"HERBAL NASAL ROLL-ON"

By

Baraiya Yagnik R.

17250429009

Dissertation Submitted to the

Gujarat Technological University, Ahmedabad, Gujarat

In partial fulfillment of the requirement for the degree of

BACHELOR OF PHARMACY

Under the guidance of

Miss. Mina Sinhar

Ass. Professor of Pharmaceutics M.Pharm.,

Department of

SHREE H.N.SHUKLA INSTITUTE OF PHARMACEUTICAL EDUCATION AND RESEARCH

B/H MARKETING YARD,

NR. LALPARI LAKE,

AMARGADH-BHICHARI, RAJKOT, GUJARAT, INDIA

GUJARAT TECHNOLOGICAL UNIVERSITY, AHMEDABAD, GUJARAT

DECLARATION BY THE CANDIDATE

I hereby declare that the matter embodied in the dissertation entitled "HERBAL, NASAL ROLL-ON" is a bonafide and genuine research work carried out by me under the guidance of Miss. Mina Sinhar Ass. Professor of Pharmaceutics M.Pharm. Department of Pharmaceutics, Shree H.N. Shukla Institute of Pharmaceutical Education and Research. The work embodied in this thesis is original and has not been submitted the basis for the award of the degree, diploma, associate ship (or) fellowship of any other university (or) institution.

Date:

Place: Rajkot **Baraiya Yagnik**

CERTIFICATE

This is to certify that research work embodied in this thesis entitled "HERBAL, NASAL ROLL-ON" was carried out by Mr. Baraiya Yagnik R. (Enrollment No.) 172504290009 at Shree H.N. Shukla Institute of Pharmaceutical Education and Research for partial fulfillment of Bachelor Pharmacy degree to be awarded by Gujarat technology University. This research work has been carried out under my supervision and is to the satisfaction of department. This student work has been accepted by for publication.

Date:

Place: Rajkot

Guide

Miss. Mina Sinhar

Dr. Dhara Chavda M. pharm, Ph.D.,

professor and HOD

Department of pharmaceutics

Still of Institute

THESIS APPROVAL

This is to certify that research work embodied in this entitled "HERBAL, NASAL ROLL-ON" was carried out by Baraiya Yagnik R. (Enrollment No.) 17250429009 at Shree H.N. Shukla Institute of Pharmaceutical Education and Research is approved for award of the degree of B.Pharm., by Gujarat Technological University.

Date:

Place: Rajkot

Examiner(s):

_____ _____ _____

( ) ( ) ( )

COPYRIGHT

DECLARATION BY THE CANDIDATE

I hereby declare that the Gujarat Technological University. Shall have the rights to preserve, use and disseminate this dissertation / thesis in print or electronic format for academic / research purpose.

Date:

Place: Rajkot **Baraiya Yagnik**

ACKNOWLEDGEMENT

I offer my adoration and gratitude to Almighty, for the continued blessings showered on me to successfully compete my dissertation. I consider this as an opportunity to express my gratitude to all the dignitaries who have been involved directly or indirectly with the successful of this dissertation.

On the occasion of presenting this thesis, it is my privilege to express my sincere thanks to my research guide Miss. Mina Sinhar, Assistant professor and Department of Pharmaceutical Shree H.N. Shukla Institute of Pharmaceutical Education and Research, who has provided excellent guidance, valuable advices, and shared intelligent thoughts, and ready to all time information to share, Which helped me to completed this work successfully.

I am thankful to Dr. Dhara Chavda , HOD, of Shree H.N. Shukla Institute of Pharmaceutical Education and Research, Rajkot for the support and encouragement.

I would like to express my sincere and heartfelt thank to Miss. Reena Korat, Assistant Professor, Department of pharmacy, Mr. Vijay Vekariya, Shree H.N. Shukla Institute of Pharmaceutical Education and Research, for timely help, encouragement, boosting my confidence in the progress of my academics.

I acknowledge the help and support of Mrs. Hetal, lab attenders, and all other non-teaching staffs of the college.

I wish to thank my project partner Mr. Preyash Virdiya, for timely help, support, and memorable company during this course.

Words cannot express my heartfelt gratitude and special thanks to All family members for their everlasting love prayers and encouragement in carrying out my work.

Last but not the least, special thanks to Management of Shree H.N. Shukla Institute of Pharmaceutical Education and Research, for providing such facilities for making success of the my work.

Sincerely thanks to all.

"Gratitude makes sense of our past, brings peace for today and creates a vision for tomorrow"

Date:

Place: Rajkot **Baraiya Yagnik**

ABSTRACT

Objective: To determine Anti nasal inhaler activity of an oily formulation containing camphor, menthol and thymol as ingredients in topical apply.

Methods: Acute toxicity studies were done as per OECD 423 guidelines. No signs of toxicity were observed up runny nose Based on was designed. Inhaler activity was performed in camphor, menthol and thymol oil spry forms.

Results: The formulation at a produced a dose dependent significant inhaler effect. Inhale as often as needed for adults. Inhaler relief nasal inhaler through a nostril while holding the nostril closed. Inhaler deeply for clear breathing.

Conclusion: In the above investigations OFCMT (oily formulation of camphor, menthol and thymol) has shown tremendous protection from inhaler & relief nasal inhaler in experimental above pharmacological effects may be due to the presence of monoterpenoids in the formulation.

Keywords: OFCMT, Anti-inhaler activity

CONTENTS

1. Introduction: -

Herbal medicine has been used since ancient era for many centuries. In today's life there is need for efficacious therapy for inhaler. In the search for new therapeutic options, novel bio-molecules of natural sources are to be investigated. Purpose of this study was to evaluate the inhaler effects of OFCMT (Oily formulation of camphor, menthol and thymol).

The common cold is an acute, self-limiting viral infection of the upper respiratory tract involving the nose, sinuses, pharynx and larynx. The virus is spread by hand contact with secretions from an infected person (direct or indirect) or aerosol of the secretions and virus.[1] The incubation period varies but is just under two days for rhinovirus.[2]Symptoms, which generally relate to the infected mucosa, typically peak at 1–3 days and last 7-10 days, although they occasionally persist for three weeks.[1,3–5] They include sore throat, rhinitis, rhinorrhea, cough and malaise.[1,4] The severity and type of symptoms will vary among individuals and with different infective agents. For example, fever is common in children but rare and mild in adults.1 The incidence of the common cold declines with age.[5–7] Children under two years have about six infections a year, adults two to three and older people about one per year.[5–9] Stress[10] and poor sleep[11] may increase the risk of the common cold among adults, whereas attendance at a daycare center[12] increases the risk among preschool children.

Rhinovirus accounts for 24%–52% of clinical cases or 52%–76% of infections with an identified pathogen.[6–8,13] No pathogen is identified in 31%–57% of upper respiratory tract infections,[8,13] likely because of a host of reasons, including poor collection technique, low pathogen count due to sampling late in the illness, or previously unidentified agents.1 Only about 5% of clinically diagnosed cases were found to have bacterial infection (with or without viral co-infection).[13]

Although self-limiting, the common cold is highly prevalent and may be debilitating. It causes declines in function and productivity at work [14,15] and may affect other activities such as driving.[16] Its impact on society and health care is large. Of individuals with an upper respiratory tract infection, 7%–17% of adults and 33% of children [17,18] visit a physician. Upper

respiratory tract infections result in an estimated increase of 12.5% in patient visits per month during cold and flu season.[19] In the United States, direct medical costs related to the common cold (physician visits, secondary infections and medications) were an estimated $17 billion a year in 1997.17 Indirect costs owing to missed work because of illness or caring for an ill child were an estimated $25 billion a year.[17]

We review the evidence underpinning preventive and treatment interventions for the common cold. We do not explore the proposed biologic mechanisms for the different products, because most are not substantiated and generally represent more supposition than science. The quality of the evidence was frequently poor, with a moderate to high risk of bias. Although preventive interventions have somewhat discrete outcomes (presence of an upper respiratory tract infection), interpretation of the evidence for treatment of the common cold is challenged by the complexity of outcome reporting.

One of the important and effective parts of herbal plants is essential oil and substances present in different parts of plants. Essential oils are components which are oil soluble that have effective smell and aroma and are separated by use of water and steam distillation and prepared by extraction with solvents and enzymatic hydrolysis. [20] The solvent system chosen was able to solubilize the drug at the desired concentration and an environment was provided where the drug has sufficient chemical stability Likewise, OFCMT of oily nature is the combination of the three active ingredients (camphor, menthol and thymol), which was emulsified using excipients. The excipients used to solubilize drugs in oral and injectable dosage forms include pH modifiers, organic solvents, surfactants, water-insoluble organic solvents, triglycerides and phospholipids. Each active individual ingredient of OFCMT has its own medicinal value. Camphor, a natural product derived from the wood of the tree *Cinnamomum camphora*, has a long history of use as antiseptic, analgesic, antipruritic, counter irritant and rubefacient [21]. Menthol is a natural compound of plant origin known to produce cool sensation. Menthol, the cooling natural product of peppermint, is widely used preparations for pain relief in sports injuries, arthritis, and other painful conditions. cymene, isomeric with carvacrol, found in oil of thyme, and extracted crystalline substance of a pleasant aromatic. [22]

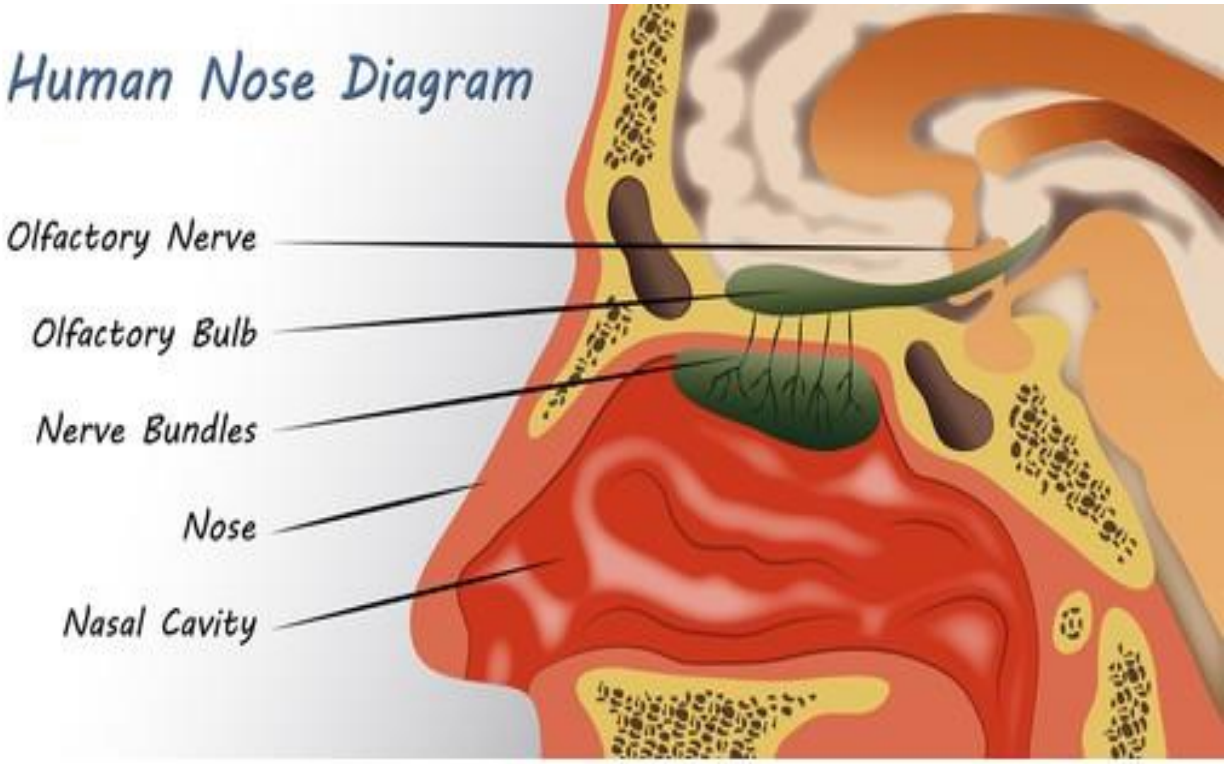
However, limited information is available on the pharmacological properties of the above individual ingredients and mixture of the above in the form of formulation. There is no scientific report on the Anti inhaler effects

of the above formulation to best of our knowledge. Based on the above claims, the present study is undertaken to evaluate anti nasal inhaler effect of the formulation.

- **Mechanism of Action**

Anatomy and physiology of nasal cavity

Researchers became interested in the nasal route for the systemic delivery of medication due to a high degree of vascularization and permeability of the nasal mucosa [30]. In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. However, it also affords an important protective activity once it filters, heat and humidity the inhaled air before reaching the lowest airways. Passage of the nasal cavity which runs from nasal vestibule to nasopharynx has a depth of approximately 12-14cm. The total surface area of the nasal cavity in human adult is about 150 cm2 and total volume is about 15 ml [31]. Each of two nasal cavities can be subdivided into different regions: nasal vestibule, inferior turbinate, middle turbinate, superior turbinate, olfactory region, frontal sinus, sphenoidal sinus, and cribriform plate of ethmoid bone. The nasal cavity also contains the nasal associated lymphoid tissue (NALT), which is mainly situated in the nasopharynx. Nasal cavity is lined with mucus layer and hairs which are involved in those functions are trapping inhaled particles and pathogens. Moreover, mucociliary clearance, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures [32]. The nasal cavity is covered with a mucous membrane which can be divided into two areas; nonolfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, whereas respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport [33] . Nasal cavity is divided by middle septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics [32]


Human Nose Diagram
Olfactory Nerve
Olfactory Bulb
Nerve Bundles
Nose
Nasal Cavity
shutterstock.com · 345234731

2. Objective of study: -

The present investigation is an effort to study the suitability of active individual ingredient of OFCMT has its own medicinal value. Camphor, a natural product derived from the wood of the tree *Cinnamomum camphora*, has a long history of use as antiseptic, analgesic, antipruritic, counter irritant and rubefacient [21]. Menthol is a natural compound of plant origin known to produce cool sensation. Menthol, the cooling natural product of peppermint, is widely used preparations for pain relief in sports injuries, arthritis, and other painful conditions. cymene, isomeric with carvacrol, found in oil of thyme, and extracted crystalline substance of a pleasant aromatic [22]

The purpose of this study is to investigate the efficiency of a camphor obtained from *Cinnamomum camphora*, this was used as a for model roll-on.

General objectives

This objective of the project is to evaluate the flow rate of mixer in rollon formulation.

Specific objectives

- To study the method of isolation & purification of mixer.
- To prepare roll-on their physical properties (bulk density, tapped density, granule flowability, spry flowability).
- To determine properties of the roll-on namely, density, porosity, flow properties and evaporation time.
- To prepare and flow roll-on of the formation and floe rate in the mixer of roll-on.

3. Review Literature: -

- In July and August 2012, a literature search was performed by one of us (G.M.A.) of PubMed, the Cochrane Database of Systematic Reviews, *ACP Journal Club* and *Evidence-Based Medicine*. Search terms included "common cold" and "upper respiratory tract infection." In PubMed, the search was restricted to randomized controlled trials (RCTs), reviews, systematic reviews and meta-analyses. Individual treatments were also searched (e.g., "vitamin C"). A similar search was performed in early 2012 by B.A. for a related project. We conducted a manual search of the bibliographies of included articles. Further details of the literature search are available from the authors upon request.
- We selected the highest level of evidence available for each intervention, focusing on systematic reviews (with or without a meta-analysis) and RCTs. We rated the quality of evidence for each intervention as high, moderate or low risk of bias. For systematic reviews, we considered the authors' assessment of methodologic quality (e.g., blinding) of included trials but also examined the quality of the systematic review itself (e.g., thoroughness of the literature search). For RCTs, we considered traditional validity criteria (e.g., allocation concealment) as well other limitations (e.g., funding or restricted populations). Lastly, we considered the overall volume (size and number of RCTs) and the consistency of the evidence. We used lower levels of evidence for general information such as epidemiology.

How can the common cold be distinguished from other conditions?

- The symptoms and signs of the common cold overlap with those of other conditions. Allergic rhinitis presents similarly, but it may have a seasonal component or clear allergic aggravation and is unlikely to have an accompanying sore throat. When sore throat is the primary complaint, streptococcal pharyngitis should be considered. Centor criteria are helpful in delineating the need for throat swabs and antibiotics.[23]

- Sinusitis (acute or subacute) is a clinical diagnosis without reliable clinical scoring criteria to help differentiate it from the common cold. Groups reviewing the evidence for the antibiotic treatment of sinusitis

recommend that symptoms be present for 7–10 days and not show signs of improvement before antibiotics are considered. [24,25]

- Ear pain and otitis media commonly accompany or follow the common cold, particularly in children. Findings on physical examination can be helpful in diagnosing otitis media (e.g., a bulging tympanic membrane has a likelihood ratio of 51),[26] and there are simple rules for prescribing antibiotics or using watchful waiting in children with possible otitis media.[27]

- People with influenza usually are sicker than those with the common cold, the former having fever, chills, headaches, myalgia and malaise. Influenza can be serious in older people and those who are immunocompromised. More serious illness should prompt consideration of meningococcal disease or septicemia.

- More details regarding primary conditions whose signs and symptoms overlap with those of the common cold are available in guidelines and review articles on allergic rhinitis, sore throat, sinusitis, otitis media[24] and influenza. In addition, the National Institute for Health and Care Excellence (NICE) has released a primary care guide for prescribing antibiotics for upper respiratory tract infections.[28]

Ingredient Profile

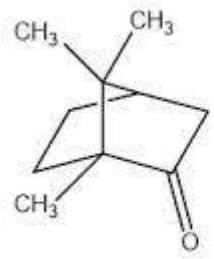
➢ Camphor [34]

Generic Name:- camphor

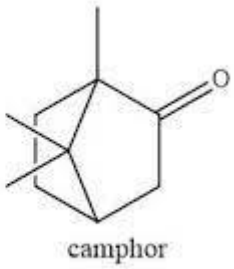
Chemical IUPAC Name:- 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one

➢ Physical Properties

Structure Formula



Camphor



camphor

Molecular Formula:-	$C_{10}H_{16}O$
Molecular Weight:-	152.237 $g.mol^{-1}$
State:-	Translucent crystals
Color:-	White,
Melting Point:-	175-177 ·C

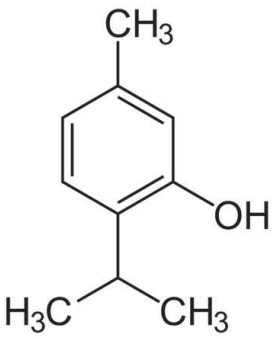
➢ Menthol [35]

Generic Name:- Menthol

Chemical IUPAC Name:- 5-Methyl-2-(propan-2-yl)phenol

➢ Physical Properties

Structure Formula



Molecular Formula:- $C_{10}H_{14}O$

Molecular Weight:- 150.221 $g.mol^{-1}$

State:- colorless crystalline solid

Color:- White,

Melting Point:- 49-51 °C

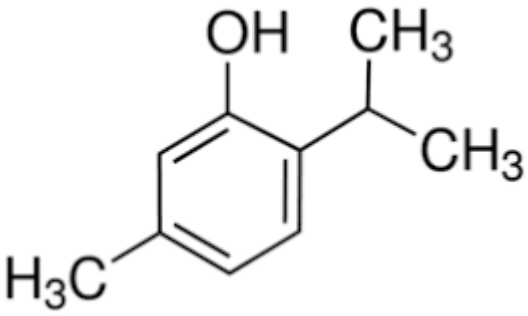
➢ Thymol [35]

Generic Name:- Thymol

Chemical IUPAC Name:- 5-Methyl-2-(propan-2-yl)cyclohexan-1-ol

➢ Physical Properties

Structure Formula



Molecular Formula:- $C_{10}H_{20}O$

Molecular Weight:- 156.269 $g.mol^{-1}$

State:- colorless crystalline solid

Color:- White,

Melting Point:- 36-38 ·C

Profile of an 'ideal' drug candidate for nasal delivery [29]

An ideal nasal drug candidate should possess the following attributes:

- Appropriate aqueous solubility to provide the desired dose in a 25–150 ml volume of formulation administration per nostril.
- Appropriate nasal absorption properties.
- No nasal irritation from the drug.
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.
- Low dose. Generally, below 25 mg per dose.
- No toxic nasal metabolites.
- No offensive odors/aroma associated with the drug.
- Suitable stability characteristics

4. Material and Method

Oily formulation containing Camphor, Menthol and Thymol in 1:1:1 w/w ratio

Material

Drug & Chemical

1. Camphor is to use in lab solution

2. Crystal Menthol is purchase by market in chemical shop

3. Thymol is purchase by market in chemical shop

Instrument

1. Electric weight balance

2. Digital PH meter

Procedure

- Clean to all glass ware property wash and dry it.
- Frist for Camphor (Kapoor) in weight to 3.3 gm in butter paper after add in porcelain dish.
- To add in equal amount of crystal Menthol and mixing in glass rod.
- After add in equal amount Thymol in mixing in room temperature.
- That is mixer in camphor is dissolute in room temperature.
- To all ingredient is equal amount in 1:1:1 w/w ratio.
- To mixer solid is soluble in all an ingredient.
- After fill in roll-on bottle and check to properly roll-on worked

5. Evulsion and parameter

1. Preformulation studies of MIG

Preformulation studies were performed on the MIG, which include extraction, purification and physiochemical characterization of the mixer in oil.

Physiochemical characterization of the mixer oil

1. Solubility Test

The separated oil mixer was evaluated for insoluble in water, in soluble in organic solvent acetone, chloroform and ethanol.

2. Flame Projection

The aerosol product is sprayed to an open flame for about extension in after flow rate is proper not worked in after irritation in the skin part in other flow rate increase

3. Leakage test

To fill in solution in 10 ml a roll-on botte in the room temperature to 24 hours and after check in quantity.

4. Roll-on quality test

The roll-on is best to apply in nasal close cloth in apply and not irritation in the skin part. To amount of drug is properly size to reduced

5. Result

Preformulatuion studies of nasal roll-on

Solubility

The solubility of pure drug in solvent was carried out and found to be soluble in acetone, and ethanol, insoluble in water.

Melting Point

Melting point of Nasal roll-on was found to be 108 ·C from this we concluded that the drug sample is pure

Flame Projection

The aerosol product is sprayed to an open flame for about extension in after flow rate is proper not worked in after irritation in the skin part in other flow rate increase

Leakage test

To fill in solution in 10 ml a roll-on bottle in the room temperature to 24 hours and after check in quantity.

No leakage in bottle to the mixer

Roll-on quality test

The roll-on is best to apply in nasal close cloth in apply and not irritation in the skin part. To amount of drug is properly size to reduced

Physiochemical Properties of Nasal roll-on	
Parameter	Result
Solubility	soluble in acetone, and ethanol, insoluble in water.
Melting Point	108 ·C
State	Liquid
Color	Pale yellow

6. Conclusion

Nasal drug delivery is a novel platform and it is a promising alternative to injectable route of administration. There is possibility in the near future that more drugs will come in the market in the form of nasal formulation intended for systemic treatment. Development of a drug with a drug delivery system is influenced by several factors. For the treatment of long illnesses such as diabetic, osteoporosis, fertility treatment novel nasal products are also expected to be marketed. Bioavailability of nasal drug products is one of the major challenges in the nasal product development. In contrast, a huge amount of money is investigated by pharmaceutical companies in the development of nasal products, because of growing demand of nasal drug products in global pharmaceutical market. So, for the avoidance of side effect and improve effectiveness of nasal products we should pay attention to basic research in nasal drug delivery.

7. References

1.Heikkinen T, Järvinen A. The common cold. Lancet 2003;361:51–9 [PMC free article] [PubMed] [Google Scholar]

2. Lessler J, Reich NG, Brookmeyer R, et al. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis 2009;9:291–300 [PMC free article] [PubMed] [Google Scholar]

3. Lober B. The common cold. J Gen Intern Med 1996;11:229–36 [PMC free article] [PubMed] [Google Scholar]

4. Arruda E, Pitkäranta A, Witek TJ, Jr, et al. Frequency and natural history of rhinovirus infections in adults during autumn. J Clin Microbiol 1997;35:2864–8 [PMC free article] [PubMed] [Google Scholar]

5. Leder K, Sinclair MI, Mitakakis TZ, et al. A community-based study of respiratory episodes in Melbourne, Australia. Aust N Z J Public Health 2003;27:399–404 [PubMed] [Google Scholar]

6. Monto AS, Sullivan KM. Acute respiratory illness in the community. Frequency of illness and the agents involved. Epidemiol Infect 1993;110:145–60 [PMC free article] [PubMed] [Google Scholar]

7. Monto AS. Epidemiology of viral respiratory infections. Am J Med 2002;112(Suppl 6A):4S–12S [PubMed] [Google Scholar]

8. Nicholson KG, Kent J, Hammersley V, et al. Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. BMJ 1997;315:1060–4 [PMC free article] [PubMed] [Google Scholar]

9. Kvaerner KJ, Nafstad P, Jaakkola JJ. Upper respiratory morbidity in preschool children: a cross-sectional study. Arch Otolaryngol Head Neck Surg 2000;126:1201–6 [PubMed] [Google Scholar]

10. Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. N Engl J Med 1991;325:606–12 [PubMed] [Google Scholar]

11. Cohen S, Doyle WJ, Alper CM, et al. Sleep habits and susceptibility to the common cold. Arch Intern Med 2009;169:62–7 [PMC free article] [PubMed] [Google Scholar]

12. Ball TM, Holberg CJ, Aldous MB, et al. Influence of attendance at day care on the common cold from birth through 13 years of age. Arch Pediatr Adolesc Med 2002;156:121–6 [PubMed] [Google Scholar]

13. Mäkelä MJ, Puhakka T, Ruuskanen O, et al. Viruses and bacteria in the etiology of the common cold. J Clin Microbiol 1998;36:539–42 [PMC free article] [PubMed] [Google Scholar]

14. Smith A, Thomas M, Whitney H. Effects of upper respiratory tract illnesses on mood and performance over the working day. Ergonomics 2000;43:752–63 [PubMed] [Google Scholar]

15. Bramley TJ, Lerner D, Sames M. Productivity losses related to the common cold. J Occup Environ Med 2002;44:822–9 [PubMed] [Google Scholar]

16. Smith AP, Jamson S. An investigation of the effects of the common cold on simulated driving performance and detection of collisions: a laboratory study. BMJ Open 2012;2:pii:e001047 [PMC free article] [PubMed] [Google Scholar]

17. Fendrick AM, Monto AS, Nightengale B, et al. The economic burden of non-influenza-related viral respiratory tract infection in the United States. Arch Intern Med 2003;163:487–94 [PubMed] [Google Scholar]

18. Vingilis ER, Brown U, Sarkella J, et al. Cold/flu knowledge, attitudes and health care practices: results of a two-city telephone survey. Can J Public Health 1999;90:205–8 [PMC free article] [PubMed] [Google Scholar]

19. Sauro A, Barone F, Blasio G, et al. Do influenza and acute respiratory infective diseases weigh heavily on general practitioners' daily practice? Eur J Gen Pract 2006;12:34–6 [PubMed] [Google Scholar]

20. Ellenhorn MJ, Barceloux DG. Camphor in medical technology: diagnosis and treatment of human poisoning. New York: Elsevier; 1998. p. 505-7.

21. Robert Strickly G. Solubilizing excipients in oral and injectable formulations. Pharm Res 2004;21:201-30.

22. Widmann O. Synthesis of thymol from cuminol. Berlin 1982;15:166-72.

23. McIsaac WJ, White D, Tannenbaum D, et al. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. CMAJ 1998;158:75–83 [PMC free article] [PubMed] [Google Scholar]

24. Chow AW, Benninger MS, Brook I, et al. ; Infectious Diseases Society of America IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis 2012; 54:e72–112 [PubMed] [Google Scholar]

25. Smith SR, Montgomery LG, Williams JW., Jr Treatment of mild to moderate sinusitis. Arch Intern Med 2012;172:510–3 [PubMed] [Google Scholar]

26. Rothman R, Owens T, Simel DL. Does this child have acute otitis media? JAMA 2003;290:1633–40 [PubMed] [Google Scholar]

27. Forgie S, Zhanel G, Robinson J; Canadian Paediatric Society, Infectious Diseases and Immunization Committee Management of acute otitis media [position

statement]. Ottawa (ON): Canadian Paediatric Society; 2009. Available: www.cps.ca/en/documents/position/acute-otitis-media (accessed 2012 Aug. 2). [Google Scholar]

28. Angier E, Willington J, Scadding G, et al. British Society for Allergy and Clinical Immunology (BSACI) Standards of Care Committee Management of allergic and non-allergic rhinitis: a primary care summary of the BSACI guideline. Prim Care Respir J 2010;19:217–22[PMC free article] [PubMed] [Google Scholar]

29. Behl C,R., Pimplaskar N.K., Sileno A.P., Demeireles J., Romeo VD. Effect of physicochemical properties and other factors on nasal drug delivery. Advanced drug delivery Reviews. 1998; 89-116.

30. Cauna N. Blood and nerve supply of the nasal lining, in: D.F. Proctor, I.B. Andersen (Eds.), Chapter in The Nose: Upper Airway Physiology and the Atmospheric Environment, Elsevier Biomedical Press, Amsterdam. 1982; 45-69.

31. Illum, L. Transport of drug from the nasal cavity to central nervous system. Eur J Pharm Sci. 2000; 11:1–18.

32. Parvathi M. Intranasal drug delivery to brain: an overview. International journal of research in pharmacy and chemistry. 2012; 2(3): 889-895.

33. Sarkar M.A. Drug metabolism in the nasal mucosa. Pharm.Res. 1992; 9: 1–9.

34. Mann JC, Hobbs JB, Banthorpe DV, Harborne JB (1994). *Natural products: their chemistry and biological significance*. Harlow, Essex, England: Longman Scientific & Technical. pp. *309–11*. *ISBN 978-0-582-06009-8*.

35. Galeotti, N.; Mannelli, L. D. C.; Mazzanti, G.; Bartolini, A.; Ghelardini, C.; Di Cesare, Mannelli (2002). "Menthol: a natural analgesic compound". *Neurosci. Lett.* **322** (3): 145–148. *doi*:*10.1016/S0304-3940(01)02527-7*. *PMID 11897159*. *S2CID 33979563*

36. "Front Matter". Nomenclature of Organic Chemistry : IUPAC Recommendations and Preferred Names 2013 (Blue Book). Cambridge: The *Royal Society of Chemistry*. 2014. p. 691. *doi*:*10.1039/9781849733069-FP001*. *ISBN 978-0-85404-182-4*