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Review of Simultaneous determination of analytes by High Performance Liquid Chromatography (HLPC) in multicomponent cough and cold oral drug products.

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ABSTRACT: The objective of this article is to review the methodologies of determination of the most widely used analytes in cough and cold preparations by HPLC.
This article studies the effect of all chromatographic parameters so as to provide a fast, reliable and cost effective methodology of testing.
KEY WORDS- High Performance Liquid Chromatography (HPLC), Over the Counter (OTC).

INTRODUCTION

Cough and cold segment is one of the major areas of over the counter . OTC is a fiercely competitive market in which traditional cough and cold remedies exist. There are many reasons why pharmaceutical companies decide to pursue switches from prescription (Rx) to over-the-counter (OTC) status for their drugs. These reasons include extending revenue generated by a drug (life-cycle management), development of a defence strategy against generic competitors, expansion and growth of an OTC drug portfolio, and broadening consumer access to innovative OTC medications.
Hence as there is an increasing need and welcome for such kind of switches it is necessary to target fast and effective method development for components which belong to OTC markets.

On such category for OTC products is the Cough and Cold category which is one of the most widespread unit in the OTC market the reason being the cough and cold which is very common across the globe..Hence if a common platform is designed to develop a common method for a vast range of components belonging to this category it will be of great help to the industry and then obviously to the community at large.
The following chart of global OTC sales depicts the share of various OTC categories where cough and cold has a whooping share of 22% of total sales. [1]

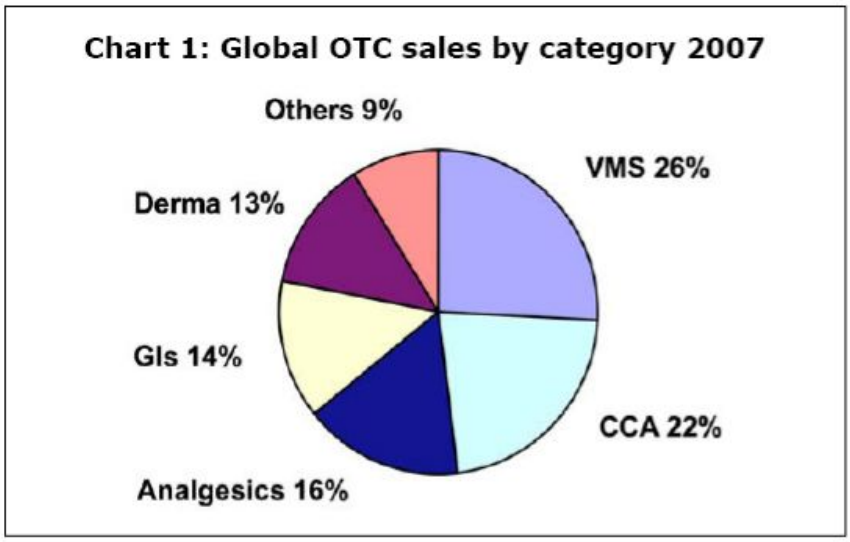

Figure 1: Global OTC Sales

VMS – Vitamins, minerals and supplements
CCA – Cough Cold and Allergy
GIs – Gastro Intestinal
Derma - Dermatology

The major need is to have a fast, reliable cost effective method developed for analyzing different components of cough and cold category products.

The goal of this review is to prepare a potential, reliable fast and efficient analytical methodologies for various dosage forms which can estimate all the major components of a cough and cold multicomponent formulation.

Several methods are being used for determining these compounds. HPLC, with Ultraviolet, Fluorimetry or Mass Spectroscopy(MS) is most widely used. Other techniques include Ultraviolet-Visible Spectroscopy, Thin layer Chromatography (TLC), Gas Chromatography(GC), GC/MS, Capillary Electrophoresis and multivariate spectrophotometric method have been used to determine few of these compounds. But there is no analytical method for simultaneous determination of most of the compounds mentioned earlier for cough and cold category of products. [2]

The cost of method development, validation and transfer in a cGMP environment is very expensive hence a common method will save the cost.
Also the method should be fast thus further decreasing the entire cost of OTC products.
This method should be readily used for an entire range of products of cough and cold category.

There are many methods reported which are developed for components used in cough and cold products. But these methods are developed either for individual components or only for that particular dosage form or for that particular product.

The selection of analytical methods is determined by several factors such as speed, convenience, specificity, accuracy, precision, sensitivity, selectivity, cost, availability of instruments, technical expertise and the number of samples to be analyzed etc.

CURRENTLY USED METHODS

The selection of analytical methods is determined by several factors such as speed, convenience, specificity, accuracy, precision, sensitivity, selectivity, cost, availability of instruments, technical expertise and the number of samples to be analyzed etc. This shows the need of new improved methods for analysis.

There are many methods reported which are developed for components used in cough and cold products. But these methods are developed either for individual components or only for that particular dosage form or for that particular product.

HPLC has become a powerful tool for analysis of pharmaceutical products. Mixtures used for the treatment of cough and colds may be complexes containing several active ingredients including a decongestant, antihistamine, analgesic, preservatives,

dyes and flavors. The active materials cover a range of structures with widely varying polarities and include both acidic and basic compounds.
A number of conventional methods have been applied to present components. Cough and cold pharmaceutical preparation are one of the most extended formulations in the world and have got many pharmaceutical forms : syrup, suspension, powders, capsules and tablets. Pheniramine maleate, Pseudoephrine Hydrochloride are widely used in combination with other drugs for the clinical treatment of common cold, sinusitis, bronchitis and respiratory allergies. Dextromethorphan Hydrobromide, Guafenesin are used as cough suppressants, antitussives for the relief of non productive cough and cold preparations. The most common formulation can be either liquid or suspension that requires the addition of preservative. Due to the characteristic and diverse properties inherent to their formulation ,these preparations offer an analytical problem.

A number of conventional methods have been applied to present series. Pseudoephedrine and acetaminophen have been determined Spectrophotometrically and GLC. Guafenesin has been determined by GLC. Spectrophotometric, GLC or methods requiring TLC separation when applied to samples such as cough mixtures can be lengthy and or subject to interferences by the matrix of the sample, and they are generally not suitable for simultaneous assay.
This study is only for small molecules and will not be covered for Ayurvedic, Herbal or Biotechnolgy related dosage forms or formulations.

LITERATURE REVIEW

Information of various separation methods for different components of cough and cold products

Acetaminophen

Acetaminophen has been analyzed in presence of Cetrizine Dihydrochloride, Phenylpropanolamine Hydrochloride by capillary zone electrophoresis. [3]
Acetaminophen is also determined on a C 18 chemical bonded silica gel as a solid phase, methanol- water (24:76) as a mobile phase in presence of caffeine in capsules. [4]
Acetaminophen is separated from Chlorpheniramine Maleate and Pseudoephedrine Spectrophotometric analysis. They could not be resolved by standard Spectrophotometric methods due to severe spectral overlap of Acetaminophen and Chlorpheniramine. Two Chemometric methods : classical least squares method (CLS) and partial least squares method (PLS) were compared for the analysis of Acetaminophen and Chlorpheniramine in which PLS finally separated Acetaminophen. [5]
Another method employed for the separation of Acetaminophen from Pseudoephedrine Hydrochloride, Doxylamine succinate, Dextromethorphan bromide is by super critical fluid chromatography. [6]
Acetaminophen is also determined simultaneously with ibuprofen in combined dosage form by high performance thin layer chromatography. [7]
Spectrophotometric methods are used for determination of Acetaminophen from tablets [8]

Guaifenesin

Guaifenesin is separated in a mixture containing Dextromethorphan, Phenylpropanolamine in an oral liquid formulation by using HPLC. [9]
It is also separated simultaneously using capillary gas chromatography for determination of Guaifenesin, Dextromethorphan and Diphenhydramine in cough and cold syrup. [10]
Simultaneous Guaifenesin is determined in presence of Nikethamide and Guaifenesin by derivative Ultraviolet Spectophotometry. [11]
Simultaneous determination of APAP, Caffeine, Guaifenesin and preservatives in syrups by micellar LC is also estimated. [12]
Simultaneous determination of Dextromethorphan, Dextrorphan and Guaifenesin in human plasma using semi automated liquid/ liquid extraction and gradient liquid chromatography tandem mass spectrometry is estimated. [13]

Pheniramine maleate

High-pressure liquid chromatographic is used to determine Methscopolamine nitrate, Phenylpropanol amine Hydrochloride, Pyrilamine maleate, and Pheniramine maleate in tablets [14]
Two different, derivative Spectrophotometric and gas-liquid chromatographic, procedures for direct quantitation of caffeine and some commonly dispensed antihistaminics in bulk forms, in their laboratory prepared mixtures and in dosage formulations, have been investigated. The limit, sensitivity, reproducibility and accuracy of each method were studied for each individual drug substance and in some usual pharmaceutical formulations. [15]

Phenylephrine Hydrochloride

Phenylephrine Hydrochloride is estimated along with Guifenesin, Chlorpheniramine Maleaste in cough syrup using gradient liquid chromatography. [16]
Phenylephrine Hydrochloride is also determined in presence of Chlorpheniramine Maleate and Methscopolamine nitrate in tablets or capsules by

liquid chromatography with two UV absorbance detectors in series. [17]
Simultaneous GLC analysis has been used to determine Salicylamide, Phenylpropanalomine Hydrochloride, Caffeine, Chlorpheniramine Maleate, Phenylephrine hydrochloride and Pyrilamine Maleate in capsule preparations. [18]
Simultaneous determination of Pseudoephedrine Hydrochloride and Dextromethorphan bromide from tablets is used to determine Phenylephrine Hydrochloride. [19]

Pseudoephedrine Hydrochloride

Simultaneous analysis of H 1-antihistamine Acrivastine and the decongestant Pseudoephedrine Hydrochloride is separated by high performance chromatography. [20]

Simultaneous determination of APAP, Chlorphenir amine and Pseudoephedrine is separated by partial least squares method. [21]

Simultaneously Pseudoephedrine hydrochloride and Ibuprofen separated from combined dosage forms by UV Spectrophotrometry. [22]

Simultaneous determination of Pseudoephedrine Hydrochloride and Dextromethorphan bromide from tablets is performed to separate Pseudoephedrine Hydrochloride.[23]
LC-MS-MS simultaneous determination of Paracetamol, Pseudoephedrine and Chlorpheniramine is done from human plasma to separate out Pseudoephedrine. [24]

Chlorphenamine Maleate

The enantioselective determination of Chlorpheniramine and its major metabolites in human plasma using chiral chromatography on a beta Cyclodextrin chiral stationary phase and mass spectrometric detection is established. [25]
Simultaneous determination of Amantadine and Chlorpheniramine in human plasma by liquid chromatography tandem mass spectroscopy is established. [26]
Simultaneous assay of Phenylpropanolamine Hydrochloride, Caffeine, Paracetamol, Chlorpheniramine Maleate in Silabat tablets using HPLC with diode array detection is estimated. [27]
Derivative Spectrophotometric determination of Chlorpheniramine Maleate in combination with Etilefrine resinate or Dextromethorphan Hydrobromide is estimated. [28]

Bromopheniramine maleate

Quantitative determination of two decongestants and an antihistamine in combination using paired ion high pressure liquid chromatography is studied. [29]

Dextromethorphan Hydrobromide

Dextormethorphan Hydrobromide is estimated by gas chromatography and HPLC in cough and cold syrup preparations. [30]
Simultaneous determination of Phenylpropanolamine Hydrochloride, Dextromethorphan Hydrobromide and Chlorpheniramine Maleate in formulations by reverse phase chromatography is established. [31}
Mixed ion pair liquid chromatography method for simultaneous assay of Ascorbic acid, Caffeine, Chlorpheniramine Maleate, Dextromethorphan Hydrobromide and APAP in Frenadol sachets is established. [32]

PROBLEMS FACED DURING SEPARATIONS OF ALL COMPONENTS

Common cold cough formulations are usually combination of an analgesic (eg acetaminophen), an antitussive (eg Dextromethorphan bromide), and antihistamine (eg Chlorphenaramine Maleate) and a nasal decongestant (eg Phenylephrine Hydrochloride). In many cases the concentration of acetaminophen is significantly higher than the other active pharmaceutical ingredients (API's). The presence of API's with different polarity and the disparity in concentration poses an analytical challenge. [33]
Pharmacopoeial HPLC methods reported for each drug are inappropriate for their simultaneous determination because of interferences due to corresponding peaks. Several methods are used for simultaneous determination of Pseudoephedrine and Dextromethor - phan. However these procedures require the use of more than one column or mobile phase or an increased flow rate which can be time consuming and uneconomical. Gradient method has been developed but it is not suitable because it increases the column re-equilibration time and baseline disturbances. On the other hand ion pairing agents also can be used but they are expensive. [33]
Also use of ion pairing agents requires use of hydrophobic additives either cationic such as triethylamine, hexalamine or anionic such as alkyl sulfonate. These additives are costly and tend to absorb very strongly on the stationary phase leading to difficulty in recovering initial column properties. Also use of ion pairing agents in mobile phase will enhance the retention time of most components thereby increasing analysis time. [35]

Guaifenesin was estimated simultaneously in the presence of Acetaminophen, Pseudoephedrine, Folcodine. However this method was not stability indicating method. [36]
Acetaminophen has been analysed with salts of Chlorphenaraminemaleate, Dextromethorphan, Phenyl propanolamine , Caffeine, Guafenesin in tablets using HPLC. One of the common problems of using LC method was high cost of mobile phase. [37]
Chlorpheniramine Maleate are analysed using HPLC or capillary electrophoresis. [38]

GAP IN EXISTING RESEARCH

HPLC is a commonly available method of testing in pharmaceutical laboratory so this method should be of choice for complete determination of all the components.
Because of the complex nature of cold medicine formulations and the need to ensure their quality, safety and efficacy the development and evaluation of new methods that can reduce the time and cost of analysis is necessary . [39]

There are many existing methods which analyse different components either single or multicomponents by a particular method.
Lot of problems related to the separation of components, peak shape, tailing effect, cost of the analysis, time of analysis, cost of mobile phase etc are encountered in these methods.
There is no common method reported in the literature for analysing all the components mentioned earlier like Acetaminophen, Guafenesin, Phenylephrine maleate, Phenylephrine Hydrochloride, Pseudoephrine Hydrochloride, Chlorpheiramine Maleate, Dextromethorphan Maleate by a single HPLC method for different cough and cold dosage forms (eg syrup, elixirs, tablets , capsules etc)

CONCLUSION

The review proposes a simultaneous determination of active ingredients used in OTC market for cough and cold where work should be performed using a HPLC technique as it is commonly used in pharma testing laboratories.

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