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Experimental Study For Preparation And Characterization Of A Mucoadhesive Gel As A Vehicle For Intranasal Delivery Of Topical Antibiotic Therapy

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ABSTRACT

Background: Mucoadhesive nasal gel provide a good platform of drug delivery to the nasal mucosa. We aimed to detect the histologic effect of mucoadhesive loaded antibiotic to the nasal mucosa of the rabbits by light microscope and scanning electron microscope to detect the ultra-structure changes.

Methods: A total of 36 adult male rabbits divided into 3 groups. Vehicle control group (A): Non-diseased, receives intranasal mucoadhesive gel. group (B): Non-diseased, receives intranasal Neomycin-loaded mucoadhesive gel. group (C): Non-diseased, receives intranasal ciprofloxacin loaded mucoadhesive gel. Part of the nasal mucosa was stained by Toluidine blue for scanning light microscopy. Other part of the Nasal mucosa was immediately fixed in 1.5% gluteraldehyde in phosphate buffered saline (pH 7.4) for 2 h at room temperature, and determination of morphological properties and microscopic ultra-structure was performed.

Results: There is statistically insignificant difference of histological changes in inflammatory cells of Ciprofloxacin group also surface mucosa showing deciliation of wide area of the epithelial cells and nasal mucosa showing necrobiosis of numerous epithelial cells. Congestion is significantly higher in Neomycin group (46.1%), than Ciprofloxacin group (7.7%).

Conclusion: Antibiotic loaded mucoadhesive gel showed minimal damage with preserved integrity of the nasal mucosa, so it could be considered safe vehicle for delivering topical antibiotics.

Keywords: mucoadhesive gel, nanoparticles, antibiotics, nasal mucosa, histopathology.

Introduction

The nose plays a crucial role in upper airway homeostasis with an abundance of air borne pathogens being drawn into the sinuses with each breath, resulting in a high probability of localized infection and chronic inflammation in various patient groups [1].

A mainstay of treatment of acute rhinosinusitis is nasal topical steroids, nasal saline wash in addition to systemic antibacterial agents. However, given certain age groups, compliance has been a huge obstacle. With recalcitrant cases, conflicting evidence has suggested a role for broader spectrum antibiotics and topical antibiotic delivery (2).

The obvious advantage of topical preparations of intravenous (IV) antibiotics is mucosal exposure to high therapeutic concentrations with limited systemic side effects, thereby effectively treating bacterial infections, such as Pseudomonas biofilms [3].

Nasal administration using mucoadhesive gels has been studied for different drugs: antibiotics such as roxithromycin and ciprofloxacin [4]. Gavini et al. (2011) observed improvements in the solubility of roxithromycin loaded into chitosan microspheres compared with the free drug when the intranasal drug absorption was assessed in vivo in rats [5].

Nanotherapeutics includes, but not limited to, solid-lipid nanoparticles, gold nanoparticles, silver nanoparticles, mesoporous silica nanoparticles, nanocrystals, magnetic nanoparticles, carbon nanotubes, nano sponges, albumin nanoparticles, fullerene nanoparticles and polymeric nanoparticles.The nanoparticles (NPs) as drug delivery systems may offer some advantages such as protection of drugs against degradation, targeting the drugs to specific sites of action, organ or tissues, and delivery of biological molecules such as proteins, peptides, and oligo nucleotides. Applications of drug nanoparticles include: both biodegradable nanoparticles for systemic drug delivery and non-biodegradable nanoparticles for drug dissolution modification have been studied [6, 7].

There is significant interest in recent years in developing biodegradable nanoparticles as a drug/gene delivery system [8, 9-12]. An ideal drug-delivery system possesses two elements: the ability to target and to control the drug release. Targeting will ensure high efficiency of the drug and reduce the side effects, especially when dealing with drugs that are presumed to kill cancer cells but can also kill healthy cells when delivered to them. Controlled drug release can decrease or even prevent its side effects.

The advantages of using nanoparticles for drug delivery applications result from their three main basic properties. First, nanoparticles, because of their small size, can penetrate

through smaller capillaries, which could allow efficient drug accumulation at the target sites [13, 14]. Second, the use of biodegradable materials for nanoparticle preparation can allow sustained drug release within the target site over a period of days or even weeks [15-17]. Third, the nanoparticle surface can be modified to alter biodistribution of drugs or can be conjugated to a ligand to achieve target-specific drug delivery [18]. The aim of study; to assess if the mucoadhesive gel can be considered as a suitable vehicle for drug delivery intranasally in an animal model using rabbits.

Materials & methods

Study design:

Experimental study to assess the effect of mucoadhesive loaded nanoparticles gel of ciprofloxacin and neomycin antibiotic on the nasal mucosa using Rabbits as an animal model.

Study setting:

It is a collaboration between different departments: Otolaryngology department faculty of medicine SCU, Faculty of Veterinary Medicine SCU, Faculty of Pharmacy SCU, Clinical pathology department faculty of veterinary medicine Assiut University.

Animal model:

A total of 36 adult male rabbits, weighing 1-1.5 kg each, was used in this study. Animals were brought from the Faculty of Veterinary Medicine, Suez Canal University. Animals was housed in polyethylene cages at room temperature (Under controlled environmental conditions) and kept with free access to standard rodent chow diet and tap water.

Inclusion Criteria

All animals passed these criteria included in the study: adult male rabbits, weighing 1-1.5 kg each, Normal not diseased animal, No signs of rhinosinusitis or nasal infections.

Exclusion Criteria

Diseased animal,

Signs of rhinosinusitis or nasal infections.

Drugs & Chemicals:

Neomycin, Ciprofloxacin, Other Chemicals & Kits.

Experimental groups:

Vehicle control group (A): Non-diseased, receives intranasal mucoadhesive gel. group (B): Non-diseased, receives intranasal Neomycin-loaded mucoadhesive gel. group (C): Non-diseased, receives intranasal ciprofloxacin loaded mucoadhesive gel.

Ethical consideration and Intervention:

Animals were having free access to both food and water and were kept under standard laboratory conditions. All experimental procedures were approved by institutional committee of animal care and use In Faculty of Medicine SCU. Animals were sacrificed using 30mg/kg Ketamine + 5 mg/kg Xylazine IM for a general anesthesia.

After animal sacrifice the nasal mucosa was harvested in all groups Using microsurgical scissors to bisect the nose sagittaly. Then by a scalpel the mucosa of the nose was harvested, Part of the nasal mucosa was stained by Toluidine blue for scanning light microscopy, other part of the Nasal mucosa was immediately fixed in 1.5% gluteraldehyde in phosphate buffered saline (pH 7.4) for 2 h at room temperature, The mucosa then washed in Phosphate buffered saline, transferred to 1% osmium solution. They then dried and gold-coated using sputter coat. And Determination of morphological properties and microscopic ultra-structure was performed, we assess morphological changes that occur in the epithelial cells (cilia, nuclei, cytoplasm).

Results

There is statistically insignificant difference in histological changes between Neomycin group and Control group regarding large vesicular nuclei, rich cytoplasm, ciliated, partially deciliated cells and Goblet cells (P.>0.05). There is statistically insignificant difference in histological changes between Ciprofloxacin group and Control group regarding ciliated, partially deciliated cells, Goblet cells, mucous gland and numerous blood vessels (P.>0.05). There is statistically insignificant difference in histological changes between Neomycin group and Ciprofloxacin group regarding ciliated, partially deciliated cells, Goblet cells and variable stain (P.>0.05). On the other hand, congestion is significantly higher in Neomycin group (46.1%), than Ciprofloxacin group (7.7%) (P.<0.05).

Discussion

In the present study we assessed the mucoadhesive gel as a suitable vehicle for drug delivery intranasally in an animal model using rabbits. Rabbits have been increasingly used in experimental sinusitis studies since the 1940s because of their large maxillary sinuses and the similarities between human and rabbit paranasal sinuses **[19].**

The nasal cavity has been emerged as an attractive route of multi-site targeting for the administration of a wide plethora of drugs, from small compounds to biological macromolecules, including peptides, proteins and vaccines. The nasal route is the natural choice for the topical administration of drugs intended for the treatment of local disorders affecting the nose and the par nasal sinuses, such as allergic or infectious rhinitis, sinusitis, rhinosinusitis and nasal epithelium lesions. Moreover, the nasal route also proves beneficial for delivering drugs to the brain, avoiding the blood brain barrier (BBB) that restricts the diffusional transport mechanisms of several therapeutic agents after oral or parenteral administration [20].

Several studies have confirmed the presence of bacterial biofilms in the sinonasal mucosa of patients with acute rhinosinusitis and some of the bacteria identified include S. pneumonia, H. influenza, and S. aureus [4, 21-23) .

Current American and European guidelines for the management acute and subacute rhinosinusitis recommend the use of topical corticosteroids and broad-spectrum or culture-directed oral antibiotics. Only patients who do not respond to these pharmacological therapies should be submitted to endoscopic sinus surgery **[2, 24-27]**.

Studies have shown that bacterial biofilms are as high as 1000 times less susceptible to antibiotics than their corresponding planktonic form, which explains the lack of effectiveness of oral antibiotics in this clinical condition [28- 30] Increasing the concentration of antibiotics, especially those with concentration-dependent antibacterial activity such as fluoroquinolones FQs, would overcome this drawback. However, high concentrations at the infected site are difficult to attain by traditional routes of administration (e.g., oral) without significant risks of systemic toxicity. Topical administration appears as an alternative approach to deliver high concentrations of antibiotics directly to the site of infection, using lower effective doses and thus minimizing systemic absorption and reducing the potential for systemic adverse effects [31, 24].

Presently, the information about topical intranasal IN administration of antibiotics in the management of acute rhinosinusitis is scarce and often inconclusive. Evidence for clear benefits of topical antibiotics in patients with acute rhinosinusitis is insufficient and therefore not recommended as first-line therapy; nonetheless, literature suggests that it is a reasonable treatment option for patients that are refractory to traditional oral antibiotics and surgical therapies. **[32, 23]**.

Ciprofloxacin is the most potent of the currently marketed FQs against P. aeruginosa **[23]**.

Nasal administration using mucoadhesive gels has been studied for different drugs: antibiotics such as roxithromycin and ciprofloxacin [4]. Gavini et al. (2011) observed improvements in the solubility of roxithromycin loaded into chitosan microspheres compared with the free drug when the intranasal drug absorption was assessed in vivo in rats [5]

An otic suspension was tested by Sahin-Yilmaz et al. (2008) to deliver the antibiotic into sinonasal mucosa and no significant improvement on the bacterial infection was found probably because of the rapid nasal clearance of the drug **[34]**.

In situ gels have recently attracted a lot of attention as favorable delivery systems used to increase drug residence time, due to their viscosity and ability to undergo transition into a gel at the infection site. Various biocompatible and biodegradable polymers have been used to formulate mucoadhesive systems. These include poly-vinyl alcohol **[36],** chitosan **[37]**, carbopol, alginate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, starch and gellan gum **[38]**.

In the current study we aimed to assess if the mucoadhesive gel consider a suitable vehicle for drug delivery intranasally in an animal model using rabbits and also if it is safe. we had three groups Group1 (13): non-diseased, received intranasal Neomycin-loaded mucoadhesive gel as a thin film of 0.5% gel twice daily for 10 days, Group2 (13): non-diseased, receives intranasal topical ciprofloxacin on mucoadhesive gel as 0.3% gel twice daily for 10 days. And Group 3 (10): Non-diseased, Control, receives no treatment.

Nasal administration using mucoadhesive gels has been studied for different drugs: antibiotics such as roxithromycin and ciprofloxacin [23], insulin [39], scopolamine hydrochloride [42], mometasone furoate [41], carvedilol [40], sumatriptan succinate [23], vaccines and proteins [34]. It was observed an improvements in the solubility of roxithromycin loaded into chitosan microspheres compared with the free drug when the intranasal drug absorption was assessed in vivo in rats[43].

The current study, does not show any significant alteration of the mucosa after both drugs application in compare to control group, as we found in neomycin group few changes as; only 7.7% of cases have dendritic nuclei, regarding organelles 15.4% of cases have rich organelles, 7.7% of cases have few organelles and 30.8% have variable organelles. Only 7.7% of cases are mostly deciliated, but different cells were found as; Goblet cell in 38.5%, apoptic cells in 30.8%, Congestion in 46.1%.

In our study regarding ciprofloxacin, 7.7% of cases are completely deciliated, 15.4% of cases have macrophages and proliferative cells, 23.1% have neutrophil and 46.1% of cases have necrotic cells that was considered as a bad effect of drug and need more studies.

We found also in the current study significant difference between neomycin and ciprofloxacin group regarding congestion with higher congestion in neomycin group. For both gels in our study, no severe damage was found on the integrity of nasal mucosa. The observed changes on nasal mucosa can be summarized as congestion of vessels in neomycin mainly, complete loss of some parts of the epithelium, and mild inflammation that occurs normally in respiratory epithelium as defense mechanism when particulate matter in inspired air is trapped in a thin layer of surface mucous. Necrotic cells were found in ciprofloxacin group.

In one study evaluate mucoadhesive nasal gels of other drugs venlafaxine hydrochloride. The histopathological study does not show any significant alteration of the mucosae after conduction of 12 h ex vivo drug permeation study. The photographs show no necrosis or removal of epithelial layer even after 12 h permeation study when compared with the normal mucosa. Also, there was no significant alteration of the nasal epithelium. Thus, the concentrations of polymers used in the study were safe for the nasal epithelium [44].

In a study; **Das et al.** evaluated different mucoadhesive polymeric hydrogels for nasal delivery of penciclovir . they illustrated chitosan gel with mild inflammation, loss of ciliary processes, and congestion of vessels, whereas more severe effects were observed with carbopol gel, which showed complete loss of epithelium layer . [45].

In **El-Hennawi et al**, study found that the topical antibiotic and steroid combination was potentially effective in treating acute bacterial rhinosinusitis as there was no significant difference in clinical improvement in group A, which received the topical antibiotic and steroid combination, and group B, which received the oral antibiotic alone **[46].**

Conclusion

The observed changes on nasal mucosa can be summarized as congestion of vessels and loss of the cilia of some epithelial cells in neomycin group and mild inflammatory reaction and Necrotic cells were found in ciprofloxacin group, however no changes were found in control group.

Antibiotic loaded mucoadhesive gel showed minimal damage with preserved integrity of the nasal mucosa, so it could be considered safe vehicle for delivering topical antibiotics.

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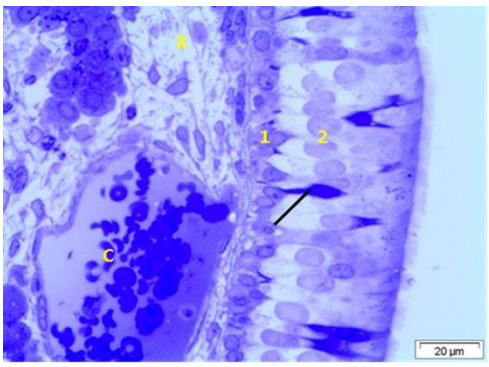
Table (1): Comparing Histological changes between Neomycin and Ciprofloxacin and control groups by Chi square test:

Histological changes	Neomycin group (n=13)		Ciprofloxacin group (n=13)		Control group (n=10)		p
	N	%	N	%	N	%	
Ciliated	4	30.8	3	23.1	5	50	0.1891
Partially deciliated	4	30.8	2	15.4	3	30	0.4106
Goblet cell	5	38.5	5	38.5	5	50	0.5896
Nuclei (large vesicular)	5	38.5	5	38.5	4	40	0.2411
Cytoplasm (rich organells)	2	15.4	2	15.4	4	40	0.1714
Mucous gland	4	30.8	4	30.8	1	10	0.2411
Blood vessels (numerous)	1	7.7	1	7.7	3	30	0.1714
Congestion	6	46.1	6	46.1	1	7.7	0.0304*
	P1=1.000, P2=0.0302* P3=0.0301*						
Stain variable (faint/deep)	3	23.1	3	23.1	2	15.4	0.6789

P, Non-significant P>0.05
P1, Neomycin group with Ciprofloxacin group
P2, Neomycin group with Control group
P3, Neomycin group with Control group



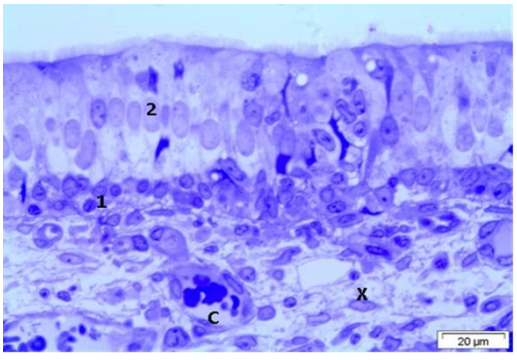
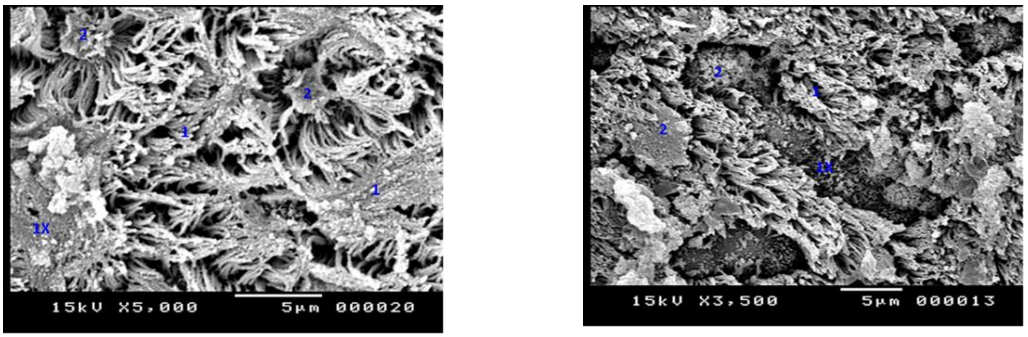


Figure (1): **Neomycin group:** Light micrograph of nasal mucosa showing the epithelial covering of pseudo stratified columnar ciliated type. The cells which on the basement membrane (1) having large round vesicular nucleus and small cytoplasm while those on the surface appeared long having large oval vesicular nucleus and large faintly stained and vacuolated cytoplasm (2) with presence of cilia on the luminal surface.



A B

Figure (2): **Neomycin group:** S.E. micrograph of the surface of the nasal mucosa showing the surface of the epithelial cells having clumped cilia with the mucus in some areas (1) and other area deciliated (1x). Also, presence of numerous Goblets cells having globular surface (2).

Ciprofloxacin group

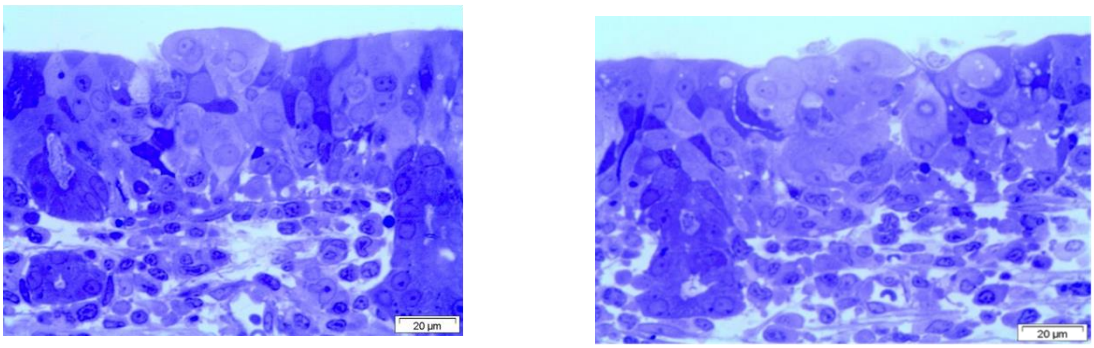
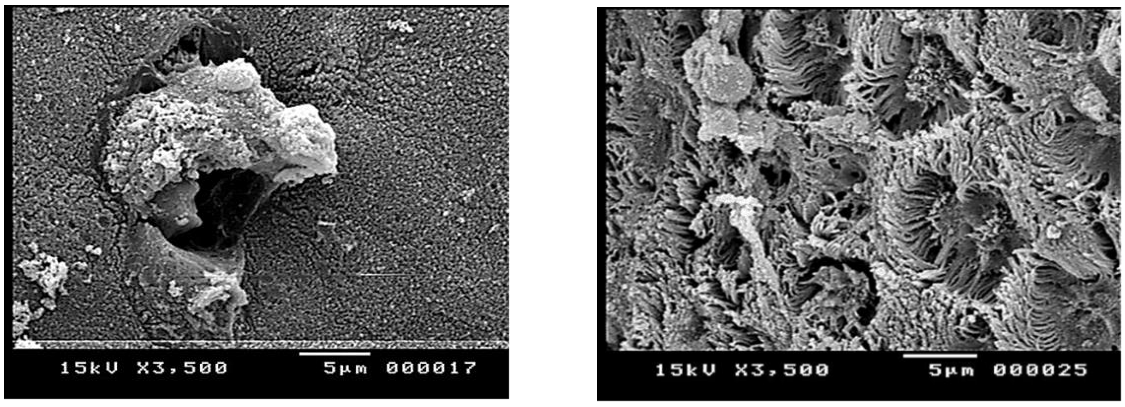


Figure (3): Ciprofloxacin group: Light micrograph of the nasal mucosa showing necrotic changes of the epithelial cells which appeared deeply stained (1) and proliferating cells (2) which appeared large faintly stained (2) with inflammatory cell infiltration in the epithelial and subepithelial layer (x). Notice, presence of mucus glands in the subepithelial layer and their secretion in the lumen (s).



A B

Figure (4): Ciprofloxacin group: A: S.E. micrograph of the nasal mucosa showing the orifice of secretory mucus gland plugged with mucus and the ciliated cells completely deciliated. B: S.E. micrograph of the surface mucosa showing the cilia of the cells clumbed with mucous, threads of mucus on the surface and presence of numerous Goblets cells.