pH and Titratable Acidity of different Cough Syrups in Nigeria

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Abstract

Background: Cough linctuses are liquid oral medicines widely used in children to treat cough and related conditions. Some of their constituents are acidic and dental erosive. **Objectives**: This *in vitro* study aimed to evaluate the endogenous pH and titratable acidity of Nigerian cough syrups and also determine their erosive potentials. **Methods**: Twenty-five commonly used cough syrups were evaluated. The pH of each cough syrup was determined using a digital pH meter. Also, the buffering capability of each cough syrup was assessed by titrating 0.1N Sodium hydroxide (NaOH) with 10mls of each sample until neutral pH of 7.0 was achieved for acidic syrups. For alkaline samples, 0.1N Hydrochloric acid (HCl) was titrated until the neutral pH of 7.0 was achieved. **Results**: The pH of the syrups ranged from 3.06 to 8.4. Twenty three (92%) of them were acidic (pH<7) while fifteen (60%) showed pH below the critical value of 5.5 which is a pH condition for enamel dissolution. Compared with the control (Coca-cola), all the samples showed comparable but slightly higher pH levels. The titratable acid values were between 0.1 and 4.1 mls. Eleven samples required at least 1.7mls of 0.1N sodium hydroxide to be neutralized. Only Deshalom – Cof needed more NaOH (4.1mls) to be neutralized compared with the control (3.1mls). **Conclusion**: Sixty percent of the sampled syrups were acidic with pH values below 5.5.

Running title: Dental erosivity of Nigerian Cough Syrups

Key Words: pH, titratable acid, dental erosion, cough syrup

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Introduction

Cough is one of the most common and frustrating symptoms of children ailments. Not only can it keep children up all night, it can also keep them away from playmates or get them sent home from school if the cough is very disturbing. Cough suppressants and expectorants are medicinal drugs used to treat cough and associated symptoms. These medicines are widely available in the form of syrup, also known as linctuses. Although no local studies cited, but in vitro studies in India (1) and Brazil (2) have revealed that cough syrups are acidic medicines and sometimes having pH less than the critical pH of enamel dissolution.

Oral administration of medications has been categorized as an extrinsic cause of dental erosion because of the low pH and high titratable acid of some of the medicines used for chronic diseases (3-5). The risk of dental erosion is increased when these syrup medications are used with a high frequency of ingestion (three or more times per day), at bedtime, or when they have side effects such as reduction of salivary flow rate, which happens with antihistamines (4,5).

The pH of liquid oral medicines are formulated to optimize efficacy and patient acceptability. Acidic preparations are often necessary for drug dispersion because solubility of some substances is pH dependent. Besides, these acidic medicines often possess pleasant taste, which may enhance patient compliance, especially children (6). Occasional use of cough syrups may not have erosive effect on the teeth but children who take them regularly may be at risk of dental erosion. Often these drugs are administered at bedtime when salivary flow is reduced, hence this practice may accentuate the erosive effect of the syrup.

The acidic content of a solution can be quantified by assessing the pH value and/or the titratable acid. The pH is the negative logarithm of the hydrogen ion concentration in the syrup and it is measured on a scale of 0 to 14 with a reading below 7 indicating acidity. The lower the pH, the more acidic the solution and the more difficult it is to bring the pH to neutrality (7). On the other hand, Titratable acidity (TA) deals with the measurement of the total acid concentration contained within the solution. It represents the amount of alkali (base) needed to be added to an acid to bring it up to a neutral pH. It actually suggests the strength and the amount of available acid (8). Zero (1996) (9) suggested that titratable acid of dietary substances should be considered more important than their pH, because it will determine the actual H+ available to interact with the tooth surface. In practice, pH is measured by pH paper or digital pH meter while the titratable acidity or the buffering capacity is assessed by measuring the weight (in grams) of standardized sodium hydroxide necessary for titration to a predetermined pH level (10).

A pH of 5.5 is traditionally considered to be the 'critical pH' at which enamel begins to dissolve. Birkhed (1984) (11) wrote that mineral loss may actually begin at higher pH levels. Drugs which alter oral pH are considered potentially harmful to the teeth because of its ability to dissolve sound tooth tissue. In a study by Hughes and colleagues (2000) (12), they found that increased erosion was found to correlate with decreasing pH and increasing acid concentration. This characteristic of liquid medicines, to be precise, its acidic pH has been stated to be directly related to factors such as chemical stability and biocompatibility of the active agent (13)

Dental erosion has been described as not an acute or a severe condition to be regarded as an adverse event which explains its exclusion from the FDA reporting system in US (14). On the other hand, Pierro and colleagues (15) in 2005 pointed out that acidic and sweetened oral pediatric syrup with the tendency for long-term use by children must be subjected to surveillance especially for localized intraoral conditions. In vitro studies (2-4, 6) investigating the physicochemical parameters of pharmaceutical products have provided valuable information on their potentials to cause dental erosion by determining endogenous hydrogen ion concentrations (pH) and titratable acids. Thus, the aims of this *in vitro* study were; to evaluate the endogenous pH and titratable acidity of cough syrups that are frequently ingested by Nigerian children and their potentiality to cause dental erosion and thereafter make appropriate recommendations.

Materials and Methods

The determination of pH and titratable acidity (TA) levels was carried out in the central science laboratory of the Obafemi Awolowo University, Ile-Ife, Nigeria. Twenty five most common cough syrups were selected after a convenient sample of 50 nursing mothers attending immunization clinic of the University Teaching Hospitals, Complex located in Ile-Ife were asked to write down three cough syrups they usually buy off-the-counter. These were then imputed into the computer and the frequencies generated. The names of all the twenty five cough syrups mentioned were noted (Table 1), and purchased from the accredited sales representatives of the companies involved. Coca-cola, a known acidic soft drink was used as control because the pH had been previously studied (16). The samples were blinded to the laboratory scientist who read the pH and titrated the syrups. That is, all identifications of each drug were removed and labeled with Arabic numbers prior to their delivery to the laboratory. Data was recorded in study-specific charts and authenticated before it was retrieved by the authors.

pH measurement

The endogenous pH of each syrup was determined at room temperature using a pH electrode meter (WPA, CD70, Cambridge, UK) placed directly into each sample syrup. The pH meter was calibrated according to the manufacturer's instructions; firstly, three buffer solutions were prepared (from the buffer powders) with the following pH; 4.0, 7.0, and 9.0. The meter was thereafter adjusted with 4.0 and 9.0 buffers and made to accurately detect the buffer solution at pH 7.0 before it was used. Ten (10) mls of each cough syrup sample was dispensed into three separate beakers i.e. each beaker receives 10 mls syrup sample and the meter's electrode dipped into the samples to obtain triplicate digital pH values. This procedure was repeated for all the 25 samples including the control.

Titratable Acidity (TA) determination

A volume of 0.1N Sodium hydroxide (NaOH) or hydrochloric acid (HCl) needed to bring the pH of 10 mls of each sample to 7.0 was measured. Ten (10) mls of each of the samples was titrated with 0.1N NaOH or HCl (in case the initial pH was above 7.0) and readings obtained using the digital pH meter. When the mean pH value of 7.0 was reached the volume of the spent NaOH or HCl was recorded.

The values were imputed into the computer and analyzed using SPSS for windows version 16 (SPSS Inc. Chicago Illinois, USA). Means and Standard Deviations were calculated for pH values.

Table1: Cough syrups (brand or generic names), Contents and Batch numbers

S/N	Cough syrup names	Contents	Batch number
1.	Deshalom – Cof	Ammonium chloride B.P., Chlorpheniramine maleate B.P., Conc Anise water, Liquorise liquid extract, Menthol B.P., Aspartate B.P. (A source of Phenylalanine)	009
2.	Zedex	Bromhexine hydrochloride B.P., Ammonium chloride B.P., Flavoured syrup base, Dextromethocphan, menthol B.P., Hydrobromide B.P., Colours(Brilliant blue, FCF,& Tartazine).	JG10756
3.	Tutolin Expectorant	Diphenhyramine hydrochloride, Trisodium citrate, Menthol, Ammonium chloride, Citric acid, Flavoured syrup base.	TCE30
4.	Cofta Non- drowsy	Ammonium chloride, Liquorice extract BPC, Aniseed oil, Ipecacuanha liquid extract BPC, Peppermint oil.	7M130011
5.	Emzolyn Expectorant	Diphenhydramine hydrochloride B.P., Sodium citrate B.P., Ammonium chloride B.P., Menthol B.P.	L838M
6.	Piriton Expectorant Linctus	Chlorpheniramine maleate, Sodium citrate, Ammonium chloride.	8C508014
7.	Emzolyn Cough Syrup for Children	Diphenhydramine hydrochloride B.P., Menthol B.P.	L439M
8.	Benylin for Children	Diphenyhyramine hydrochloride Ph. Eur., Sodium citrate Ph. Eur.	U323
9.	Benylin with Codeine	Diphenhyramine hydrochloride Ph. Eur., Sodium citrate Ph. Eur., Codine Phosphate Ph. Eur., Menthol B.P.	U523
10.	Tuxil – N Cough linctus	Chlorpheniramine maleate B.P., Ephedrine hydrochloride B.P., Ammonium chloride B.P., Menthol USP, Sodium citrate B.P.	A78063
11.	Benylin Expectorant	Diphenhyramine hydrochloride Ph. Eur., Ammonium chloride Ph.Eur.	U317
12.	Dr. Meyer's Coflin Cough Linctus	Chlorpheniramine maleate, Sodium citrate, Ephedrine hydrochloride, Ammonium chloride, Menthol.	L11808
13.	Coflax Children Cough Syrup	Diphenhydramine hydrochloride, Ammonium chloride, Sodium citrate, Menthol	08570701
14.	Kufdryl Expectorant & Mucolytic	Diphenhydramine hydrochloride, Ammonium chloride, Menthol.	240807
15.	Neofylin Cough Syrup	Chlorpheniramine maleate B.P., Sodium citrate B.P, Menthol B.P., Ammonium chloride B.P., Citric acid B.P., Ipecacuanaha tincture B.P., Conc Anise water.	04108
16.	Dr. Meyer's Cofmix Cough Syrup	Diphenhydramine hydrochloride B.P., Sodium citrate B.P., Ammonium chloride B.P., Menthol B.P.	80514
17.	Dr. Meyer's Cofmix with Codeine	Diphenhydramine hydrochloride B.P., Sodium citrate B.P., Codeine phosphate B.P., Menthol B.P.	80102
18.	Dr. Meyer's Cofmix Junior	Diphenhydramine hydrochloride B.P., Sodium citrate B.P., Codeine phosphate B.P., Menthol B.P.	80515
19.	D- Koff Cough Expectorant	Diphenhydramine hydrochloride B.P., Sodium citrate B.P., Bromhexine hydrochloride B.P., Menthol B.P., Ammonium chloride B.P.	L7011
20.	Menthodex Cough Mixture	Ammonium chloride B.P., Liqiud extract of Horehound, Tolu tinctureB.P. 1959, Sodium citrate B.P., Liquid extract of Tussilago, Menthol B.P., Squill tincture B.P. 1980.	697J1
21.	Tutolin Children Cough Syrup	Diphenhyramine hydrochloride, Trisodium citrate, Menthol, Ammonium chloride, Citric acid, Flavoured syrup base.	TCC51
22.	Dipenkof Sirop Enfant	Diphenhyramine hydrochloride B.P., Sodium citrate B.P.	DC12U
23.	Diphenkof Expectorant Adultes	Diphenhyramine hydrochloride B.P., Sodium citrate B.P., Ammonim chloride, Menthol B.P..	DA15U
24.	Linctifed F- Expectorant	Tripolidine hydrochloride B.P., Codine phosphate B.P., Pseudoephedrine hydrochloride B.P., Potassium guaiacolsulphate	X071BP
25.	De- Shalom Cough Expectorant	Ammonium chloride B.P, Chlorpheniramine maleate B.P, Conc Anise water, Liquorise liquid extract, Menthol B.P, Aspartate B.P	001

Results

Table 2 displays the distribution of mean pH values and the HCL and NaOH volumes needed to bring the pH of the 25 evaluated cough syrups to 7.0. The mean pH of the syrups ranged from 3.06 to 8.4. Twenty three (92%) of the syrups were acidic with 15 of them (60%) recording endogenous mean pH values below 5.5. Individual assessment of the samples showed that sample 2 (Deshalom – Cof) had the lowest mean pH of 3.06 followed by sample 3 (Zedex with mean pH 3.26) and sample 4 (Tutolin Expectorant with mean pH 3.78). Samples 26 (De- Shalom Cough Expectorant) and 25 (Linctifed F- Expectorant) were basic with mean pH of 8.4 and 7.1, respectively. The rest showed pH values comparable but slightly higher than 2.81 recorded for Coke.

The table shows, also, that the volume of 0.1N Sodium hydroxide needed to raise the pH of the syrups to 7.0 ranged from 0.1 to 4.1 mls while the control required 3.1mls. Eleven of the samples needed, at least, 1.7 mls of the base to be neutralized. Sample 2 (Deshalom – Cof) needed the largest volume while sample 24 (Diphenkof Expectorant Adultes) needed the lowest volume. Also only sample 2 needed a higher volume of NaOH (4.1mls) to be neutralized compared with the control. Two cough syrup samples (De-Shalom Cough Expectorant and Linctifed F- Expectorant) presented mean pH values above the standard (8.4 and 7.1, respectively). These syrups needed 0.1 t0 2.9 mls of HCl to lower their pH to 7.0.

Table 2: Mean pH values and volumes of NaOH and HCL needed to bring pH of the evaluated cough syrups to 7.0

S/N	Syrup (brand or generic) names	Mean pH on opening the syrup	Standard deviations	Volume (mls) of NaOH needed to bring the pH to 7.0	Volume (mls) of HCl needed to bring the pH to 7.0
1	Cocacola (Control)	2.81	0.06	3.1	
2	Deshalom - Cof	3.06	0.05	4.1	
3	Zedex	3.26	0.05	1.5	
4	Tutolin Expectorant	3.78	0.04	0.6	
5	Cofta Non- drowsy	4.08	0.04	2.6	
6	Emzolyn Expectorant	4.40	0.06	3.0	
7	Piriton Expectorant Linctus	4.58	0.04	3.0	
8	Emzolyn Cough Syrup for Children	4.58	0.04	1.6	
9	Benylin for Children	4.82	0.04	1.9	
10	Benylin with Codeine	4.88	0.04	2.7	
11	Tuxil – N Cough linctus	5.02	0.04	2.3	
12	Benylin Expectorant	5.12	0.04	2.2	
13	Dr. Meyer's Coflin Cough Linctus	5.14	0.12	1.8	
14	Coflax Children Cough Syrup	5.18	0.04	1.2	
15	Kufdryl Expectorant & Mucolytic	5.18	0.04	1.3	
16	Neofylin Cough Syrup	5.36	0.08	1.3	
17	Dr. Meyer's Cofmix Cough Syrup	5.56	0.08	1.7	
18	Dr. Meyer's Cofmix with Codeine	5.58	0.04	2.2	
19	Dr. Meyer's Cofmix Junior	5.68	0.04	0.8	
20	D- Koff Cough Expectorant	5.68	0.04	1.3	
21	Menthodex Cough Mixture	5.70	0.06	0.9	
22	Tutolin Children Cough Syrup	5.84	0.05	1.0	
23	Dipenkof Sirop Enfant	6.02	0.04	0.6	
24	Diphenkof Expectorant Adultes	6.02	0.04	0.1	
25	Linctifed F- Expectorant	7.10	0.04		0.1
26	De- Shalom Cough Expectorant	8.4	0.04		2.9

NOTE: 15 out of 25 (60%) had pH below critical value (5.5)

Discussion

In investigating the process of dental erosion, analysis of pH is usually considered to be an important variable (17). A number of investigations on liquid medicines belonging to different therapeutic classes have been conducted since the last decade in order to produce reliable information on the physicochemical profile of medicines ingested by children. Informatively, antitussives are one of the therapeutic classes found to have shown the lowest pH values 1,18)

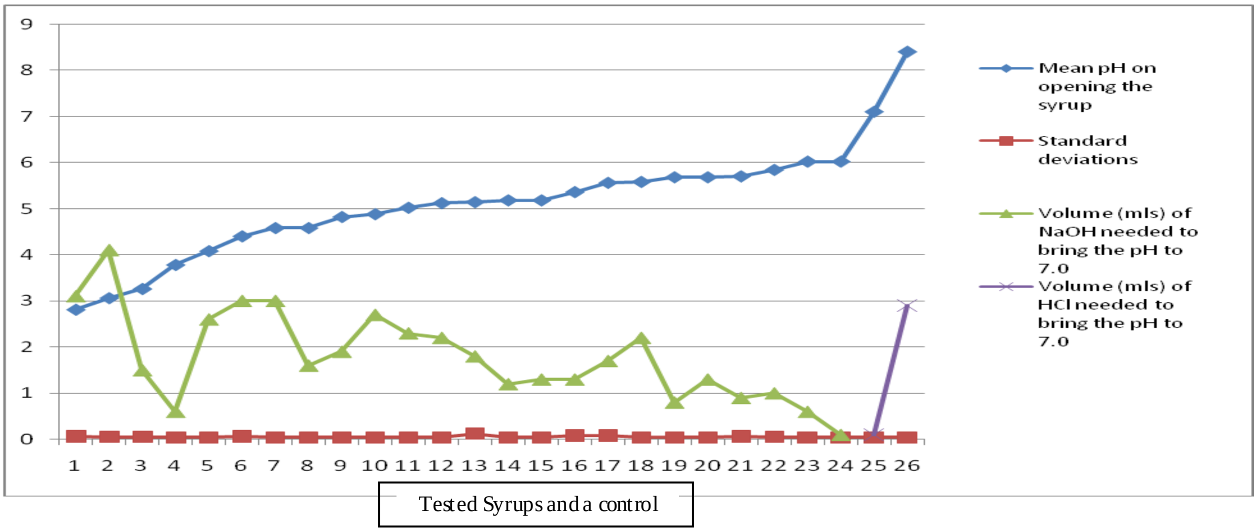

Figure 1: Volume of HCl or NaOH solutions needed to bring the pH of the cough syrups (represented by numbers, see Table 2) to 7.0

Our findings show that most of the syrup samples evaluated were acidic, i.e. pH <7. Although our study was narrowed to cough syrups, this finding is similar to that of studies done in Brazil by Neves and colleagues (19) in (2010) and Xavier and colleagues (18) in (2013) where the liquid medicines evaluated were predominantly acidic. The later researchers (18) opined that despite the shortcomings of an in vitro study, the presence of low pH in the formulations is characterized as a predictor of dental erosion by direct action of the medicines. Explaining this scenario, Johansson (2002) (20) wrote that the salivary concentration of calcium and phosphate is normally supersaturated in relation to enamel hydroxyapatite. An acid challenge results in under-saturation of these salivary salts, and tooth demineralization with softening of dental enamel occurs. Gray (21) had previously in 1962 clarified in details that the dissolution of enamel in acid occurs as a result of reaction between the hydrogen ion and the inorganic material (hydroxyapatite) which forms the principal part of enamel. The reaction results in dissolution of enamel leading to liberation of calcium and phosphate ions along with water molecules.

Many of the pH values observed in this study are compared to several soft drinks, fruit juices and teas considered potentially erosive (16, 22). Marquezan and colleagues (23) in 2007 surmised that low endogenous pH of liquid medicines markedly contribute to their erosive potential, and may cause dental erosion, especially after long-term contact with enamel surface.

Most of the acidic syrups we evaluated showed low pH values below the critical value of 5.5 at which enamel dissolution occurs. One of the syrups (sample 2) in the study had a relatively low pH of 3.06 more or less compared to the pH of the Coca-cola, a known acidic drink (16). This result is in accordance with those of previous researchers Maguire et al. (6) in 2007; Marquezan et al. (23) in 2007; Cavalcanti et al. (2) in 2008 and Sunitha et al. (1) in 2009 . Birkhed (11) in 1984 pointed out that pH of 5.5 is traditionally considered to be the 'critical pH' of enamel dissolution loss of mineral may actually begin at higher pH values.

Liquid medicines with pH <5.5 can acidify the dental biofilm by diffusion process, promoting adequate environment to the reproduction of pH-strategist microorganisms, thus substantially favoring acid production as consequence of their intense metabolism and resulting in the enamel demineralization (24) by indirect medicines action. The erosive potentials of syrups are not only a measure of the pH but more worrisome is the fact that these medicines are consumed in high frequency. Most cough syrup manufacturers recommend at least 4 to 6 hours frequency of administration. Also there has been anecdotal report of overuse of cough syrups to prevent coughing in the night in order not to disturb the child's sleep. Coupled with fact that salivary flow in the night is reduced, thus the teeth are constantly exposed to the syrup. This high frequency of daily ingestion associated with lower levels of mineralization, reduced thickness and maturation of the deciduous teeth (22) may aggravate their susceptibility to dental erosion. Hunter and his colleagues (25) showed that frequent use of low-pH solutions; as we have found in this study, results in a non-proportional increase in enamel erosion especially in patients having dental erosion from other causes.

Studies by Zero (7) in 1994 and West and colleagues (26) in 2000 showed that the titratable acid(TA) of beverages is the primary factor in the development of dental erosion because it determines the actual hydrogen ion availability for interaction with the tooth surface. The higher the titratable acid, the more the process of enamel and dentine dissolution is enhanced and also the longer it is for saliva to neutralize the acid (27). The titratable acid or the buffering capacity of the investigated cough syrups in the study ranged from 0.1 to 4.1. This range is comparable to the TA of Coca-cola (3.1) which is generally considered as acidic and dental erosive. Thus, we suspect that this high titratable acid may be significant in the initiation of dental erosion particularly in children with extended period of administration.

Many of the cough syrups contain a variety of ingredients that can maintain or impact low pH levels and high acidity such as citric acid, ammonium chloride and sodium citrate. Sodium citrate and citric acid are commonly used as flavour and acidulant. Citric acid is considered to be especially erosive because of its acidic nature and the ability to chelate calcium at higher pH (28). Most of the cough syrups investigated contain citrate which may therefore be partly responsible for the generally low pH levels shown. Aqueous ammonium chloride solution is mildly acidic and used in cough syrup preparation. Its expectorant action is caused by its irritative action on the bronchial mucosa. This causes the production of excess respiratory tract fluid which presumably is easier to cough up. However, there was no literature that supports its contribution to low pH and acidity of cough syrups.

It is evident from the literature that other factors such as type of acid, chelating properties, calcium and phosphate concentrations, temperature, exposure time and frequency of exposure contribute to enamel erosion and demineralization. The protective factors such as saliva also play a role in the dynamism of dental erosive process. Saliva is known to modify dental erosion by causing the formation of an enamel pellicle, which protects the surface from dissolution (29). Considering the limitation of laboratory studies, thus in reality, the erosive effect of the evaluated liquid medicines may not be as strong as what we observed in this *in vitro* study. As the use of pediatric medicines is increasing in many countries, it is important that health professionals, particularly pediatricians and child health care providers, be aware of the risk of oral health imbalance during the continuous and long-term use of cough syrups.

Conclusion:

Our findings show that majority of the evaluated cough syrups showed pH and titratable acidity compared to Coca-cola widely considered as dental erosive. With the exception of two all the syrup formulations presented acidic pH values. 60% of these samples had pHs lower than the critical pH (5.5) of enamel dissolution. They also show variability and high titratable acidity with the highest value being shown by the sample with the lowest pH. The results certainly support previous studies that cough syrups possess inherent and sufficient potentials to cause dental erosion.

Recommendations

At the time of prescription of cough syrups, patients should be advised to rinse the mouth with water immediately after the ingestion of these liquid medicines and tooth brushing should deliberately be delayed.

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