Cariogenic Potential of Pediatric Liquid Medicaments– An *in vitro* Study

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Pediatric liquid medicaments (PLM) are popular and are easily accepted by both parents and children. They are widely prescribed and easily available. However the sugar content and properties of these preparations determines their cariogenic potential. ***Aims and Objectives:*** *This study assessed the pH and viscosity of pediatric liquid medicaments, type and concentration of sugars present in them and their effect on the growth of Streptococcus mutans.* ***Methodology:*** *PLM included two each of the most commonly prescribed analgesics, antibiotics, nutritional supplements, antitussive and antiepileptic preparations. The endogenous pH was measured using a digital pH meter and the viscosity was measured using a digital Brookefield viscometer. Analysis of sugars (sucrose, glucose and sorbitol) was performed using High Performance Liquid Chromatography. The effect of PLM on Streptococcus mutans was done by ditch plate method.* ***Results:*** *The pH of PLM ranged from 3.70 to 7.04 and viscosity varied from 307.33cP to 2408.33cP. Fifty percent of the PLM contained sucrose, glucose and sorbitol, and sucrose was present in nine of the PLM. The antibiotic preparations showed zones of inhibition against growth of streptococcus mutans.* ***Conclusions:*** *The physical properties of Pediatric Liquid Medicaments as well as the type and concentration of sugars present in them can be indicative of their cariogenic potential.*

Keywords: *pediatric liquid medicaments, cariogenic, pH, viscosity, sucrose, streptococcus mutans.*
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INTRODUCTION

Systemic administration of drugs include oral, sublingual, rectal, cutaneous, inhalation, nasal and parental routes. Among these routes, the oral route is the oldest and the most common mode of drug administration. Pediatric liquid preparations are popular and are easily accepted by both parents and children. Syrups have a long history of use in pediatric medicine. They are widely prescribed, and are easily available. Their use is usually for a short duration, but for some children it may be a daily occurrence.

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Although, the active ingredients in these medicines are necessary for improvement or maintenance of health, some of the inactive ingredients pose a risk to dental health.[1] The AAPD caries risk assessment tool (CAT) stipulates that children with chronic conditions and who are taking medicines may be at higher risk for dental diseases.[2,3] Most of these liquid preparations are made palatable in order to gain patient compliance and are used extensively in children.[4,5,6] The inclusion of sugars, in children's medicines is, primarily to mask the less pleasant taste of active ingredients.[7] However sugars added to medicines can be fermented by oral bacteria leading to acid formation and a drop in intra oral pH. Only few studies provide information about the concentration of free sugars present in liquid medicines and they are usually based on drug labels and on information from pharmaceutical industries.[8,9,10]

There is growing concern among pediatric dentists about the increased consumption of 'hidden sugars' by children, especially those who are chronically ill. It is important to assess the cariogenic potential of commonly used PLM. Hence the purpose of this study was to assess the endogenous pH and viscosity of pediatric liquid medicaments, type and concentration of sugars present in them and their effect on the growth of *Streptococcus mutans*

MATERIALS AND METHOD

The study was conducted on ten pediatric liquid medicaments (PLM) of different pharmaceutical companies. These

medicaments were selected based on a preliminary questionnaire type of survey conducted to find out the most commonly prescribed preparations among pediatricians in Bangalore city, India. A similar type of preliminary survey has been done in earlier studies.[11,12] From the responses obtained, two each of the most commonly prescribed and available analgesics, antibiotics, nutritional supplements, antitussives and antiepileptic syrups were selected.

The Pediatric Liquid Medicaments (PLM) included two each of the most commonly prescribed analgesics, antibiotics, nutritional supplements, antitussive and antiepileptic preparations (Table I). The labels of each medicament were examined to gather information on their composition.

Evaluation of pH [9,11,13] **and Viscosity**[14]

The endogenous pH of each PLM was measured using a digital pH meter (Methron, 781 pH/ Ionmeter). The viscosity was measured in centipoises (cP) using a digital Brookefield viscometer. Parameters for each medicament were evaluated in triplicate.

Analysis of Type and Concentration of Sugars [9,12]

Analysis of sugars (sucrose, glucose and sorbitol) was performed using High Performance Liquid chromatography (HPLC) (Agilent 1100 system, UK). Five ml of each PLM was pipetted into a 10ml volumetric flask, to which 2ml of diluent was added and sonicated for 5 minutes. Microdilutions of 1ml were passed through a 0.45 mm filter paper and the supernatant was used for chromatography. All samples were prepared in triplicate.

The chromatographic conditions were maintained as follows:

Column	: 0.3 mm X 7.8 cation exchange resin column
Flow rate	: 0.5 ml/minute
Injection volume	: 20.0mL
Detector	: Refractive Index Detector
Run time	: 85.0 minutes
Column Temperature	: 35°C

Degassed water was used both as the mobile phase and as a diluent.

Evaluation of Effect on *Streptococcus Mutans*[15]

The effect of PLM on *Streptococcus mutans* was done by ditch plate method as it is simple and inexpensive. Freeze-dried forms of *Streptococcus mutans* MTCC 497 was obtained from Microbial Type Culture Collection, Chandigarh, India.[15]

After preparation of the inoculum, 1ml of inoculum suspension was added to sterilized Muller-Hilton agar medium and mixed thoroughly. About 20ml was then dispensed into sterile petridishes and allowed to solidify. Cylindrical cavities/ wells were bored in the media after solidification using the sterile borer.

Two dilutions of each sample of PLM were prepared using sterile water to give 1:2 dilution (1ml of sample + 1 ml of sterile water) and 1:10 dilution (1ml of sample + 9ml of sterile water). 0.1ml of each diluted sample was pipetted into the prepared wells on the agar plate. The plates were then kept at room temperature for 2-4 hours for pre-incubation diffusion. The plates were then incubated for 24 hours at 30°C -35°C, following which the plates were observed for zones of inhibition and/or exhibition. The maximum diameter of the zones was measured using digital vernier calipers.[16,17]

The data obtained with regard to the pH, viscosity, type and concentration of sugars and zone of inhibition/exhibition with *Streptococcus mutans* were subjected to statistical analysis using Kruskal-Wallis test and Mann-Whitney test. The SPSS software was also used for statistical analysis of data.

RESULTS

Among all the PLM, Gardenal showed the highest pH of 7.04, while a very low pH of 3.7 was seen with Taxim-O. Visyneral Z was found to be most viscous (2408.3 cP) whereas, Mit's Linctus Codeinate Co showed the least viscosity (307.33 cP). (Table 1)

Fifty percent of PLM contained sucrose, glucose and sorbitol. Sucrose was observed in 9 PLM and glucose in 7 PLM. The highest concentration of sucrose was seen in Ibugesic (18.80 g%). The lowest concentration of sucrose, glucose and sorbitol was seen in Mit's Linctus Codeinate Co. Taxim-O contained only sucrose, whereas Mox-Clav contained both sorbitol and sucrose (lowest concentration of 0.08g%). The only PLM that did not contain sucrose or glucose was Gardenal. However, it had the highest concentration of sorbitol (25.97 g%).(Table 2)

Zones of inhibition were seen with Taxim-O and Mox-Clav, at both dilutions. Only Zincovit showed zones of exhibition at both the dilutions. (Table 3)

DISCUSSION

Pediatric medications and/or nutritional supplements are commonly available as drops and syrups. Studies on pediatric oral medications have primarily focused on their erosive potential.[12,18] However, the cariogenic potential of these medications depends on factors such as pH, viscosity, sugar content, high frequency of ingestion, bedtime consumption and reduced salivary flow caused by the use of some drugs.

Many parents are aware that sugars cause tooth decay but commonly relate this solely to the consumption of sweets and biscuits. They are often unaware of the hidden sugars added to many foods and drinks including pediatric liquid medicines.[19,20] Oral liquid medications seem to have composition and pattern of repetitive application that makes them particularly prone to the production of dental caries.[21] Children on an average take medicine every eighth hourly on a day or ten times in a week. The risk of dental caries especially concerns chronically sick children, who require long term medication[22,23] and children who receive medications frequently because of coughs and colds.[9,19] However other healthy children who take medicine infrequently and for short periods are also at a risk.

Table 1. Mean pH and Viscosity of Paediatric Liquid Medicaments

PLM	PRINCIPAL INGREDIENT	TRADE NAME	PHARMACEUTICAL COMPANY	pH Mean±SD	Viscosity(cP) Mean±SD
Analgesic	Paracetomol	Calpol	Glaxo Smithkline Pharmaceuticals Limited	6.08±0.04	2040.00±10.00
Analgesic	Ibuprofen	Ibugesic	CIPLA Ltd.	4.57±0.02	1800.00±20.00
Antibiotic	Cefixime	Taxim- O	Alkem Laboratories Ltd	3.70±0.06	1620.00±20.00
Antibiotic	Amoxicillin and potassium clavulanate	Mox Clav	Rexcel (A division of Ranbaxy Laboratories Limited)	6.01±0.01*	1396.67±15.28
Antitussive	Codeine phosphate Chlorpheniramine maleate	Mit's Linctus Codeinate Co	Vivimed Labs Ltd	5.02±0.01	307.33±3.06
Antitussive	Dextramethorphan Hydrobromide,Chlor-pheniramine maleate, Phenylephrine hydrochloride	Chericof	Sobrex Pharmaceuticals Company (for Ranbaxy Laboratories Limited)	4.66±0.01	1755.00±5.00
Nutritional supplement	Multivitamins	Visyneral Z	Crest healthcare (P) Ltd	3.81±0.01	2408.33±2.89*
Nutritional supplement	Multivitamins and minerals	Zincovit	Apex laboratories private limited	3.84±0.02	708.33±2.89*
Antiepileptic	Phenobarbitone	Gardenal	Nic.Piramal	7.04±0.03	1455.00±5.00
Antiepileptic	Phenytoin	Eptoin	Knoll pharma	5.07±0.03	800.00±5.00

*P= 0.001; P≤0.05 significant

The increase of prescribed medicine intake and of self-medication in developed countries exposes a growing number of children to medication caries, which can be considered a public health problem.[19] The most common Over-The-Counter(OTC) preparations given to children are analgesics, cough medicines and vitamins.[24,25] It has been reported that everyday up to 60% of the population of developed countries take some form of medicine, of which half are bought over the counter without prescription and 17% of children are given a non-prescription cough medicine.[26]

The erosive potential of an acid is based on three properties:(1) the concentration of H^+ ions (endogenous pH); (2) amount of acid available (titratable acidity); and (3) relative

Table 2. Concentration of Sugars in Paeditric Liquid Medicaments and Effect on growth of *Streptococcus Mutans*

PEDIATRIC LIQUID MEDICAMENTS	CONCENTRATION OF SUCROSE, GLUCOSE AND SORBITOL (g%)		
	Sucrose Mean±SD	**Glucose** Mean±SD	**Sorbitol** Mean±SD
Calpol	7.94±0.02	0.84±0.01*	0.70±0.01*
Ibugesic	18.8±0.02*	1.71±0.01	0.83±0.02*
Taxim-O	13.59±0.05	0.00±0.00*	0.00±0.0
Mox-Clav	0.08±0.0.0*	0.00±0.01	4.68±0.01
Mit's Linctus Codeinate Co	7.09±0.06	0.79±0.03	0.60±0.01
Chericof	17.55±0.31	1.71±0.01	0.00±0.0
Visyneral Z	8.11±0.07	5.49±0.04	0.00±0.00
Zincovit	16.09±0.08	2.02±0.03	2.91±0.74
Gardenal	0±0.00*	0.00±0.00	25.97±0.55
Eptoin	16.67±0.02	2.13±0.02	3.90±0.01

*P=0.001;P≤0.05 significant

Table 3. Effect of Paediatric Liquid Medicaments on growth of *Streptococcus mutans*

PEDIATRIC LIQUID MEDICAMENTS	ZONE OF INHIBITION AND/OR EXHIBITION WITH *STREPTOCOCCUS MUTANS*	
	1:2 dilution Mean ±SD (in mm)	**1:10 dilution** Mean ±SD (in mm)
Calpol	Nil	Nil
Ibugesic	Nil	Nil
Taxim-O	37.68±0.21 (**inhibition**)	29.56±0.04 (**inhibition**)
Mox-Clav	48.52±1.66 (**inhibition**)	43.74±0.25** (**inhibition**)
Mit's Linctus Codeinate Co	Nil	Nil
Chericof	Nil	Nil
Visyneral Z	Nil	Nil
Zincovit	11.80±0.58 (**exhibition**)	14.57± 0.13 (**exhibition**)
Gardenal	Nil	Nil
Eptoin	Nil	Nil

**Z= -2.121; Z0 ≤ .05 significant
**P =0.034; P0 ≤ .05 significant

strength of the acid or ease with which the acid will give up free H^+ ions (pKa).[27] The exact contribution of various acidic components of medicines in eroding enamel is unclear, especially *in vivo*.[14] Our study did not aim to analyze the extent to which each PLM might cause erosion. Rather it focused only on inherent characteristics that could influence dental caries. Hence only the endogenous pH of the PLM was assessed using a digital pH meter, which is more accurate and efficient than a conventional electrode pH meter.[9,11,18] The pH of 70% of PLM was below 5.5, that is similar to that of a Brazilian study.[9] The pH of PLM showed a wide range of 3.70 to 7.04, which is in accordance with earlier studies.[9,18] However, in another study that used a pH electrode meter, higher pH values were reported for all PLM.[1]

However, it is not just the pH, that is important, but rather the titratable acidity. The greater the buffering capacity of the liquid, the longer it will take for the saliva to neutralize the acid.[9,28]

Decreased salivation and lack of masticatory movements during the night increase the cariogenic potential of medicines.[19] Sugar-containing analgesics are given at night to relieve pain and a night-time cough may be soothened by a cough syrup, so as to help the child sleep. Very often the last daily dose of antibiotic syrup may be given at bedtime. These viscous syrup medicines with prolonged oral clearance can constitute a risk to dental health.[29] Information about the relation between viscosity and dissolution of the dental hard tissues is rare in literature. In our study viscosity varied from 307 cP to 2408 cP. Neves et al reported that the viscosity of PLM in their study ranged between 4.7 to 412.3 cP.[9]

An unrecognized and significant supply of cariogenic carbohydrates is in the form of sugar-containing liquid oral medicines. Medicines intended for pediatric use have a mean sugar content of approximately 50% and syrups contain 10% to 80% sucrose, most commonly about 55%. The sugar content of 24 liquid medicines frequently prescribed for infants and young children showed a range of 29.4-61.2%.[30]

Barring the sugar free medicines, we observed that the drug labels only provided information on the presence or absence of sugars in the syrup medicines, rarely mentioning the type of sugar present. A similar finding was also reported in PLM available in Brazil.31 High Performance Liquid Chromatography (HPLC) used in our study,[9,12] enables the discrimination of individual sugars present in the syrup as well as its concentration with remarkable accuracy.[12] Studies have concluded that although Paper Chromatography (PC) and Thin Layer Chromatography (TLC) of sugars are high speed and require simple instrumentation their results are limited and can only be used as a reference about constituent mono- or oligosaccharides identification.[32]

The selection of sugars for analysis was based on the frequency of their inclusion in PLM. Sucrose, followed by glucose, are the commonly added bulking and sweetening agents present in almost all PLM. Fructose is not used frequently in most preparations. Among the sugar substitutes, sorbitol is commonly used.

The percentage of pediatric medicines with sucrose in their compositions varies from 0% to 58.30%.[9,33] Pomorico *et al* reported that sucrose present in 7 of the 10 samples studied ranged between 5 to 54 g%.[18] Another study detected sucrose in 10 of the 23 samples investigated, with concentrations ranging from 11.36 g% to 85.99 g%.[9] The other sugar that has been commonly identified in pediatric medicines is glucose. Brazilian studies have reported the presence of glucose in several PLM, with the range varying between 2.10g% and 40.19 g%.[9,12,18] In our study, 7 PLM had glucose ranging from 0.84 g% to 5.49 g%.

Presently a number of products for infants and children including PLM/medicines have been formulated using sugar substitutes. Although some parents are aware of the availability of sugar-free medicines, they are more likely to purchase sugar-containing medicines that are prescribed by most practitioners or use medicaments that are recommended by pharmacists.

Polyalcohols such as sorbitol and xylitol are important sugar substitutes since they are not efficient substrates for plaque bacteria and therefore produce only a minimal plaque pH drop. Polyols are sugar derivatives in which the reactive aldehyde or keto groups have been reduced to hydroxyl groups. The metabolism of polyalcohols is related to that of sugars: they are oxidized to either ketose or an aldose group. In our study, sorbitol was detected in 7 PLM, with the sorbitol content ranging upto 26%. This was in accordance with reports on PLM in Brazil.[11,18] However, Neves *et al* found the sorbitol content of PLM to range from 5.39% to 46.09%.[14]

Masters suggested that the large number of antibiotics prescribed as syrups to the children in his study may have contributed to the observed reduction in dental caries, although this effect disappeared after 4 years of age.[34] Other researchers have claimed that antibacterial syrup medication is associated with a significant decline in dental caries.[35] Although zones of inhibition were expected with both antibiotic PLM, we wanted to know which one was more effective against streptococcus mutans. The zone of inhibition was significantly greater with Mox-Clav in comparison to Taxim-O. This could also be due to the higher pH of Mox-Clav and its negligible sucrose content. Although antibiotics are antimicrobial in nature, their use over long term cannot be ignored. These preparations are also of concern due to the sweeteners present.

A zone of exhibition was seen with Zincovit probably because nutritional supplements contain constituents that can promote growth of microorganisms. This preparation had a low pH and a higher content of sucrose. The presence of sodium selenite equivalent to 10 mcg of selenium in Zincovit could have also contributed to the promotion of *Streptococcus mutans* growth.[36] Although, the other medicaments studied showed neither zone of inhibition nor exhibition their other properties should be considered for ascertaining their cariogenic potential.

Pharmaceutical preparations with acidic pH and high sugar contents have a potential for increasing dental caries

when used several times each day over long periods of time. It has been shown that children aged 3-7 years have larger variations and slower salivary sugar clearances and also lower salivary flow rates than older children and adults.[37] Primary teeth are known to be less mineralized than permanent teeth and since their enamel surface is not as mature as that of permanent teeth, they are more to dental caries and erosion.

Parents should be informed about the presence of 'hidden sugars' in medicines. It can be recommended that all sugar containing medicines particularly for paediatric use should be labelled with the type of sweetener and its concentration. Whenever possible, paediatric dentists should take the responsibility of informing pediatricians about the profile of the routinely prescribed medications.

This *in vitro* study was limited to a small number of PLM and could have assessed different sugars present in each of them. *In vivo* studies using the same PLM could further relate the effect of composition and properties of these preparations on the primary dentition and/or oral environment.

CONCLUSIONS

1. The cough syrup, Chericof can be regarded cariogenic because of its acidic and viscous nature, together with its high sucrose content. This preparation can be potentially harmful on night-time administration and/or when frequently given to children in-between the regular prescribed doses.
2. With regard to dental health, Mox-clav appears to be less detrimental due to its relatively higher pH, sorbitol content, negligible amounts of other sugars and higher inhibition of *Streptococcus mutans* growth.
3. Zincovit can be considered to be the PLM with the most cariogenic potential due to its acidic pH, high viscosity and promotion of *Streptococcus mutans* growth.
4. For long term use in children with convulsive disorders, Gardenal would be less cariogenic as it has a pH of above 7 and apart from sorbitol, it does not contain any other sugar. The other anticonvulsant Eptoin, though less viscous was acidic and had a very high sucrose content.

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