

British Journal of Medicine & Medical Research 5(4): 525-532, 2015, Article no.BJMMR.2015.057 ISSN: 2231-0614



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# Erosive Potential of Medicated Syrups on Primary Teeth: An *In vitro* Comparative Study

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## Authors' contributions

This work was carried out in collaboration between all authors. Author KJK designed the study, wrote the protocol and managed the literature searches. Author CV wrote the first draft of the manuscript. Authors KJK and VM Conducted the tests to measure pH, viscosity and titratable acidity of samples used in the study. Authors CV, KJK and RKA managed the experimental process and analyses of the study performed the Profilometer analysis. Authors RCS and KSU managed the Statistical analyses. All authors read and approved the final manuscript.

#### Article Information

DOI:10.9734/BJMMR/2015/13434 <u>Editor(s):</u> (1) Chan Shen, Department of Biostatistics, MD Anderson Cancer Center, University of Texas, USA. <u>Reviewers:</u> (1) Anonymous, Abant Izzet Baysal University, Turkey. (2) Anonymous, Birjand University of Medical Sciences, Iran. Complete Peer review History: <u>http://www.sciencedomain.org/review-history.php?iid=663&id=12&aid=6196</u>

**Original Research Article** 

Received 16<sup>th</sup> August 2014 Accepted 3<sup>rd</sup> September 2014 Published 24<sup>th</sup> September 2014

# ABSTRACT

**Aims:** This in vitro study was designed to investigate the exogenous erosive potential of most commonly used pediatric syrup medicaments on primary teeth.

**Place and Duration of Study:** Department of Pediatric Dentistry, Vishnu Dental College, Bhimavaram, India, 2012 to 2013.

**Methodology:** The erosive potential of 17 syrups was assessed by measuring their inherent pH, titratable acidity, viscosity and ability to erode enamel. The inherent pH and titratable acidity of syrups were measured using digital pH meter and viscosity was determined using Brookfield viscometer. Enamel surface changes were evaluated using optical 3D profilometer.

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**Results:** Api –up (appetizer) showed the least pH and Azee (Azithromycin) exhibited the highest pH. The titratable acidity was greater for Api-up (5.40ml) and least for Tonoferron (0.20ml). Asthalin exhibited highest viscosity and Ondem showed least viscosity. All the test syrups caused some degree of enamel loss, however, Api – up caused the greatest and Azee caused the least degree of enamel loss at three time intervals.

**Conclusion:** The medicated syrups with low inherent pH and high viscosity showed to cause a greater dissolution of enamel. However, certain syrups with low viscosity had shown higher degree of enamel loss due to their inherent acidic pH and those with high viscosity Showed lesser degree of enamel loss due to their basic pH. Hence, these results proved that inherent pH is the most critical factor for erosion.

Keywords: Dental erosion; pediatric liquid medicaments; pH; viscosity.

# **1. INTRODUCTION**

Pleasant tasted syrups have a long history of use in pediatric practice to aid compliance with medication. Chronically ill young children receive a variety of oral liquid medications for improvement or maintenance of health. Pharmaceutical firms sweeten liquid drug preparations with sucrose to increase the palatability, compliance and also to act as a preservative [1]. Additionally, these syrups contain agents which aid in improvement of the appearance, bioavailability and stability. These pharmaceutical adjuvants are usually considered to be inert and do not add to or affect the intended action of the therapeutically active ingredients [2]. However, these inert agents pose dangers like dental caries and erosion.

The effect of long term consumption of sugarcontaining liquid medications on the teeth is an issue of concern for the dental health. Syrups sweetened with sucrose produced a marked and long term drop in plaque pH leading to dissolution of enamel [3-5]<sup>•</sup> Many medicated syrups have an endogenous low pH that may itself contribute to enamel erosion [2].

A medication with a low pH that comes in frequent and /or sustained contact with teeth has a greater potential to cause dental erosion. In addition to pH, viscosity of the medicated syrups is an important factor to be considered in erosion process. The syrup with high viscosity has more adhesiveness and less flowability. The greater the adherence of the syrup, the longer will be the contact time with the tooth surface and higher the likelihood of erosion.

The indiscriminate use of liquid medicines in young children can increase the risk for development of dental erosion and dental caries. The ingestion of liquid oral medications at

bedtime is frequently not followed by proper oral hygiene. Bedtime intake of liquid medications is harmful to the teeth because the reduced salivary flow during sleep limits the natural cleansing action of saliva [6].

Since self medication with over-the-counter medicines has increased in recent times, this could pose greater threat of detrimental effects to oral tissues. Usually, parents are not aware that foods. beverages and pediatric several medications in the form of syrups contain sugar. Many studies have confirmed that frequent ingestion of fruit juices, carbonated beverages and sports drinks cause enamel erosion [7-10]. Hence, this in vitro study was designed to investigate the exogenous erosive potential of some commonly used pediatric medicated syrups on primary teeth.

## 2. MATERIALS AND METHODS

Most commonly used 17 pediatric medicated syrups including antibiotics, analgesics, antihistamines, anti- tussives, anti- asthmatics, antiepileptic, anti- diarrhoeals, appetizers, calcium supplement, iron supplement, multi vitamin syrups were included. The erosive potential of each syrup was assessed by measuring its inherent pH, neutralizable acidity, viscosity and ability to erode enamel.

## 2.1 Measurement of pH

The pH of pediatric medicated syrups was measured using a digital pH meter. Twenty millilitres of each medicated syrup in a glass beaker was placed in a thermostatically controlled water bath at 37 ℃ and a glass electrode was inserted into the syrup which displayed pH on the meter. Each sample was tested three times to record a mean measurement.

### 2.2 Measurement of Titratable Acidity

The titratable acidity of syrups was measured by placing 20ml of the product in a glass beaker placed in a thermostatically controlled water bath at  $37 \,^\circ$ C. Then, 0.1 M sodium hydroxide solution was gradually pipetted into the beaker until the pH reaches neutral and the samples were stirred continuously. The volume of sodium hydroxide required to increase the pH of the sample to neutrality was recorded; and the process was repeated three times for each sample to record a mean measurement.

## 2.3 Measurement of Viscosity

The viscosity of the medicated syrups was measured using Brookefield viscometer. The speed control was set at 60 rpm and the appropriate spindle for measuring the viscosity of syrups was selected. The spindle of the viscometer was released into the syrup sample and the readings were recorded on viscometer gauge as torque reading. The procedure is repeated for three times for each sample to obtain a mean measurement in centi Poise (cP).

#### 2.4 Measurement of Enamel Loss

Enamel specimens were prepared from extracted or exfoliated deciduous molars which were caries and restoration free. The crowns of the extracted teeth are sectioned from the root and cut vertically to produce approximately two equal sections. Each section is embedded in a vacuum- formed polyurethane mould filled with a low exothermic epoxy resin. All the specimens were stored in deionized double distilled water prior to testing.

The enamel loss was measured using optical 3D profilometer [Fig. 1]. The baseline readings of enamel surface were recorded and then the samples were randomly allocated and immersed in the respective pediatric liquid medications. The depth of erosion of each sample is recorded in micrometers at 10 minutes, 1 hour and 8 hour intervals.

## 2.5 Statistical Analysis

The data was analyzed using statistical software (SPSS version 16, Chicago). The statistical tests used were one way Analysis of Variance (ANOVA), Tukeys multiple post hoc procedure, Paired 't' test and Karl Pearson correlation coefficient method. For all the tests, a P-value of 0.05 or less was set for statistical significance and a value of 0.001 or less represents a highly significant relation.



Fig. 1. 3D Prifilometer used in the study for characterization of enamel surface changes

## 3. RESULTS

The one way ANOVA demonstrated a significant variation among the pH, titratable acidity and viscosity of the test medications and the enamel loss caused by the medicated syrups at 10 minutes, 1 hour and 8 hours time intervals respectively (p = .05) [Table 1].

Among all the test syrups, Api – up (an appetizer, Ayurvedic preparation) showed least pH (3.53) (most acidic) and Azee (Azithromycin) showed highest pH (8.14) (most basic). 12 out of 17 syrups showed pH at or below the critical level (pH<5.5). An enormous variation was observed in the neutralizable acidity among the test syrups. The amount of sodium hydroxide to neutralize Api -up (an appetizer, Ayurvedic preparation) (5.40ml) was greatest and that for Tonoferron (Iron supplementation) (0.20ml) was least. Asthalin (Salbutamol) is most viscous (1906.60cP) and Ondem (Ondansetron) is least viscous (7.67 cP) among the test syrups. All the syrups caused some degree of enamel loss, however, Api - up caused highest and Azee caused least degree of enamel loss at all the three time intervals.

Comparison between syrups was done in pairs using Tukeys multiple post hoc test with respect to pH, neutralizable acidity, viscosity and enamel loss and most of the test syrups exhibited statistically significant (p = .05) difference between each other. Paired 't' test demonstrated a significant difference in the enamel loss caused by the test medicated syrups at different time intervals [Table 2].

Karl Pearson correlation coefficient showed that there was an increase in enamel loss with decrease in pH, indicating a negative correlation (r = -0.18) [Table 3]. A positive correlation was observed between neutralizable acidity and enamel loss caused by majority of the test syrups (r = 0.612), [Table 4]. A negative correlation was observed between viscosity and enamel loss caused by majority of the test syrups (r = -0.04), however, a few syrups exhibited positive correlation (r = 0.8810) [Table 5].

Table 1. Table depicting the mean values of	pH, titratable acidity, Viscosity and Enamel loss		
caused by test syrups			

Syrups	Mean pH	Mean	Mean	Enamel loss			
	-	titratable	viscosity†	Baseline‡	10	1 hour‡	8 hours‡
		acidity <del>‡</del>		-	minutes‡	-	-
Azee	8.12 ±0.04	1.20±0.20	373.49±4.19	0.71 ±0.12	1.1±0.28	1.39±0.13	1.58±0.04
Valparin	7.52±0.03	0.63±0.15	14.36±0.12	0.82±0.02	1.12±0.13	1.39±0.14	1.78±0.09
Tonoferron	6.81 ±0.09	0.20±0.10	90.88±1.71	0.84±0.20	1.18±0.02	1.43±0.13	1.80±0.33
Shelcal	6.77±0.03	2.77±0.15	59.03±0.11	0.94±0.14	1.2±0.14	1.49±0.28	1.83±0.21
Crocin	5.77±0.01	4.50±0.21	41.54±0.60	0.95±0.19	1.23±0.13	1.49±0.08	1.99±0.07
Ibugesic	5.43±0.20	2.99±0.13	55.16±0.63	1±0.10	1.24±0.13	1.51±0.08	2.00±0.20
Bandy	4.87±0.01	1.47±0.15	58.3±3.55	1.03±0.12	1.26±0.14	1.56±0.08	2.00±0.17
Normet	4.69±0.03	3.63±0.15	21.15±0.26	1.03±0.26	1.31±0.05	1.6±0.12	2.00±0.05
Neopeptine	4.66±0.01	1.83±0.25	26.9 ±0.16	1.04±0.01	1.33±0.11	1.66±0.15	2.02±0.50
Ondem	4.63±0.04	1.13±0.21	7.67±0.60	1.06±0.31	1.39±0.14	1.66±0.13	2.03±0.12
Wikoryl AF	4.58±0.05	1.20±0.10	36.91±0.15	1.1±0.04	1.39±0.10	1.69±0.22	2.08±0.27
Ascoril-D	4.55±0.03	5.23±0.21	508.41±7.10	1.17±0.37	1.44±0.35	1.73±0.21	2.15±0.12
Becousles	4.23±0.01	4.03±0.21	14.18±0.73	1.19±0.41	1.45±0.44	1.75±0.23	2.26±0.06
Mox	3.81±0.33	5.20±0.30	106.53±0.95	1.19±0.09	1.46±0.12	2.17±0.28	2.26±0.28
Asthalin	3.78±0.02	2.97±0.95	1906.5±28.74	1.19±0.18	1.47±0.10	2.22±0.17	2.66±0.38
Zincovit	3.61±0.02	4.13±0.31	621.88±4.71	1.26±0.20	1.64±0.30	2.62±0.44	2.83±0.45
Api-Up	3.53±0.09	5.40±0.56	58.3±0.57	1.26±0.05	1.91±0.55	2.75±0.56	2.85±0.5
p- value	0.00*	0.00*	0.00*		0.02*	0.00*	0.00*

+ millilitres, †centi Poise, ‡ in micrometers, \* p = .05 - significant

#### Table 2. Table showing comparison of enamel loss at different time intervals

Syrups Time intervals com					S	
	Baseline vs 10minutes	Baseline vs 1hour	Baseline vs 8hours	10minutes vs 1hour	10minutes vs 8hours	1hour vs 8hours
Crocin	0.0356*	0.0168*	0.0049*	0.0143*	0.0021*	0.000*
Ibugesic	0.0052*	0.0041*	0.0092*	0.0037*	0.0127*	0.0216*
Mox	0.0251*	0.0115*	0.0149*	0.0263*	0.0145*	0.5464
Azee	0.0623	0.0094*	0.0024*	0.1151	0.0766	0.0991
Valparin	0.0607	0.0218*	0.0033*	0.0041*	0.0019*	0.0130*
Ondem	0.0837	0.0303*	0.0138*	0.0028*	0.0005*	0.0015*
Normet	0.1469	0.0197*	0.0146*	0.0200*	0.0000*	0.0097*
Wikoryl AF	0.0138*	0.0338*	0.0194*	0.0633	0.0225*	0.0054*
Ascoril-D	0.0351*	0.1118	0.0291*	0.2247	0.0406*	0.0227*
Asthalin	0.1595	0.0211*	0.0320*	0.0169*	0.0079*	0.7598
Becousles	0.1159	0.058	0.0345*	0.145	0.0667	0.0333*
Zincovit	0.0251*	0.0115*	0.0149*	0.0263*	0.0145*	0.5464
Shelcal	0.0011*	0.0288*	0.0036*	0.0818	0.0051*	0.0161*
Tonoferron	0.0908	0.0078*	0.0154*	0.0642	0.0742	0.0903
Api-up	0.0279*	0.0007*	0.0100*	0.0036*	0.0206*	0.0766
Neopeptine	0.0393*	0.0179*	0.0759	0.0066*	0.0946	0.2183
Bandy	0.0041*	0.0087*	0.0057*	0.0297*	0.0076*	0.0138*

\* p = .05 - significant

#### Table 3. Table demonstrating correlation analysis between pH and enamel loss caused by test syrups

Relationship between	r value**	p value*
pH and enamel loss	-0.16	0.27, NS
at 10 min		
pH and enamel loss	-0.15	0.30, NS
at 1Hr		
pH and enamel loss	-0.18	0.19,NS
at 8 Hrs		

\* p = .05 - significant NS – Not Significant, \* \* Karl Pearson's Correlation coefficient

#### Table 4. Table demonstrating correlation analysis between neutralizable acidity (NA) and enamel loss caused by test syrups

r value**	p value*
0.626	0.007
0.594	0.012
0.612	0.009
	0.626 0.594

\* p < 0.01 - significant, \*\* Karl Pearson's Correlation coefficient

#### Table 5. Table demonstrating correlation analysis between viscosity and enamel loss caused by test syrups

Relationship between	r value*	* p value*
Viscosity and enamel	0.06	0.67, NS
loss at 10 min		
Viscosity and enamel	-0.05	0.71, NS
loss at 1 Hr		
Viscosity and enamel	-0.04	0.74, NS
loss at 8 Hrs		

\* p = .05 - significant NS - Not Significant,

\*\* Karl Pearson's Correlation coefficient

## 4. DISCUSSION

Tooth erosion is the chemical dissolution of the dental tissues without bacterial involvement. The underlying etiology of erosion is believed to be a source of acidic action on the susceptible tooth [11]. The erosive effect of dietary acids on dental tissue can be influenced by a number of factors including pH, dissociation constant of acid (pKa), titratable acidity, temperature, acid character, concentration and chelation potential. Furthermore, frequency, timing of intake, duration of exposure in the oral cavity and fluoride content in the liquid preparation are some other important factors to be considered [12]. In addition to the above factors, pellicle layer and variations in tooth structures also contribute to the erosion process [13,14].

Dental erosion becomes a potential issue when medicines with prolonged oral clearance are taken long term for chronic illness. The active ingredients in these medicines are necessary for improvement or maintenance of health whereas some inactive ingredients pose dangers like dental caries and dental erosion [11]. In the present study, the pH of the 17 medicated syrups were measured using a digital pH meter and it was found that the syrups had varied pH values (3.53 - 8.14). Most of the syrups had acidic pH except Azee (antibiotic) and Valparin (antiepileptic). In this study, 12 out of 17 syrups exhibited pH at or below the critical pH (pH<5.5). At critical pH, enamel gets unsaturated and sufficiently high concentrations of un-ionized acid ensure the inward diffusion of enough acid to extend the lesion [14].

The commonly used liquid medications included in the study were antibiotics, anti tussives, anti histamines, multivitamins wherein all these syrups showed an acidic pH. Antibiotic syrups have antibacterial action and hence reduce demineralization in cases of recurrent treatment despite sucrose content [15,16].

The medications with low pH have greater potential for causing erosion. Alessandro Leite Cavalcanti et al. [6] showed that many pediatric antitussives had pH below the critical value and had greater cariogenic and erosive potentials. Passos et al. [17] reported that pediatric syrups with low pH have ability to initiate the dental demineralization by direct action on enamel surface, without any influence on the oral micro flora. The development of erosion was also influenced by the enamel type, temperature and acid exposure time.

The total acid level of the syrup, termed as titratable acid is considered to be the primary factor in causing dental erosion rather than the pH, because it determines the actual hydrogen ion availability for interaction with the tooth surface. The amount of sodium hydroxide required to neutralize the pH is greater for Api-up (5.40ml) and least for Tonoferron (0.20ml). Azee (Azithromycin) and Valparin (Sodium Valproate) had basic pH and so they were neutralized using 0.1N Hydrochloric acid. The amount of sodium hydroxide required to neutralize the neutralize the acidity is dependent on the inherent pH of the test syrup.

Liquid preparations are usually sweetened with sucrose, which can be readily fermented by oral acidogenic bacteria. Medicines in the form of syrups intended for pediatric use contain 10% to 80% sucrose, on an average about 55% [2]. The medicines that have sucrose as sweetening agent possess high viscosity [18]. As a result these medicines have slow salivary clearance and can cause greater dissolution of enamel. The additives generally used as emulsifiers and thickening agents are Hydroxy propyl methyl cellulose, Sodium carboxy methyl cellulose, Guar gum, Xanthum gum, Methyl cellulose, Carbopol which accounts for the desired viscosity.

The syrup Asthalin (Salbutamol) showed highest viscosity (1906.5 cP) and Ondem (Ondancestron) least viscosity (7.67 cP). The variations observed in viscosity among the test syrups are due to their sugar content and other ingredients included in the formulation.

The pH is an accurate indicator and an important variable in investigating the erosive potential of liquid medicines. In addition to pH and neutralizable acidity, viscosity of the syrup also influences degree of surface enamel dissolution. Syrups with high viscosity retain on the tooth surface for a longer duration leading to enamel erosion. Liquid medicines with low pH and high viscosity when administered frequently have greater synergetic potential to cause dental erosion.

Non –contact optical profiling device is used to characterize surface changes in tooth enamel. This is a highly sensitive technique for surface characterization and dynamic measurements with the capability to resolve repeatedly, large surface areas with sub- nanometer resolution. Previous studies have evaluated the erosive effect of pediatric liquid medicines under SEM by observing the surface topography, etched enamel patterns and crater formation, but the depth of enamel loss was not quantified [13,19]. In order to quantify the degree of erosion, optical 3D profilometer was employed in this study which characterized surface changes precisely and quantitatively.

Three intervals are considered to evaluate the surface changes of the enamel, to find out the minimum time required to cause enamel erosion and also to check the degree of enamel erosion with time interval. Most of the syrups (12 out of 17) exhibited acidic pH (at or below critical pH) indicating that majority of liquid medicines had

acidic pH which could cause more enamel erosion. All the test syrups caused enamel surface loss, but the degree of erosion varied. Lesser duration of exposure to the test syrup caused less erosion and increased with time.

Api–up (an Ayurvedic appetizer) caused greatest loss of enamel and Azee (Azithromycin) caused least erosion of enamel at all time intervals. *Emblica officinalis* (amla), a citrus fruit is a major ingredient of Api – up and is responsible for the greatest dissolution of enamel. Many studies have confirmed the increased erosive potential of citrus fruit juices like lemon and orange [7,8,9].

Syrups with acidic pH and higher viscosity cause a greater degree of enamel loss. However, pH is the most critical factor to cause enamel erosion. Highly viscous Asthalin (Salbutamol) (1906.6 cP) with acidic pH (3.78) caused a greater loss of enamel. Valparin (Sodium valproate) caused a lesser degree of enamel loss due to its basic pH (7.53) and low viscosity (14.36 cP). Least viscous Ondem (Ondansetron) (7.67 cP) caused a higher degree of enamel loss due to its acidic pH (4.63). Azithromycin preparation (Azee) caused lesser enamel loss due to its basic inherent pH (8.14), though it had moderate viscosity (373.43cP).

Therefore, it is understandable that dissolution of enamel caused by liquid medications is due to number of factors like low pH, high viscosity, high titrable acidity, greater sugar content and chemical composition of the medicine. Also, frequency of consumption of the syrup and the time of intake may also add to the potential erosive challenge.

Perhaps, the degree of enamel loss caused by the medications in this laboratory study could be greater than clinical situations as the oral environment cannot be exactly simulated. In oral cavity, the enamel surface is covered by a protective pellicle and/or plaque layer and subjected to flushing, buffering and remineralizing effects of saliva [10].

## 5. CONCLUSION

The medicated syrups with low inherent pH and high viscosity had shown to cause a greater dissolution of enamel. However, certain syrups with low viscosity had shown higher degree of enamel loss due to their inherent acidic pH and those with high viscosity had shown lesser degree of enamel loss due to their basic pH, confirming that inherent pH is the most critical factor for erosion.

It is important to sensitize the parents of the diseased children, paediatricians, pharmacists and the manufacturers to the fact that medicated syrups cause erosion of dental hard tissues. Since the majority of the medicated syrups have acidic pH, the medical and dental specialists should be extra cautious while prescribing syrups and instruct the parents to dilute the prescribed dose of the formulation with water or to rinse their mouth with water soon after ingestion of syrup, if not diluted. Future clinical trials are warranted to verify the role of pediatric liquid medicaments causing erosion of dental hard tissues.

# CONSENT

Not applicable.

## ETHICAL APPROVAL

Not applicable.

## **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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Peer-review history: The peer review history for this paper can be accessed here: http://www.sciencedomain.org/review-history.php?iid= 663&id=12&aid=6196