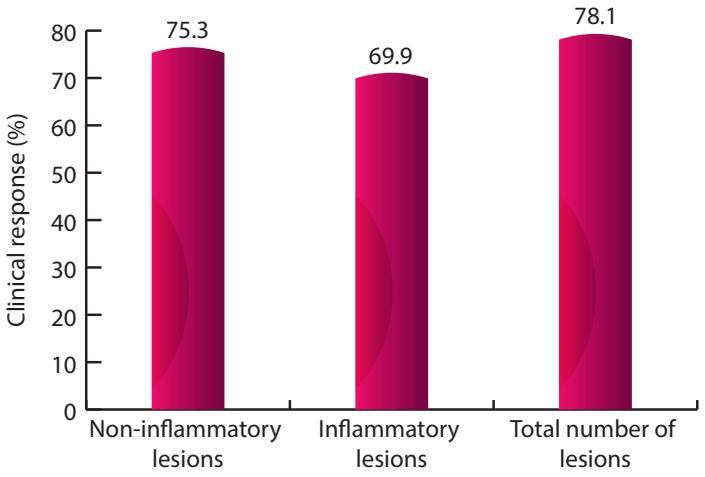
of acne vulgaris. Out of 79 recruited patients, 73 concluded the study. At the end of the study, 75.3% of patients had a reduction of >50% in non-inflammatory lesions, 69.9% in inflammatory lesions and 78.1% in total number of lesions (Figure 3). Overall, 71.2% patients showed improvement from good to excellent in acne control.

OVERCOMES EVEN RESISTANT PATHOGENS

- Chitosan nanoparticles allow the delivery of multidrug regimes to combat resistant microbes.[16]
- The advantage of using these molecules that target conserved membrane structures versus enzyme antagonists is the low possibility of microbe resistance, given the low probability of a single mutation leading to altered bacterial membrane structure.[6]
- Chitosan can be combined with BPO, which is capable of destroying drug-resistant bacteria.
- A combination of chitosan with BPO could avoid side effects associated with highly concentrated BPO.[7]

Together, these data suggest that chitosan can be utilized as an antimicrobial, anti-inflammatory and reducing acne scars. Thus, it could be inferred that, there may be

Figure 3: A good clinical response in acne management using combination of adapalene 0.1% and benzoyl peroxide 2.5% gel



Adapted from: Sittart JA de S, da Costa A, Mulinari-Brenner F, Follador I, Azulay-Abulafia L, de Castro LCM. Multicenter study for efficacy and safety evaluation of a fixed dose combination gel with adapalen 0.1% and benzoyl peroxide 2.5% (Epiduo® for the treatment of acne vulgaris in Brazilian population. *An Bras Dermatol.* 2015;90(6 Suppl 1):1-16.

potential utility of topical delivery of chitosan encapsulating commonly used drug such as retinoids (adapalene) and BPO for the management of acne.

CONCLUSION

Acne is common and burdensome, with potential for adverse psychosocial impact and physical sequelae. Topical therapy is the most well-known and mainstream approach to treat acne and there are a number of treatments options often in combination to have a synergistic effect and target simultaneous various pathogenic components. In order to enhance the therapeutic performance, chitosan encapsulated drug therapy may be useful for the treatment of dermatologic conditions with infectious and inflammatory components such as acne vulgaris.

> To enhance the therapeutic performance, chitosan encapsulated drug therapy may be useful for the treatment of dermatologic conditions with infectious and inflammatory components such as acne vulgaris

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